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Australasian Anaesthesia 2023

Edited by
MATTHEW DOANE

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Australasian Anaesthesia 2023

Invited papers and selected continuing education lectures

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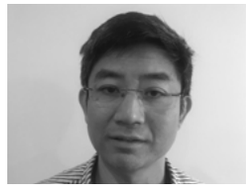

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Preface

What an immense honour.

The opportunity to help support *Australasian Anaesthesia* as the new editor in chief is an inspiring challenge that I have thoroughly enjoyed. I have the privilege of standing alongside an illustrious history of previous editors, the most recent of which, Richard Riley, has stewarded *Australasian Anaesthesia* to the respect it is now regarded with.

As of today, there is a new publication in the medical literature every 30 seconds. One hundred and twenty new publications every hour. In a year, over a million new articles. If each article was only a single page, stacked in a pile, it would reach over 105 meters in height. The speed and voraciousness of this growth is easily overwhelming to the clinician who is simply trying to keep abreast of best practice. Yet here, today, we ironically present a biennial publication. This unique format provides a platform to highlight diverse and unique clinical advancements, challenges, and considerations that are curated to be relevant for the regional and temporal nuances of our specialty.

2023 marks a point of continued emergence from a pandemic that has impacted us all in ways we are still coming to terms with. Despite this, we have seen a steadfast commitment within our specialty to moving forward and engaging. The engagement I have seen from our contributing authors and editors has enabled the production of a wonderful compendium of articles, which we now are pleased to present to you.

To our editors who have since moved on since the previous edition, I would like to express my gratitude for your efforts. The contributing editors, both past and present, were gracious with their support as I came on board. The initial conversations with you provided fruitful insights and guidance that have been instrumental to the changes we have made and are planning to implement.

I'd like to extend a warm welcome to our new editors, and specifically note the fantastic addition of two new editors from Hong Kong. Their clinical expertise and local knowledge will provide greater diversity and representation to the content we support and the readership we connect with.

As you, the reader, look through the articles that follow, I'd ask that you turn a lens to your own practice. Consider your individual expertise. Reflect on the uniqueness of your clinical environment. The skills that you refine and utilise each day are invaluable to your patients. The benefit from your culmination of knowledge and its application can move beyond the bedside in front of you though. I'd encourage anyone with an interest and an idea to contemplate producing an article for the next edition. Let us help you promote the ever-evolving excellence within our speciality, across Australasia.

Finally, I cannot provide enough thanks to the amazing staff that have generated this year's edition. Liane Reynolds (the operations manager for ANZCA's design and communications) has provided essential support, feedback, organisational acumen, professionalism, and patience*. Siobhan Spence (ANZCA's digital communications advisor) delivered unwavering assistance and meticulous diligence. Lastly, our designers Elizabeth Short and Michelle Nightingale, and the ANZCA Library team including Laura Foley and John Prentice supplied skills and knowledge that have laid the groundwork for many future advancements. Developing a cohesive idea into a functional article is challenge enough for any of us. Coordinating, constructing, vetting, and producing an edition of this size would be impossible without their teamwork.

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* As I write this, Liane and I are debating whether we need to reformat the Twitter logo in our finalised articles (as the company has spontaneously decided to completely change it just 24 hours ago). Thanks, Elon.

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Social media and the scholar role: Helping anaesthetists to find substance in the FOAM

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INTRODUCTION

Widespread social media is a defining characteristic of our times. Platforms such as Twitter, Facebook, Instagram, Reddit and YouTube influence everything from presidential elections to the practice of regional anaesthesia.[1,2] Many professional organisations, including the Australian and New Zealand College of Anaesthetists (ANZCA), use social media to raise their institutional profile and to undertake advocacy in policy domains relevant to their strategic plan. Indeed, recognising that social media is a credible and acceptable tool for communication and collaboration, ANZCA recently released a new social media policy to support appropriate use of this technology by trainees and fellows.[3] However, attention has not yet been given to the relevance of social media and free open access medical education (FOAM) to the scholar role in anaesthesia training.

ANZCA trainees are expected to be self-directed learners who critically evaluate information and its sources. Traditionally, anaesthetists have been able to develop these skills through face-to-face study groups, journal clubs, grand rounds and conferences. However, changing work patterns, the impacts of Covid 19 and the ubiquity of smart devices in their pockets have motivated many trainees to engage with online communities of learning. Thoughtfully used, social media can allow trainees to identify key bodies of anaesthesia research and evaluate supporting literature, in the company of like minds from diverse practice settings all around the world. In doing so, trainees can emerge from their silos and interact with others in and beyond their in-person life, creating and disseminating knowledge to professionals and lay audiences in the fullest expression of the ANZCA scholar role.

In this paper, we will describe the utility of social medial and digital scholarship in anaesthesia training and continuing professional development (CPD). We will summarise the literature examining the impact of social media on postgraduate learning and explore how specialty training programs might evolve to incorporate digital scholarship in the scholar role and CPD activities.

A SHORT HISTORY OF SOCIAL MEDIA AND MEDICAL EDUCATION

A simple definition of social media is any platform that allows users to create and share content through virtual communities. The concept of social media is nearly three decades old, with the earliest definitions emphasising social media's role as a conduit for users who were linked by existing friendships or common interests to 'upload' or 'exchange' material online. Contemporary understanding places greater emphasis on user-generated content that may be shared broadly.[4]

In the second decade of the 21st century, expansion of social media, combined with widespread availability of broadband internet and smart devices, served as important enablers of the nascent Free Open Access Medical Education (FOAM or #FOAMEd) movement.[5] As described by one of its early proponents, FOAM is a 'globally accessed crowd-sourced educational adjunct providing inline (contextual) and offline (asynchronous) content to augment traditional educational principles'.[6,7] Characterised thus, it can be seen that FOAM is a broad church, spanning the continuum of scholarship from 'corridor conversation' to post-publication peer review.[6]

Initially, the FOAM paradigm was championed by a handful of enthusiasts and in the eyes of some educators and clinicians, early resources such as *Life in the Fast lane* and *Academic Life in Emergency Medicine (ALiEM)* were not at first considered worthy of scholarly credit. However, in the succeeding decade, there has been a proliferation of FOAM providers who now constitute a diverse community of practice. Within this community, it has become possible for clinicians to interact directly with investigators, as well as with translational educators whose aim is to bridge the gap between research and practice. The massive increase in FOAM content has necessarily created an 'attention economy' in which social media educators are incentivised to find more sophisticated means of presenting information and more effective mechanisms for dissemination.[8]

Today, social media platforms are the primary medium for many specialists and specialists-in-training to share ideas and experiences, translating knowledge into practice.[9] Recognising this reality, medical educators have turned their attention from *whether* our andragogy should make use of social media, to *how* we should best do so. Similarly, academic institutions are working to characterise the discipline of digital scholarship to support practitioners becoming intelligent consumers of FOAM and for academics to claim appropriate credit for their activities on social media. Guidelines on citing social media posts in traditional academic publications are now routine.[10-12]

SOCIAL MEDIA AND THE COLLEGE

Until recently, medical colleges and healthcare organisations have advocated an abstinence approach around social media due to concerns that inadvertent ill-considered engagement could threaten the professional standing of both the individual and their affiliated organisations. However, there has been a paradigm shift where it is now acknowledged that social media is mainstream, that its use will continue to increase and that it has many potential benefits. Not engaging carries greater risk, including a limitation on the impact of institutions' ability to influence consumers, professionals, and decision makers. Most large organisations now have social media policies which allow responsible engagement, but caution against the dangers. ANZCA launched its first social media policy in 2022,[3] approving of engagement by members and explicitly acknowledging the value of social media in 'advocacy and awareness raising'. The document addresses several roles in practice – communicator, leader, health advocate and professional, but its scope does not extend to consideration of social media and the scholarship role.

The ANZCA social media policy is an important first step in promoting effective engagement of members in the digital domain. In this paper, we consider how other medical institutions have addressed the challenge of applying traditional principles of scholarship and professional development in the age of FOAM and how these lessons could inform ANZCA's future efforts to support best practice engagement with social media.

TRADITIONAL MODELS OF SCHOLARSHIP

Academics have traditionally built their reputation through publications in peer-reviewed journals, invited presentations at national or international conferences, or through acceptance of academic appointments at prestigious educational institutions. These scholarly achievements are readily appreciated and can be supported by established metrics such as an individual's h- or G-index. In recent years though, there has been substantial discourse relating to evaluation of scholarly activities that previously went unrecognised, including digital scholarship. This debate is particularly prominent in the United States, where promotion and tenure (P&T) has traditionally been highly structured.

Theoretical models of scholarship have been developed to appraise traditional academic activities for faculty development and promotion. Boyer's Scholarly Domains outline four broad fields of scholarship: discovery,

the search for new knowledge; integration, bringing findings together from different disciplines or sources; application, discovering new ways that knowledge can be used to solve real world problems; and teaching, applying best practices to develop skills and disseminate knowledge.[13] Subsequent authors have suggested that effective educational scholarship is that which is peer-reviewed, publicly disseminated, and capable of being built upon by others.[14] On this basis, educational innovation and educational research has become more widely recognised within the P&T system.[15]

Some models have moved beyond classification of scholarship to its evaluation. According to Glassick's Criteria, high quality scholarship has six characteristics: clear goals, adequate preparation, appropriate methods, significant results, effective presentation and reflective critique.[16,17] These features, or similar markers of quality, would be familiar to anyone who has submitted a manuscript for pre-publication peer review. Taken together with author- and publication-level metrics, these qualitative measures of academic output form the basis for academic appointments in many countries. However, this process may not be well suited to evaluation of digital scholarship.

EMERGING CONCEPTS OF DIGITAL SCHOLARSHIP

Digital scholarship is variously defined, but at its simplest, the term refers to digital dissemination of original content, including research findings, teaching materials, enduring resources, commentaries, or other academic products.[16] Products of digital scholarship may be very similar to traditional media, such as online-only journal publications; however, the digital landscape includes many new scholarly contributions, such as post-production peer review journals,[18] blogs,[19] self-published online textbooks,[20] 'tweetorials'[21,22] and even virtual hospitals.[23] Digital scholarship has been embraced by academics, clinicians, and trainees alike, immensely accelerating and broadening the dissemination of scientific information over the past 10 years. Ongoing growth is facilitated by the ease of use and low cost of many online content sharing platforms.

In 2015, Sherbino and colleagues undertook a consensus conference to identify criteria for social media-based scholarship in health professions education.[24] Appositely, this hybrid meeting was partially hosted on Twitter. The expert panel identified four key features that define social media scholarship (digital scholarship). It must be original; advance the field of health professions education by building on theory, research or best practice; be archived and disseminated; and provide the health professions education community with the ability to comment on and provide feedback in a transparent fashion that informs wider discussion.

Building upon this theoretical foundation, Husain and colleagues developed consensus guidelines for digital scholarship in academic promotion.[16] They propose that academics begin by ensuring that the body of work being considered meets the criteria of scholarship outlined by Glassick and Sherbino et al. Subsequently, they suggest that content is evaluated with respect to its impact, reflecting the extent to which a person's work reaches its intended audience. They recommend that academics explain their role or 'brand' in the social media landscape; helping to establish recognition by others of a scholar's areas of expertise. Finally, their guidelines put forward various metrics particular to social media that can help reviewers gauge the overall scientific rigour and quality of a digital scholar's work. In applying this framework, academics would demonstrate their role within virtual communities of practice, citing the impact and quality of selected digital outputs.[24]

Various methods have been proposed for measuring digital scholarship impact. These 'altmetrics' (alternative metrics) are based upon the premise that scientific impact cannot be solely measured in terms of scholarly citations, but that it should also consider the extent to which a work is seen, read, discussed, shared, and stored.[25] The reach of social media content is easier to gauge than that of traditional media. It is not possible to know how often a printed journal article has been read by others, if at all; or how many were in an audience during a conference presentation. Authors can access data regarding pageviews, downloads and average 'time on page'.[16] Every social media platform has its own impact metrics. For example, Twitter allows users to view the number of times each tweet is seen (an 'impression'), clicked on ('an engagement'), and shared with others in the form of 'retweets' and 'likes'.[22] In addition to overall audience size, which some consider the best measure of digital scholarship impact, other metrics include geographic reach and number of followers from professional social media accounts such as professional societies or educational institutions. Finally, just as some authors may choose to highlight publications in journals that have a high Impact Factor, digital scholars can draw upon metrics such as the Social Media Index (SMi), which ranks FOAM websites according to their Alexa Rank, number of Twitter Followers and number of Facebook Likes. SMi correlates well with other measures of educational resource quality and has been proposed as one tool to help creators and consumers of digital scholarship identify the most reputable forums for online academic discourse.[26,27]

Beyond demonstrating the impact or reach of discrete pieces of online content, individuals may benefit from efforts to articulate their roles in digital scholarship, which ultimately contribute to a personal 'brand' within their virtual communities of practice. Common roles include author of original content or commentary, editor, curator,

reviewer and guest presenter. Role and impact may also be presented together as part of a digital scholarship portfolio; for example, a clinician-academic might indicate that they are editor-in-chief of a clinical blog with more than 5000 page-views per calendar month, which would represent an important role in a moderate-impact organisation.[25]

The impact of digital scholarship readily stretches beyond professional circles and academia. Dr Morgan Edwards, obstetric anaesthetist at North Shore Hospital, Auckland and current president of the New Zealand Society of Anaesthetists, utilised Instagram to disseminate critical health information to her 52,000 followers during the height of the Covid-19 pandemic.[28] One author (NS) can attest to parturients in their institution describing how Dr Edward's educational social media posts allayed their fears and was the catalyst for their decision to get vaccinated during pregnancy. If the ultimate aim of academic scholarship is to improve patient outcomes and wellbeing, there is an argument that digital scholarship – which is accessible to patients – has a far greater reach and more direct impact compared to traditional academic discourse hidden behind paywalls.

Digital scholarship is more readily produced than some traditional academic media. This low barrier to entry, combined with digital scholarship's apparent similarities to recreational social media, has raised scepticism about the general quality of online content. Accordingly, several groups have endeavoured to develop direct quality assessments for specific digital works.[16] The emergency medicine community have contributed significantly to this field of research. In 2014, the Academic Life in Emergency Medicine (ALiEM) collaborative developed the Approved Instructional Resource (AIR) series to help specialist training programs incorporate high quality digital scholarship as an aid to asynchronous professional development.[29] The AIR scoring matrix has five domains: the Best Evidence in Emergency Medicine (BEEM) rating scale, content accuracy, educational utility, Evidence Based Medicine (EBM), and Referencing. Content for the AIR Series is sourced from the SMi-50, a list of the top 50 FOAM sites, ranked by the Social Media Index. Other similar tools exist, including several versions of the Medical Education Translational Resources: Impact and Quality (METRIQ) score[27,30] and the Quality Checklists for Health Professions Blogs and Podcasts.[31] The AIR Series is now widely incorporated into US residency programs and it, along with the other aids to structured appraisal mentioned above, typify the ongoing pursuit of academic rigour within the digital scholarship community.

BARRIERS TO EFFECTIVE DIGITAL SCHOLARSHIP

In the past decade, digital scholarship has expanded in scope and has acquired a more mature framework of supporting educational theory. But the place of social media in academia and specialty education is still not universally acknowledged. Barriers to acceptance must be explored by the digital scholarship community if it is to continue to grow in legitimacy and influence.

One of the major criticisms of digital scholarship relates to the use of altmetrics. As described above, these metrics allow us to understand how content is consumed by both professional and lay users. From this we may draw inferences about the scholarly impact of a particular work, complementing the insights gleaned from traditional bibliometrics such as citation counts and journal impact factor. However, like most indices, altmetrics is susceptible to gaming. Authors may choose to blog or tweet about their own work or that of friends to carve out a bigger stake in the economy of attention. This is no different to the practice of 'self-referencing' that occurs in traditional academia. Additionally, some authors are concerned that social media popularity does not discriminate between positive and negative attention [32] and that, to an extent, there is no such thing as bad publicity in digital scholarship. Recent research has drawn inconsistent conclusions about the relationship between social media activity and traditional markers of impact, such as citation counts, with some studies finding that metrics such as Twitter activity are strongly correlated with citations,[33,34] while others suggest only a weak association.[35] These legitimate concerns should motivate digital scholars to adopt holistic approaches to evaluation of their academic output, clearly articulating their roles within relevant communities of practice and incorporating various quality assurance tools alongside simpler measures of social media reach.

A related criticism of digital scholarship is that academics may not sharply demarcate their personal and professional activities, and that popularity from one virtual community may lead to inflated social media impact in online academic discourse, giving 'undue' prominence to their scholarship.[36] A well-known researcher may in short order tweet about their latest trial, their cat, the traffic, and international politics. Users initially attracted by one post may then explore further and opportunistically engage with the researcher's academic content. To an extent, online interactions of this nature could be said to confer a competitive advantage on more digitally extroverted researchers over less socially engaged but equally deserving colleagues. Equally, it could be said that by establishing an online presence that is convivial and authentic, academics are setting the conditions for engagement with lay audiences and creating opportunities for real-world translation of their scholarship. Social media policy, such as that recently published by ANZCA, can help practitioners to achieve appropriately balanced social media engagement, cultivating a personal brand that is both genuine and professional.

Digital scholarship's heterogenous approach to peer review may be confronting to some academics. While some argue that peer-review is absent from FOAM and digital scholarship more generally, an alternative perspective is that the commitment to peer review is unchanged and that practitioners employ a diverse range of approaches, from traditional pre-publication review by deidentified external experts, to post-publication peer review via online comments or question and answer sessions.[16] Post-publication peer review enables rich interactions between researchers with potential for corrections, clarifications, and generation of new hypotheses or research projects.[18] Responses to social media posts may act as a raw form of peer review, one that is unencumbered by hierarchy, occasionally brutal in its assessment, and itself subject to further review by others.

There is an argument that the risk of disseminating specious research findings may be heightened in the absence of a pre-publication gatekeeper. Even if egregious errors are identified early in the post-publication period, it is possible that erroneous conclusions will already have been drawn by media or lay audiences, who are now much more likely to encounter research findings incidentally as a component of their various social media feeds. However, conventional peer review and editorial oversight does not prevent this occurrence in traditional academic publishing. *The Lancet* took 12 years to retract the widely discredited paper falsely linking autism to the MMR vaccine[37] and there are almost 300 retracted or withdrawn articles related to Covid-19 alone.[38] The most robust approach is likely to be one in which digital scholars retain elements of pre-publication peer review, even when their main focus is post-publication discourse, while traditional publishers seek opportunities to engage with their readership in the period after articles are made available online.[18]

Most social media platforms monetise their users' presence to generate advertising revenue. Their primary aim is not the propagation of academic discourse, but profit generation for shareholders. In-built algorithms are unlikely to consider academic merit or social impact when selecting which posts to disseminate widely. Whilst this is a valid observation regarding digital scholarship, it is no more concerning than exploitative elements of traditional academic publishing, such as volunteer peer review valued at over $US2 billion annually,[39] free content generation, expensive institutional access fees to bypass paywalls, and profit margins higher than the largest tech companies.[40]

SOCIAL MEDIA AND TRAINING IN THE SCHOLAR ROLE

The ANZCA Roles in Practice outline the expected roles of a specialist anaesthetist and how they apply to contemporary practice.[41] Scholar role activities are intended to facilitate the development of trainees as teachers and learners.[42] Accordingly, trainees are expected to develop skills in critical appraisal of information, as well as application of research evidence to specific clinical settings or problems. Key learning activities in this domain include teaching a skill, facilitating a tutorial, critiquing a paper, and completing an audit. Additionally, trainees are expected to engage with the anaesthesia community through attendance at regional meetings and participation in quality assurance programs. Completion of scholar role learning objectives is supported by a departmental scholar role tutor (DSRT) who assists trainees in planning and conducting each learning activity.

Importantly, both the ANZCA Roles in Practice and its ideological antecedent, the Canadian CanMEDS Framework,[43] aim to prepare trainees for *contemporary* practice. Evidence of this aspiration can be found in the most recent revisions to the scholar role, which have deemphasised the historical concept of a formal project in favour of a broader research literacy and audit skillset for most trainees.[44] However, our local curriculum does not presently give weight to digital scholars who contribute to the body of FOAM, except in so far as social media may be used for broader dissemination of previously submitted audit or research findings. The CanMEDS Framework by contrast is presently under review in preparation for its next iteration in 2025[45]; social media has been identified as an emerging theme for inclusion, both as a tool for clinical communication with patients and for its role in teaching.

Trainees are presently faced with a superabundance of FOAM that is easy to access but inconsistent in quality. The anaesthesia community has not yet developed mature resources such as the ALiEM AIR Series and therefore the burden of appraising online content largely falls on trainees themselves. Even FOAM platforms that may be viewed as reliable by specialists may not be suitable for trainees because of the relative paucity of foundational knowledge included in many online resources.[8] This creates potential for trainees to assimilate the views of those they follow, falling into the trap of eminence-based medicine and superficial learning. Recognising this and the incomplete translation of traditional quality metrics to the digital arena, it could be argued that educational institutions have a duty of care to specifically equip learners with the tools necessary to develop as independent digital scholars.

HOW MIGHT ANZCA SUPPORT GROWTH OF DIGITAL SCHOLARSHIP?

In this paper, we have explored the dramatic impacts of digital scholarship on medical teaching, learning and research around the world. We have also established that digital scholarship cannot solely be appraised using tools designed to evaluate traditional academic output. ANZCA has recently acknowledged the importance and legitimacy of social media as a means of communication and advocacy. Consistent with this, ANZCA is now ideally positioned to support appropriate use of social media across the remaining roles in practice, in particular by championing a culture of digital scholarship among both trainees and fellows. We propose the following practical initiatives for ANZCA to achieve this goal.

Acknowledge the role of digital scholarship and outline strategic priorities for developing this domain of practice in the next iteration of the Social Media Policy. Social media platforms constantly evolve and current platforms of choice may be replaced in the future, but the role of digital scholarship in education and training will only grow. Institutions that fail to recognise and embrace digital scholarship risk being left behind and unable to deal with the consequences of its impact.

Establish a process to allow recognition of digital scholarship within the ANZCA and FPM CPD Program. This process could include development of a tool for appraising online content that considers the impact and quality of each piece of work, as well as the role of the fellow in their virtual communities of practice.

Incorporate novel digital teaching and learning methods within the ANZCA Educators Program. Training in development of high-quality blog posts, tweetorials, and infographics would allow enthusiastic educators to engage with a broader community of learners than can be found in any one hospital or regional hub, creating an enduring online record of their teaching.

Curate a collection of high impact, high quality FOAM in a manner similar to the ALiEM AIR Series. The feasibility of such a body of work has already been contemplated in these pages by Juniper & Ganska (2019).[46] This may be done by the ANZCA Library or in collaboration with other anaesthesia training institutions. Other activities may include producing educational material on how to optimise social media feeds to receive content aligned with personal clinical or academic interests. Beyond any collection's value as a repository of knowledge, such a project would also develop ANZCA's reputation as a global leader in digital scholarship. It would also be possible for trainees to contribute to this body of work as part of their scholar role activities, with appropriate mentorship. An enduring and widely used resource produced through scholar role activities would demonstrate that scholarship is an integral part of anaesthesia practice, rather than an activity undertaken by only a small proportion of our colleagues.

Digital scholarship should be incorporated into the next revision of trainee scholar role activities. Trainees are already using social media extensively to learn, teach, and mentor, and ANZCA has an obligation to develop this scholarship with a higher degree of professionalism and academic rigour. Development of online exam revision slide decks and tweetorials could readily be incorporated as evidence of scholar role achievement, as could post-publication peer review activities and contributions to any future ANZCA curated collection of FOAM.

CONCLUSION

Our recent history has been marked by the many losses and compromises forced on us by the pandemic. For many of us, the collegiality, belonging and growth of conferences and special interest meetings seems like a distant memory. But with these challenges have come opportunities. ANZCA fellows and trainees who would never previously have chosen to pursue asynchronous learning or online journal clubs have been exposed to new forms of scholarship, and trainees have learned new ways to support each other remotely while tackling training requirements. These experiences and ANZCA's steps to establish professional standards for other forms of social media engagement have created an environment in which digital scholarship within our specialty can expand and mature. Learning the lessons from overseas and capitalising upon our existing strengths in research and education, ANZCA is now well positioned to help all fellows and trainees find substance in the FOAM.

REFERENCES

1. Schwenk ES, Chu LF, Gupta RK, Mariano ER. How Social Media is Changing the Practice of Regional Anesthesiology. Current anesthesiology reports. 2017;7(2):238-45.
2. Fujiwara T, Müller K, Schwarz C. The effect of social media on elections: Evidence from the United States. National Bureau of Economic Research; 2021.
3. ANZCA. Social Media Policy. Melbourne: ANZCA; 2022.
4. Twenty-Five Years of Social Media: A Review of Social Media Applications and Definitions from 1994 to 2019. Cyberpsychology, Behavior, and Social Networking. 2021;24(4):215-22.

5. Juniper R. Free open access online education in anaesthesia. Australasian Anaesthesia. 2017(2017):317-23.
6. Nickson CP, Cadogan MD. Free Open Access Medical education (FOAM) for the emergency physician. Emergency Medicine Australasia. 2014;26(1):76-83.
7. Cadogan MD. FOAM 2020 [Available from: https://litfl.com/foam-free-open-access-medical-education/.
8. Chan TM, Stehman C, Gottlieb M, Thoma B. A Short History of Free Open Access Medical Education. The Past, Present, and Future. ATS Scholar. 2020;1(2):87-100.
9. Sterling M, Leung P, Wright D, Bishop TF. The Use of Social Media in Graduate Medical Education: A Systematic Review. Academic medicine : journal of the Association of American Medical Colleges. 2017;92(7):1043-56.
10. Auckland University of Technology. Citing social media: AUT; 2023 [Available from: https://aut.ac.nz.libguides.com/APA7th/social-media.
11. Victoria University. APA 7th Referencing: Social Media: Victoria University; 2023 [Available from: https://libraryguides.vu.edu.au/apa-referencing/7SocialMedia.
12. Monash University. Citing and Referencing: Websites and social media 2023 [Available from: https://guides.lib.monash.edu/citing-referencing/apa-websites-social-media.
13. Petegem W, Bosman J, de Klerk M, Strydom S. Evolving as a Digital Scholar2021.
14. Sherbino J, Arora VM, Van Melle E, Rogers R, Frank JR, Holmboe ES. Criteria for social media-based scholarship in health professions education. Postgraduate Medical Journal. 2015;91(1080):551-5.
15. Van Melle E, Lockyer J, Curran V, Lieff S, St Onge C, Goldszmidt M. Toward a common understanding: supporting and promoting education scholarship for medical school faculty. Medical education. 2014;48(12):1190-200.
16. Husain A, Repanshek Z, Singh M, Ankel F, Beck-Esmay J, Cabrera D, et al. Consensus Guidelines for Digital Scholarship in Academic Promotion. The western journal of emergency medicine. 2020;21(4):883-91.
17. Scanlon E. Concepts and Challenges in Digital Scholarship. Frontiers in Digital Humanities. 2017;4:15.
18. O'Sullivan L, Ma L, Doran P. An Overview of Post-Publication Peer Review. Scholarly Assessment Reports. 2021;3(1):6.
19. Johng SY, Mishori R, Korostyshevskiy VR. Social Media, Digital Scholarship, and Academic Promotion in US Medical Schools.
20. Barrett KP, Mac Sweeney R. Social Media in Critical Care. International Anesthesiology Clinics. 2019;57(2).
21. Breu AC. From Tweetstorm to Tweetorials: Threaded Tweets as a Tool for Medical Education and Knowledge Dissemination. Semin Nephrol. 2020;40(3):273-8.
22. Breu AC, Cooper AZ. Tweetorials: Digital scholarship deserving of inclusion in promotion portfolios. Medical Teacher. 2022;44(4):450-2.
23. Emin EI, Emin E, Bimpis A, Pierides M, Dedeilia A, Javed Z, et al. Teaching and Assessment of Medical Students During Complex Multifactorial Team-Based Tasks: The "Virtual on Call" Case Study. Advances in Medical Education and Practice. 2022;13:457-65.
24. Sherbino J, Arora VM, Van Melle E, Rogers R, Frank JR, Holmboe ES. Criteria for social media-based scholarship in health professions education. Postgraduate Medical Journal. 2015;91(1080):551.
25. Cabrera D, Vartabedian BS, Spinner RJ, Jordan BL, Aase LA, Timimi FK. More Than Likes and Tweets: Creating Social Media Portfolios for Academic Promotion and Tenure. Journal of graduate medical education. 2017;9(4):421-5.
26. Thoma B, Sanders JL, Lin M, Paterson QS, Steeg J, Chan TM. The social media index: measuring the impact of emergency medicine and critical care websites. The western journal of emergency medicine. 2015;16(2):242-9.
27. Thoma B, Chan TM, Kapur P, Sifford D, Siemens M, Paddock M, et al. The Social Media Index as an Indicator of Quality for Emergency Medicine Blogs: A METRIQ Study. Annals of emergency medicine. 2018;72(6):696-702.
28. McEnaney A. Meet Dr Morgan Edwards, the Kiwi doctor busting Covid myths online: Stuff; 2021 [Available from: https://www.stuff.co.nz/laife-style/wellbeing/300443025/meet-dr-morgan-edwards-the-kiwi-doctor-busting-covid-myths-online.
29. Lin M, Joshi N, Grock A, Swaminathan A, Morley EJ, Branzetti J, et al. Approved Instructional Resources Series: A National Initiative to Identify Quality Emergency Medicine Blog and Podcast Content for Resident Education. Journal of Graduate Medical Education. 2016;8(2):219-25.
30. Colmers I, Krishnan K, Chan T, Trueger NS, Paddock M, Grock A, et al. The Revised METRIQ Score: A Quality Evaluation Tool for Online Educational Resources. AEM Education and Training. 2019;3.
31. Colmers I, Paterson Q, Lin M, Chan T, Thoma B. The Quality Checklists for Health Professions Blogs and Podcasts. The Winnower. 2015;2.
32. Maggio LA, Leroux TC, Meyer HS, Artino AR. #MedEd: exploring the relationship between altmetrics and traditional measures of dissemination in health professions education. Perspect Med Educ. 2018;7(4):239-47.
33. Robinson DBT, Powell A, Waterman J, Hopkins L, James OP, Egan RJ, et al. Predictive value of Altmetric score on citation rates and bibliometric impact. BJS open. 2021;5(1).
34. Llewellyn NM, Nehl EJ. Predicting citation impact from altmetric attention in clinical and translational research: Do big splashes lead to ripple effects? Clinical and translational science. 2022;15(6):1387-92.
35. Haustein S, Peters I, Sugimoto CR, Thelwall M, Larivière V. Tweeting biomedicine: An analysis of tweets and citations in the biomedical literature. Journal of the Association for Information Science and Technology. 2014;65(4):656-69.
36. Acquaviva KD, Mugele J, Abadilla N, Adamson T, Bernstein SL, Bhayani RK, et al. Documenting Social Media Engagement as Scholarship: A New Model for Assessing Academic Accomplishment for the Health Professions. Journal of medical Internet research. 2020;22(12):e25070.
37. Eggertson L. Lancet retracts 12-year-old article linking autism to MMR vaccines. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2010;182(4):E199-200.
38. Retraction Watch. Retracted coronavirus (COVID-19) papers 2023 [Available from: https://retractionwatch.com/retracted-coronavirus-covid-19-papers/.

39. Aczel B, Szaszi B, Holcombe AO. A billion-dollar donation: estimating the cost of researchers' time spent on peer review. Research integrity and peer review. 2021;6(1):14.
40. Buranyi S. Is the staggeringly profitable business of scientific publishing bad for science? 2017 [Available from: https://www.theguardian.com/science/2017/jun/27/profitable-business-scientific-publishing-bad-for-science.
41. ANZCA. Roles in Practice Melbourne: ANZCA; 2022 [Available from: https://www.anzca.edu.au/education-training/cme-courses-and-resources/roles-in-practice.
42. ANZCA. ANZCA Handbook for Training. v 2.6 ed. Melbourne: ANZCA; 2022.
43. Frank JR, Danoff D. The CanMEDS initiative: implementing an outcomes-based framework of physician competencies. Medical teacher. 2007;29(7):642-7.
44. Graham I. Training program improvements for 2017. ANZCA Bulletin. 2016;25(4):61.
45. Thoma B, Karwowska A, Samson L, Labine N, Waters H, Giuliani M, et al. Emerging concepts in the CanMEDS physician competency framework. Canadian Medical Education Journal. 2022.
46. Juniper R, Ganska A. Feasibility of an open access collaborative anaesthesia knowledge base. Australasian Anaesthesia. 2019;2019:319-23.

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Principles of visual design in cognitive aid development

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INTRODUCTION

Design is interwoven into our lives, and we are all experts – to paraphrase Tim Brown, industrial designer and CEO of the global design consultancy firm IDEO[1]:

" Design is everywhere, inevitably everyone is a designer."

And we agree! – in the sense that everyone is able to say "That looks good" or "I don't like the look of that!" instinctually and quickly. Understanding this interplay between the designer and the user is critical in producing cognitive aids that are effective.

There is an ongoing groundswell in the use of cognitive aids to assist clinicians in the time-critical and high-stakes environment of acute care medicine. This article provides a practical overview on the principles of visual design and its application in the development of these cognitive aids.

Well-designed cognitive aids are important contributors to safe and appropriate patient management in complex clinical situations. However, designs that have been disadvantaged by time and production constraints or other factors may be less clinically helpful.

We will share lessons that we have learnt within our non-profit organisation, Anaesthesia Cognitive Aids and Research (ASCAR) – and we hope these are helpful to anyone involved, or interested, in the development of cognitive aids.

DESIGN

Purpose

Design is about purpose.

> *"Design is a plan for arranging elements in such a way as best to accomplish a particular purpose."*
> – Charles Eames, American designer (of Eames chair fame), architect, and filmmaker[2]

And, as such, the first question that must be asked and answered when designing something is "Why?". Why are we doing this? To create a visual summary for a lengthy clinical practice guideline? To improve upon an existing cognitive aid? To simplify a crisis management process? To incorporate recent updates in clinical management?

Content first

The next step in our process of designing a cognitive aid is the content. When the content has been established, the necessary layout and visual design often flows naturally. Different designs will lend themselves better to different situations, and it is much easier to experiment with moving things around when the content is "locked in". That said, the content can be – and should be – edited and improved with new evidence and user feedback.

This principle can be related back to the purpose of design. With the content established, the design process is then about arranging elements in such a way to accomplish a particular purpose. This approach ensures that the cognitive aid solves the problem that prompted its creation. A beautiful raincoat that doesn't keep out the rain would not be considered great design, just as a perfectly waterproof raincoat that doesn't allow mobility would be considered poor design.

Respect

It is very important to be respectful when reviewing or updating existing designs. There must be an appreciation of the time and effort invested in any creative endeavour. We feel very strongly in favour of viewing all previous designs as a success – design is an iterative process, and getting a design "out there" for user feedback and subsequent improvement should be appreciated.

We echo this quote from Michael Bierut, a renowned graphic designer and creator of the Verizon, Mastercard, Billboard logos (among many other achievements):

> *"For all that, though, these are all deliberate decisions. So someone clearly designed it, which is a cause for applause."*
>
> – Michael Bierut, graphic designer, design critic, educator[3]

User feedback

The user experience is primarily shaped by both the form (aesthetics) and function (purpose) of the product – but there are multiple secondary modulators, such as human factors and the specific context of its use. Therefore, the interplay of form and function for any product can only be determined by releasing it to the intended audience – for use "in the real world". Feedback should be actively requested, and barriers to its delivery should be minimised (for example, a form on your website/a contact email). User research and product feedback are very important tools in design – "just making things pretty" will not create great cognitive aids.

Iteration and versioning

The advent of digital documents, and the movement away from physical print material has made the iterative process much easier. At ASCAR, we version stamp our designs, initially with a "v1.0 2023" after the launch product is achieved. Subsequent minor revisions, such as typos or minor text changes will have a "version bump" to v1.1 and so on. Major revisions, such as significant content or layout changes – usually from user feedback! – will be versioned to v2.0 and so on. In addition, if these assets are stored in the cloud, then a generic URL (such as example.com/anaphylaxis-cognitive-aid) should be distributed to users. The document can continue to be iterated upon, updated, and re-versioned – but the user always gets the most recent version upon accessing that URL.

VISUALS

Fundamentals

Visual design and the principles of effective graphic design and communication are expansive topics that can be daunting to tackle. One useful approach is to start with a set of design fundamentals, which include balance, alignment, hierarchy, contrast, rhythm, proximity, colour, and space.[4,5] There is infinite value in investing time and effort into understanding and implementing these concepts into your designs. It is helpful to note that there are a vast amount of online (both free and paid) resources available. Curated collections of these resources can provide a useful list of higher quality options.[6]

Layout

Some principles behind effective document layout are worth a particular mention:

- Don't overcrowd the design – use white space to create balance
- Use position and grouping to create visual hierarchy[7]
- Ensure consistent vertical and horizontal alignment – use the ruler and spacing tools of your chosen design software program

Left-alignment should be used for both lists and paragraphs – the human eye scans down the left-hand side when appraising a block of left-to-right text (a concept known as the F-pattern).[8,9]

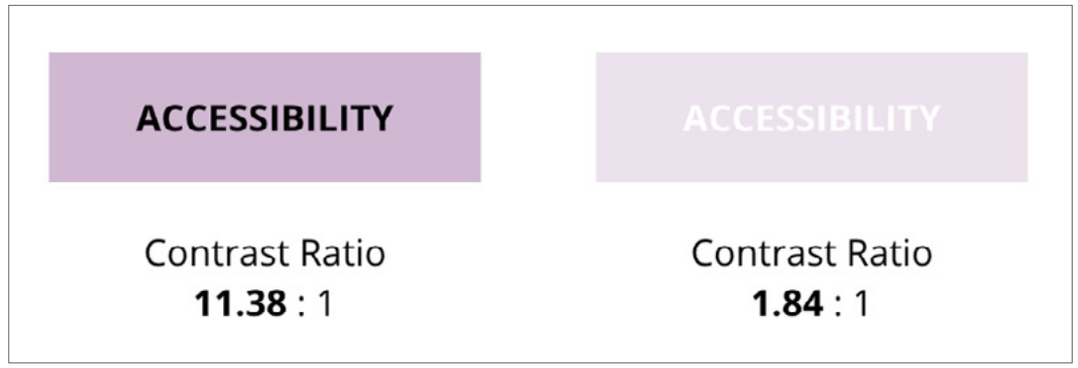
Colour

Colour theory is a huge topic, replete with confusing terminology such as hue, chroma, saturation, value, tone, shade, tint – in addition to colour scheme concepts such as monochromatic, analogous, and complementary colours.[10] Here are our tips on effective colour management:

- Establish a specific colour palette of approximately 6 colours
- Technology can assist with colour decisions (for example, Adobe Color Wheel)[11]
- Consider the emotion of colour – do you want to convey a bright or formal mood?
- Conventional colours can assist with cognitive association
  - Red = neuromuscular blocking agents
  - Purple = vasopressors/inotropes

Accessibility

Particular attention should be given to colour accessibility – ensuring that the contrast of colours between the text and background is readable. Use online tools, such as WebAIM, to establish objective assessment of contrast – all components should have a contrast ratio of at least 4.5:1.[12]



Typography

Typography is another complex area in visual design. A broad understanding of the terminology is important[13]:

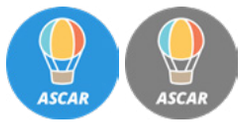
- Typeface – a family of fonts
- Font – a specific variation in weight and size of a typeface
- Typography – how text and letters are arranged within a design

While endless hours can be spent deliberating over typeface choices, here are some helpful principles for effective typography:

- Use online tools to assist with your choices (for example, Typewolf)[14]
- Sans serif typefaces (e.g. Arial / Helvetica) are cleaner and more legible than serif typefaces (e.g. Times New Roman)
- A single typeface for a document is more effective than multiple typefaces (for example, one for headings, one for subheadings, one for body text)
- Prefer simple fonts that are legible over novelty fonts that are playful

Icons

Icons can be a very effective method of assisting visual communication in a cognitive aid. They also introduce visual interest and can help with creating intuitive sections within a layout. While we were fortunate at ASCAR to have the resources to create our own library of icons, this is definitely not a necessity – there are many free icon libraries available online. However, this did confer a unique and unified visual identity across our cognitive aids, and we were able to create icons for more specialised medical equipment. Icons, with simple lines and considered colours, can also create positive emotions and evoke a sense of joy – effects that influence human performance significantly.

	Some ASCAR airway icons ▪ ETT, Video Laryngoscope, LMA ▪ We chose blue for our “airway colour”
	Some ASCAR custom icons ▪ Transport (ventilator and drugs) ▪ Epidural catheter ▪ EZ-IO
	ASCAR logo ▪ A tri-coloured symmetric balloon to convey design, creativity, and joy

Style guide

One of the most effective ways to establish consistent design with a cognitive aid – and between multiple cognitive aids – is to create a visual style guide.[15] This document becomes a reference repository of all the visual design decisions that have been made, such as the colour palette, typography, and so on. Style guides are often incorporated with broader organisational resources such as logos and mission statements.

TECHNICAL

Spelling and grammar

This is a non-negotiable. All professional documents should have correct spelling and grammar. Use a spell checker – and address the red wriggly lines! Another tip: change your computer’s language settings to UK/Australia (this will prevent incorrect spell checks using US spelling).

Units of measurement

It is important to ensure that the units of measurement are written correctly – with reference to the International Bureau of Weights and Measures (BIPM)[16] and the National Institute of Standards and Technology (NIST) Reference on Constants, Units, and Uncertainty.[17] There are also excellent guides available from the Australian government[18] and the Cochrane community.[19] Some important examples:

- Put one space between the numerical value and the unit symbol
  - Correct: Paracetamol 15 mg/kg (max 1 g)
  - Incorrect: Paracetamol 15mg/kg (max 1g)
- Degrees of temperature require a preceding space
  - Correct: Cool patient to 38 °C
  - Incorrect: Cool patient to 38°C
- Degrees of arc do not require a preceding space
  - Correct: Turn the bevel 90°
  - Incorrect: Turn the bevel 90 °
- Use correct case
  - Correct: Fluid bolus 20 mL/kg
  - Incorrect: Fluid bolus 20 ml/kg
- No plural “s” for units
  - Correct: Adrenaline 1 mg
  - Incorrect: Adrenaline 1 mgs

Drug names

Pharmaceutical drugs should be referenced using their generic names – use the Recommended International Nonproprietary Name (RINN).[20] While it is often recommended to use lowercase for generic names, and Capital case for brand names,[21] we have often used Capital case for generic names to improve visual clarity. As always, choose one convention and keep it consistent across all your documents. Example:

- Correct: Draw up midazolam and fentanyl
- Our preference: Draw up Midazolam and Fentanyl
- Incorrect: Draw up Midazolam and fentanyl

Capitalisation and emphasis

It is important to adopt consistent usage of capitalisation.[22]

- Title Case: Management of Intraoperative Hypotension
- Sentence Case: Management of intraoperative hypotension
- Initial Case: Management Of Intraoperative Hypotension
- All Caps: MANAGEMENT OF INTRAOPERATIVE HYPOTENSION

We feel that Title Case is a very sensible choice for headings in cognitive aids. We also advise strongly against using All Caps for any headings, because it reduces legibility and prolongs reading time.[23] Emphasis can be more effectively achieved with the use of underline or **bold** or *italic* – but not in ***combination***.

Legal

A disclaimer is a statement that denies legal responsibility. Most medical organisations will have a legal disclaimer on their website to reduce the legal risk associated with producing clinical resources. While there are many free templates available on the internet, we would recommend seeking formal legal advice to ensure that this is managed appropriately.

A decision also needs to be made with regards to copyright and intellectual property rights to the cognitive aids being produced. All the cognitive aids and resources we make at ASCAR are released under a Creative Commons licence, which gives other people the right to share, use, and build upon those aids.[24] The specific licence we have chosen is termed Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0),[25] but it is important to decide upon a licence that is best suited to your individual circumstances.

Language

Language must be used effectively when creating any visual designs. This is obviously a huge topic, and is excellently covered by experts – such as The Elements of Style.[26] Some practical points that we have learnt:

- Aim for brevity
- Omit the "articles of speech" (the / a / an)
- With: Determine the cause
- Without: Determine cause
- Minimise tautology, for example, prefer "administer" over "rapidly administer"
- Prefer dot points over paragraphs or blocks of text
- Use a consistent and appropriate tone of voice
- Advisory statements ("consider Magnesium") confer more legal protection than prescriptive statements ("use Magnesium")

A good example of how language can be confusing – a website about malignant hyperthermia contained multiple different instructions for temperature management:

- Cool the patient to 38 °C
- Cool patient to 38 °C
- Stop cooling measures when temperature falls to 38 °C
- Cool the patient if core temperature is > 39 °C
- Stop cooling when the temperature has decreased to < 38 °C

We would advocate "Cool patient to 38 °C" for these (opinionated) reasons:

- It is the simplest sentence
- It omits the article "the" – brevity without losing meaning
- "Cool" – focuses on the therapy, whereas "stop cooling" focuses on the cessation of therapy
- The word "temperature" is unnecessary
- The "greater than" (>) and "less than" (<) symbols add cognitive load

The careful and deliberate choice of language will elevate the performance of cognitive aids – and language that is consistent and simple is equally important.

ASCAR

History

ASCAR (Anaesthesia Cognitive Aids and Research) was formed in 2019 at Royal North Shore Hospital in Sydney, Australia, by Jessie Maulder and Daniel Zeloof when they were anaesthesia registrars, and later joined by Daniel Moi and Dushyant Iyer, with a goal of developing and refining high-quality cognitive aids to assist anaesthetists in crisis management. During this process, we have had the privilege of working together with many clinicians across many specialties, including anaesthesia, intensive care, emergency, surgery, and retrieval medicine. There has been close collaborative work involved in developing these cognitive aids, as well as in expert review for clinical governance. We are pleased that our cognitive aids have evolved to be used in the wider critical care context, including medical education and clinical simulation.

We have been very fortunate to have had tremendous support and advocacy from our magnificent department and colleagues at Royal North Shore Hospital. In addition to the clinical environment of a major tertiary referral hospital, our department has always fostered a strong focus on human factors and non-technical skills in crisis management, as well as an ongoing close affiliation with the Sydney Clinical Skills and Simulation Centre.[27]

As a result of this ongoing team effort, we have been able to release cognitive aid booklets for neuroanaesthesia, obstetric anaesthesia, paediatric anaesthesia, and trauma – as well as collections of aids on airway management, cardiothoracic anaesthesia, general procedures, COVID-19, and human factors. All our cognitive aids are presently available for free in our mobile iOS and Android applications, and we maintain an active social media presence on Twitter and Instagram to maximise our contribution to the wider medical community.

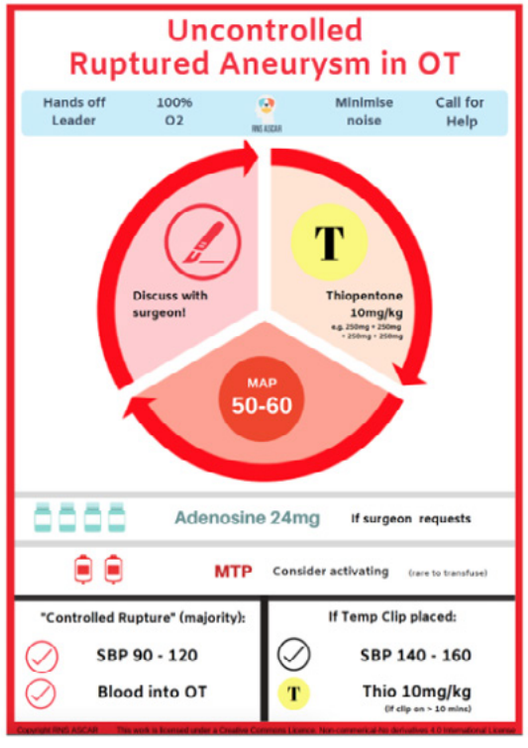
Toolbox ideas

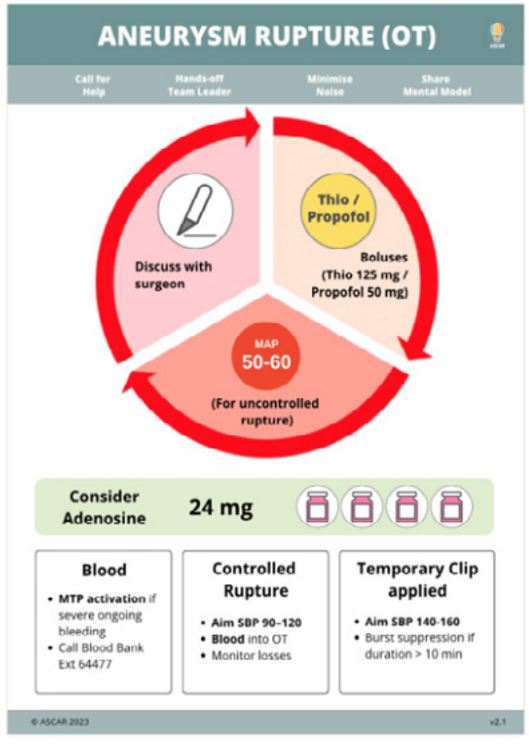
A common question that we get asked is what tools and software we use in our development pipeline. The tools available to the designer change constantly, and we appreciate the broad variation in technical backgrounds of people interested in developing cognitive aids. We champion the use of tools that are intuitive, easy-to-use, and that facilitate collaboration. Our toolbox adapts to our needs, and we encourage this flexibility – from paid subscription software from established players (for example, Adobe Illustrator, InDesign, Photoshop), to their newer and free/freemium counterparts (for example, Canva, Figma, Google Docs, Draw.io).

Example of cognitive aid development

We thought it would be interesting to close with a closer look at the iterative process of one of our own cognitive aids. Intracranial aneurysm rupture is a neurosurgical emergency, and we feel the development of this cognitive aid provides a useful practical review of the areas we have addressed in this article.

- Design. The purpose of this aid was to provide assistance in the crisis management of a neurosurgical emergency.
- Visuals. The overall simple layout has been retained, with the 3-sector centrepiece, a highlight panel (Adenosine), and secondary panels (Blood, Controlled rupture, and Temporary Clip). Some changes include a revised header and subheader, implementation of our new icons, and some adjustments in the layout, balance, palette, and rhythm of the cognitive aid.
- Technical. The language has been modified to promote the active voice, and the spacing of the units of measurement has been corrected.
- Overall. While the content has remained broadly the same (the content being the foundation of all visual documents), we feel that the visual impact and user experience has been improved due to an (ongoing) process of iteration and user feedback.





Contact details

We are always available at hello@ascargroup.com and on Twitter and Instagram (@ascargroup) 👋 – drop us a line!

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We are deeply appreciative of the support, training, and mentorship that we have received at the Royal North Shore Hospital Department of Anaesthesia and all the other centres that we have had the privilege of working at. We look forward to many more ongoing iterative collaborations and encouraging similar endeavours – as we help each other in improving patient safety and outcomes in anaesthesia and crisis management in the critical care environment.

REFERENCES

1. Lavender P. Ideo CEO Tim Brown: 'Everyone Is A Designer' [Internet]. HuffPost; 2014 [cited 2023 June 5]. Available from: https://www.huffpost.com/entry/tim-brown-davos_n_4635681.
2. Kim M. The Meaning of Design: What Design Is and Why It's Important [Internet]. Shakuro; 2020 [cited 2023 May 28]. Available from: https://shakuro.com/blog/the-meaning-of-design-what-design-is-and-why-its-important.
3. Dunlap D. Reviews Trickle In for New Taxi Logo [Internet]. The New York Times; 2007 [cited 2023 June 27]. Available from: https://archive.nytimes.com/cityroom.blogs.nytimes.com/2007/10/15/reviews-trickle-in-for-new-taxi-logo/.
4. Hayward-Cole A. 7 basic principles of graphic design [Internet]. London College of Contemporary Arts; 2019 [cited 2023 June 27]. Available from: https://www.lcca.org.uk/blog/careers/7-basic-principles-of-graphic-design/.
5. Cheyenne M. Design Fundamentals: Elements & Principles [Internet]. Berkeley Library, University of California; 2021 [cited 2023 June 27]. Available from: https://guides.lib.berkeley.edu/design.
6. Fleck R. 10 Excellent Free Online Graphic Design Courses [Internet]. Dribbble; 2022 [cited 2023 June 27]. Available from: https://dribbble.com/resources/free-graphic-design-courses-online.
7. Murchie K, Diomede D. Fundamentals of graphic design—essential tools for effective visual science communication [Internet]. Facets; 2020 [cited 2023 June 27]. Available from: https://www.facetsjournal.com/doi/10.1139/facets-2018-0049.
8. Babich N. F-Shaped Pattern for Reading Content [Internet]. UX Planet; 2017 [cited 2023 June 27]. Available from: https://uxplanet.org/f-shaped-pattern-for-reading-content-80af79cd3394.
9. Doreng-Stearns N. Using F and Z patterns to create visual hierarchy in landing page designs [Internet]. 99designs; 2016 [cited 2023 June 27]. Available from: https://99designs.com/blog/tips/visual-hierarchy-landing-page-designs/.
10. Chapman C. Color Theory for Designers, Part 3: How To Create Your Own Color Schemes [Internet]. Smashing Magazine; 2021 [cited 2023 June 23]. Available from: https://www.smashingmagazine.com/2010/02/color-theory-for-designer-part-3-creating-your-own-color-palettes/.
11. Adobe. Adobe Color [Internet]. Adobe; 2023 [cited 2023 June 27]. Available from: https://color.adobe.com/.
12. WebAIM. Contrast Checker [Internet]. WebAIM; 2023 [cited 2023 June 27]. Available from: https://webaim.org/resources/contrastchecker/.
13. Kramer L. Typeface vs. font: what's the difference? Does it matter? [Internet]. 99designs; 2021 [cited 2023 June 27]. Available from: https://99designs.com/blog/tips/typeface-vs-font/.
14. Typewolf. Guides & Resources [Internet]. Typewolf; 2023 [cited 2023 June 27]. Available from: https://www.typewolf.com/guides.
15. Jordan C. How to create a visual brand style guide [Internet]. Canva; 2023 [Available from: https://www.canva.com/learn/your-brand-needs-a-visual-style-guide/.
16. Bureau International des Poids et Mesures. SI Brochure: The International System of Units (SI) [Internet]. Bureau International des Poids et Mesures; 2022 [cited 2023 May 28]. Available from: https://www.bipm.org/en/publications/si-brochure.
17. National Institute of Standards and Technology. International System of Units (SI) [Internet]. National Institute of Standards and Technology; 2019 [cited 2023 June 27]. Available from: https://physics.nist.gov/cuu/Units/index.html.
18. Australian Government. Measurement and units [Internet]. Australian Government; 2023 [cited 2023 June 27]. Available from: https://www.stylemanual.gov.au/grammar-punctuation-and-conventions/numbers-and-measurements/measurement-and-units.
19. The Cochrane Collaboration. Units and systems of measurement [Internet]. The Cochrane Collaboration; 2019 [cited 2023 June 27]. Available from: https://community.cochrane.org/style-manual/numbers-statistics-and-units/units-and-systems-measurement.
20. World Health Organisation. International Nonproprietary Names Programme and Classification of Medical Products [Internet]. World Health Organisation; 2023 [cited 2023 June 27]. Available from: https://www.who.int/teams/health-product-and-policy-standards/inn/.
21. The Cochrane Collaboration. Names [Internet]. The Cochrane Collaboration; 2022 [cited 2023 June 27]. Available from: https://community.cochrane.org/style-manual/names-common-terms-and-terminology/names.
22. Knowadays. How to Capitalize Titles [Internet]. Knowadays; 2023 [cited 2023 June 27]. Available from: https://knowadays.com/blog/how-to-capitalize-titles/.

23. Baines P. Road signs: Why Britain's designs rule [Internet]. The Independent; 2015 [cited 2023 June 27]. Available from: https://www.independent.co.uk/news/uk/home-news/road-signs-why-britain-s-designs-rule-10466510.html.
24. Wikipedia. Creative Commons license [Internet]. Wikipedia; 2023 [cited 2023 June 27]. Available from: https://en.wikipedia.org/wiki/Creative_Commons_license.
25. Creative Commons. Attribution-NonCommercial-NoDerivatives 4.0 International [Internet]. Creative Commons; 2023 [cited 2023 June 27]. Available from: https://creativecommons.org/licenses/by-nc-nd/4.0/
26. Strunk W, White E. The Elements of Style. 4th ed: Pearson; 1999.
27. Sydney Clinical Skills and Simulation Centre. Improving Patient Care Through Quality Learning & Research [Internet]. Sydney Clinical Skills and Simulation Centre,; 2023 [cited 2023 June 27]. Available from: https://www.scssc.edu.au/.

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A narrative review of the perioperative management of DMARDs

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INTRODUCTION

Disease-modifying antirheumatic drugs (DMARDs) have been used in clinical practice since the 1950s, when hydroxychloroquine, azathioprine and methotrexate were made widely available for clinical use.[1] Since the late 1990s, so called 'non-conventional DMARDs' have emerged, including biologic DMARDs such as tumour necrosis factor inhibitors (TNFi) and monoclonal antibodies, as well as targeted synthetic agents such as Janus kinase inhibitors (JAKi). The development of these agents was driven largely by the identification of key molecular mediators that drive autoimmune inflammatory conditions encountered in the fields of rheumatology, gastroenterology, dermatology and neurology.[2,3] Although collectively referred to as 'anti-rheumatic drugs', these medications have transformed the management of these autoimmune conditions.[4,5] Examples of therapeutic effects of these drugs include reduction of disease activity and structural joint damage in rheumatoid arthritis,[2,6] remission in patients with active ulcerative colitis,[7] and disease regression in psoriasis.[3] Common conditions for the use of DMARDs are presented in Table 1. Biologic agents now dominate the Australian Pharmaceutical Benefit Scheme charts for highest overall cost, and represent a significant proportion of the fastest growing drug costs.[8]

Table 1. Common conditions

Gastroenterology	Crohn's disease Ulcerative colitis
Dermatology	Psoriasis Cutaneous sarcoidosis
Neurology	Multiple sclerosis Myasthenia gravis
Rheumatology	Rheumatoid arthritis Systemic lupus erythematosus Ankylosing spondylitis Psoriatic arthritis Juvenile idiopathic arthritis

Increasing numbers of patients are presenting for both elective and emergency surgery taking conventional and non-conventional DMARDs. These operations can be related to their autoimmune condition, such as joint replacement in inflammatory arthropathies,[9] or abdominal procedures in inflammatory bowel disease,[10] but many patients present for surgery for unrelated conditions.

Perioperative management of patients receiving this diverse group of agents must navigate both consideration of the underlying disease and complications that may result from the actions of the medications themselves. There has long been a mechanistic concern that the immunosuppressive nature of DMARDs may increase the risk of postoperative complications, including infection and poor wound healing. However, temporary cessation of these medications in the preoperative period could lead to a disease flare, which might also increase perioperative complications and lead to worse outcomes overall.

Most international guidelines mainly cover the evidence for use of DMARDs in the context of managing the specific autoimmune conditions, with only a small section dedicated to perioperative considerations and recommendations. The limited guidelines which have focused on the perioperative management of DMARDs only cover specific conditions or surgical procedures.

We aim to present a narrative review of the existing guideline literature on the perioperative management of DMARDs, highlight discrepancies between guidelines, and identify controversies in the recommendations. Evidence will be summarised by the three major drug groups: i) conventional DMARDs, ii) biologic DMARDs, and iii) targeted synthetic DMARDs, with consideration given to the underlying pathologies and potential surgical interventions.

EXISTING GUIDELINES

A total of 25 international guidelines were identified from a search of Ovid Medline, Google Scholar, and Guidelines International Network between 2010 and 2023 (Table 2). While corticosteroids are a mainstay treatment for many autoimmune conditions, this review will focus exclusively on DMARDs. Additionally, this review will not cover the use of biologic agents as they apply to the treatment of cancer. Guideline recommendations on the perioperative management of this group of medications are summarised below.

Table 2. Guidelines

YEAR	TITLE & PROFESSIONAL ASSOCIATION
Gastroenterology	
2023	Korean clinical practice guidelines on biologics and small molecules for moderate-to-severe ulcerative colitis *Korean Association for the Study of Intestinal Diseases*
2021	Preoperative Management of Gastrointestinal and Pulmonary Medications *Society for Perioperative Assessment and Quality Improvement*
2020	ECCO Guidelines on Therapeutics in Crohn's Disease: Surgical Treatment *European Crohn's and Colitis Organisation*
2019	ACG Clinical Guideline: Ulcerative Colitis in Adults *American College of Gastroenterology*
2019	British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults *British Society of Gastroenterology*
Dermatology	
2020	British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020: a rapid update *British Association of Dermatologists*
2019	Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics *American Academy of Dermatology, National Psoriasis Foundation*
2016	From the Medical Board of the National Psoriasis Foundation: Perioperative management of systemic immunomodulatory agents in patients with psoriasis and psoriatic arthritis *National Psoriasis Foundation*
2016	British Association of Dermatologists' guidelines for the safe and effective prescribing of methotrexate for skin disease 2016 *British Association of Dermatologists*
Neurology	
2022	Preoperative Management of Medications for Neurologic Diseases *Society for Perioperative Assessment and Quality Improvement*
Rheumatology	
2023	An Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis *Australia & New Zealand Musculoskeletal Clinical Trials Network, The Australian Rheumatology Association, Cochrane Musculoskeletal*
2023	Perioperative management of patients with inflammatory rheumatic disease. Updated recommendations of the German Society for Rheumatology *German Society for Rheumatology*
2022	Preoperative Management of Medications for Rheumatologic and HIV Diseases *Society for Perioperative Assessment and Quality Improvement*
2022	Preoperative evaluation and perioperative management of patients with rheumatic diseases *UpToDate®*
2022	2022 American College of Rheumatology/ American Association of Hip and Knee Surgeons Guidelines for the Perioperative Management of Antirheumatic Medication in Patients with Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroscopy *American College of Rheumatology, American Association of Hip and Knee Surgeons*
2022	Perioperative management of disease-modifying antirheumatic drugs and other immunomodulators *Portuguese Society of Rheumatology*
2021	Recommendations for psoriatic arthritis management: A joint position paper of the Taiwan Rheumatology Association and the Taiwanese Association for Psoriasis and Skin Immunology *Taiwan Rheumatology Association, Taiwanese Association for Psoriasis and Skin Immunology*
2019	Clinical Practice Guidelines. Management of Rheumatoid Arthritis *Malaysian Society of Rheumatology, Ministry of Health, Academy of Medicine Malaysia*
2019	The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis *The British Society for Rheumatology*
2019	2018 update of the APLAR recommendations for treatment of rheumatoid arthritis *Asia-Pacific League of Associations for Rheumatology*
2017	BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs *The British Society for Rheumatology, British Health Professionals in Rheumatology*
2017	2016 updated Thai Rheumatism Association Recommendations for the use of biologic and targeted synthetic disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis *Thai Rheumatism Association*
2015	2014 Update of the Consensus Statement of the Spanish Society of Rheumatology on the Use of Biological Therapies in Rheumatoid Arthritis *Spanish Society of Rheumatology*
2013	Recommendations for using TNFα antagonists and French Clinical Practice Guidelines endorsed by the French National Authority for Health *French National Authority for Health*
2012	Canadian Rheumatology Association Recommendations for the Pharmacological Management of Rheumatoid Arthritis with Traditional and Biologic Disease-modifying Antirheumatic Drugs: Part II Safety *Canadian Rheumatology Association*

ECCO: European Crohn's and Colitis Organisation; ACG: American College of Gastroenterology; AAD: American Academy of Dermatology; NPF: National Psoriasis Foundation; HIV: human immunodeficiency virus; DMARD: disease-modifying antirheumatic drugs; APLAR: Asia-Pacific League of Associations for Rheumatology; BSR: British Society for Rheumatology; BHPR: British Health Professionals in Rheumatology; TNFα; tumour necrosis factor alpha.

CONVENTIONAL DMARDS

Conventional DMARDs exert their effects on the inflammatory cascade through a range of mechanisms, leading to a broad array of anti-inflammatory and immunomodulatory effects. Table 3 presents mechanistic-focused categories of current DMARDs and specific medications within each group.

Table 3. Categories of conventional DMARDs

Antimetabolites	methotrexate, 6-mercaptopurine, azathioprine, thioguanine, mycophenolate, leflunomide
Antimalarials	hydroxychloroquine
Aminosalicylates	sulfasalazine, mesalazine
Calcineurin inhibitors	ciclosporin, voclosporin, tacrolimus

DMARDs: disease-modifying antirheumatic drugs.

Methotrexate and other antimetabolites

Antimetabolites exert their effect by preventing cell replication, though the exact mechanisms by which these agents dampen the autoimmune response is still unclear.[11] Methotrexate and the thiopurines (azathioprine, 6-mercaptopurine, and thioguanine) are the main antimetabolites used in clinical practice for autoimmune disease. These medications act to inhibit nucleotide synthesis by enzyme inhibition, and some, like the thiopurines, also inhibit lymphocytes.[12]

Antimetabolite DMARDs are used for a wide range of autoimmune diseases including rheumatoid arthritis and inflammatory bowel disease.

Of the 25 reviewed guidelines, 14 discuss the use of methotrexate in the perioperative period. All 14 guidelines recommend continuing methotrexate in the perioperative period,[9,10,13-24] as studies have demonstrated no increase in postoperative complications following abdominal or orthopaedic surgery with continuation, noting that most published data is for patients taking low dose methotrexate (<15 mg/week).[25-35] Six of the 14 guidelines recommend temporary cessation for patients at risk of poor wound healing, however this recommendation appears to be based on expert opinion.[9,14-18] The German Society for Rheumatology recommend that patients taking high dose methotrexate (>20 mg/week) be given a temporary dose reduction perioperatively, given the limited evidence of safety in these patients.[18]

Five guidelines recommend perioperative continuation of thiopurines,[10,15,23,24,36] as studies have shown no increased risk of postoperative infection,[37,38] though two rheumatology guidelines recommend withholding thiopurines for 1-2 days prior to surgery based primarily on expert opinion.[18,39]

Despite conflicting data regarding risk of postoperative infection with continuation of leflunomide in the perioperative period,[40-43] guidelines still recommend its continuation in this period.[9,15,18-22] In patients where there is concern for increased risk of postoperative infection, such as prior prosthetic joint infection, washout procedures to facilitate accelerated drug elimination, or withholding the medication prior to elective surgery may be considered.[9,15,18,20]

Hydroxychloroquine

Hydroxychloroquine inhibits the activation of Toll-like receptors on the surface of endosomes, suppressing production of tumour necrosis factor and reducing the release of pro-inflammatory cytokines.[44] It is a first-line treatment for systemic lupus erythematosus (SLE) and is also used in rheumatoid arthritis and antiphospholipid syndrome. Seven of the reviewed guidelines explored the perioperative management hydroxychloroquine, and whilst there is little safety data on perioperative continuation of hydroxychloroquine, all guidelines recommend continuation, especially given its half-life of 45-50 days, except where there is a history of severe or recurrent infection, or QT interval prolongation.[9,15,18-22]

Sulfasalazine

The mechanism of action of sulfasalazine and other aminosalicylates is not known, but is thought to involve inhibition of cytokine synthesis and T-lymphocyte proliferation, as well as inhibition of leukotriene and prostaglandin synthesis through cyclooxygenase and lipoxygenase.[45]

Aminosalicylates are used in inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. Guidelines recommend that aminosalicylates are continued perioperatively.[15,18]

Cyclosporine and tacrolimus

Cyclosporine and tacrolimus are calcineurin inhibitors and used mainly in solid organ transplantation. Their use in autoimmune disease is limited to being a third- or fourth-line agent, due to the risk of nephrotoxicity with long-term use. Calcineurin inhibitors impair the transcription of cytokines, in particular interleukin-2 (IL-2) and tumour necrosis factor (TNF).

Guidelines recommend perioperative continuation based on safety data from the gastroenterology and neurology populations.[13,15,17,22,45]

Patients with systemic lupus erythematosus

Perioperative management of people with SLE is complex. The American College of Rheumatology (ACR) and American Association of Hip and Knee Surgeons (AAHKS), UpToDate® and Society for Perioperative Assessment and Quality Improvement (SPAQI) recommend differential medication management based on disease severity. For people with non-severe SLE (based on an absence and low risk of clinical and/or serological flares), guidelines recommend withholding SLE medications for 1 week preoperatively including mycophenolate mofetil, mycophenolic acid, cyclosporine, mizoribine, azathioprine and tacrolimus.[9,19,22] In practice however, if a patient's disease is difficult to control, specialists may elect to continue these medications. For people with severe SLE (e.g. frequent flares, haemolytic anaemia, vasculitis, severe organ impairment, or multiorgan involvement), guidelines recommend continuation of these medications.[9,19,22,23]. However, patients at high risk of postoperative infection (e.g. history of recurrent or severe infection, such as prosthetic joint infections or sepsis), and with stable disease for more than six months, sometimes have medications withheld. Even in these high risk situations though, hydroxychloroquine and methotrexate are often continued.[9] Due to the wide range of disease severity and often complex decision-making required in this cohort, consultation with a rheumatologist is mandatory.

BIOLOGIC DMARDS

Biological products are isolated from living cells or tissues in humans, animals, or microorganisms.[46,47] Biologic DMARDs are currently used to modulate the immune system through three main mechanisms[48]:

1. Inhibition of cytokine function
2. Inhibition or depletion of lymphocytes
3. Inhibition of the complement system

Biologic DMARDs work through a variety of inhibitory pathways. These medications are collated by their general and specific pathways and targets, in Table 4.

Table 4. Categories of biologic DMARDs

Mechanism of action	Example medications
Inhibition of cytokine function	
TNF inhibitors	adalimumab, certolizumab, etanercept, golimumab, infliximab
BlyS-specific inhibitor	belimumab
IL-1 inhibitors	anakinra, canakinumab, rilonacept
IL-6 inhibitors	tocilizumab, sarilumab, satralizumab
IL-17 inhibitors	brodalumab, ixekizumab, secukinumab
IL-23 inhibitors	guselkumab, risankizumab, tildrakizumab, ustekinumab (IL-12/IL-23 inhibitor)
IFNAR1 inhibitor	anifrolumab
Inhibition or depletion of lymphocytes	
CD20 inhibitors	rituximab, ocrelizumab, ofatumumab, ublituximab
CD19 inhibitor	inebilizumab
CD52 inhibitor	alemtuzumab
CD80/86 inhibitor	abatacept
Integrin inhibitors	vedolizumab, natalizumab
Inhibition of the complement system	
C5 inhibitor	eculizumab

DMARDs: disease-modifying antirheumatic drugs; TNF: tumour necrosis factor; BlyS: B-lymphocyte stimulator; IL: interleukin; IFNAR1: interferon alpha and beta receptor subunit 1.

Inhibitors of cytokine function

Cytokines are small proteins released from a variety of cells and form an integral part of cell signalling and the immune response. Examples of cytokines relevant to biologic DMARDs are tumour necrosis factor (TNF), B-lymphocyte stimulator (BlyS), interleukins (IL), and interferons. Anti-cytokine medications are commonly the first biologic DMARD class used for many rheumatological, gastrointestinal and dermatological conditions, and they function to reduce the autoimmune-mediated inflammatory response that characterise these conditions.

Infliximab is a TNF inhibitor (TNFi) and was the first biologic DMARD approved for use by the United States of America (US) Food and Drug Administration (FDA) in 1998[49] and in Australia by the TGA in 2000.[50] Since then, four additional TNFi have been developed. Infliximab, adalimumab, certolizumab, and golimumab are monoclonal antibodies against TNF, and etanercept is a fusion protein of IgG and TNF receptor fragments.[51] TNFi agents exert their effect by neutralising TNF, a key proinflammatory cytokine released by white blood cells. TNFi are used in inflammatory bowel disease, rheumatoid arthritis, and psoriasis. Additionally, belimumab is a BlyS, belongs to the TNF superfamily and is an inhibitor used in SLE to try and target the B-cell dysfunction commonly observed with the disease.

IL inhibitors such as anakinra (first approved by the FDA in 2001) inhibit ILs or IL receptors. These are used in rheumatoid arthritis, giant cell arteritis, systemic sclerosis, psoriasis, and inflammatory bowel disease.

Finally, in the last two years, the US and Australia have both approved anifrolumab, an interferon receptor inhibitor for the treatment of moderate to severe SLE.

There is mainly low quality, conflicting evidence regarding whether cytokine inhibitors should be continued perioperatively. As a result, international organisations have produced different recommendations assessing similar evidence. When organisations recommend perioperative cessation, they generally recommend that surgery be scheduled at or after the next dose of biologic was to be given, or after 3-5 half-lives, to allow sufficient time for washout of the biologic agent prior to surgery. Dosing cycles are dependent on the drug, indication, and patient.

Gastroenterology

The European Crohn's and Colitis Organisation (ECCO) recommends that TNFi and IL inhibitors be continued in patients with Crohn's disease undergoing abdominal surgery, even with primary anastomosis.[36] This recommendation is based on a multicentre prospective cohort study and meta-analysis demonstrating no increase in surgical site infection or anastomotic leak.[52,53]

Conversely, the British Society of Gastroenterology recommend that TNFi be discontinued, where possible, prior to elective surgery, and ask that clinicians consider the presence of fistulae, abscesses, anaemia, low albumin and corticosteroid use when deciding[10]. These recommendations are based on six positive meta-analyses and systematic reviews (versus one negative review[54]) showing greater risk of infectious complications with biologic continuation.[37,55-59] The SPAQI also recommend withholding TNFi for at least one dosing interval before surgery (more so for patients with Crohn's disease[10,60]), but base their recommendations on the American College of Rheumatology (ACR) guidelines.[23]

Similarly, Korean guidelines recommend that patients with moderate-to-severe ulcerative colitis continue TNFi[61] based on previously cited studies, and other retrospective data demonstrating no increase in postoperative complications.[58,62-66]

Dermatology

The British Association of Dermatologists (BAD) recommend perioperative cessation of biologic agents[67] to reduce the risk of postoperative infection, while American and Taiwanese guidelines recommend an approach based on surgical invasiveness, with cessation for moderate-to-high risk procedures, but continuation for low risk procedures.[13,17,68] It is important to note however, that most of the studies relied upon in dermatology were underpowered and recommendations ultimately relied on expert opinion and concern for disease flare. Consideration of commencement of methotrexate or cyclosporin in the perioperative period has also been suggested to prevent disease flare when biologics are withheld.[13,17]

Rheumatology

All rheumatology guidelines recommend that TNFi be withheld perioperatively in patients with inflammatory arthritis[9,16,18,19,21,22,39,69-73] with the exception of one.[20] This latter guideline recommends considering temporary cessation only if individuals are at a high risk of infection, or if the impact of infection would be severe. As with dermatology, most studies used to form the guidelines have been of low quality, without adjustment for known confounders, and have unsurprisingly produced conflicting results. Several studies and meta-analyses demonstrate an increase in risk of infections if continued in the perioperative period.[74-81] Others have demonstrated no significant association with postoperative complications.[29,82-89] Studies of length of cessation prior to surgery have failed to show any outcome differences.[90,91]

There is limited evidence regarding the perioperative management of IL inhibitors. Registry data has demonstrated no association between biologic washout time and postoperative complcations,[92] yet nine guidelines recommend that IL inhibitors be withheld.[9,18,22,23,39,69,70,73,93]

The ACR and AAHKS guidelines state that if disease is difficult to control, and that symptomatic relief from the surgery outweighs the risk of postoperative infection, rheumatologists may elect to continue TNFi and IL inhibitors.[9]

Inhibition or depletion of lymphocytes

These biologic agents inhibit or deplete the number of lymphocytes by using inhibitors of lymphocyte surface antigens, which are labelled according to cluster of differentiation (CD) such as CD20, or the integrin transmembrane receptors.

Rituximab is a monoclonal antibody against CD20 that was first approved for use by the FDA in non-Hodgkin's lymphoma in 1997, and later for rheumatoid arthritis in 2006. CD20 inhibitors are now used in rheumatoid arthritis, some forms of vasculitis, SLE, antiphospholipid syndrome, multiple sclerosis and myasthenia gravis. There are a number of other lymphocyte antigenic targets used for drugs in current use including CD19 (inebilizumab), CD52 (alemtuzumab) and CD80/86 (abatacept). The first two are used primarily for neurological disorders while abatacept is used for rheumatoid and psoriatic arthritis.

Integrin, the transmembrane receptor, provides another fruitful target for inhibition. Vedolizumab and natalizumab are receptor antagonists used for inflammatory bowel disease and multiple sclerosis.

Rheumatology

For patients with inflammatory arthritis, guidelines have generally recommended perioperative cessation of biologics including rituximab and abatacept for at least one dosing interval prior to elective surgery,[9,19,21,22,39,70,73] with the caveat that rheumatologists may elect to continue biologics if the risk of disease flare outweighs the risk of postoperative infection.[9]

Given the paucity of quality data, and long rituximab dosing interval of 4-12 months, other guidelines recommend just scheduling surgery 3-4 months following the last infusion, but at least four weeks prior to the next infusion.[18,20,22] One guideline also suggests to consider measuring and treating preoperative immunoglobulin levels if required, particularly in patient populations with a high risk of infection or history of recurrent infections, as low immunoglobulin levels increase the risk of infection.[93]

Neurology

Rituximab, ocrelizumab and ofatumumab are used in multiple sclerosis (MS) and myasthenia gravis, and alemtuzumab is used in MS. SPAQI recommend continuing these perioperatively,[24] but do concede that the recommendation is based on expert opinion due to limited available evidence.

On the other hand, a few studies have demonstrated an increased risk of MS relapse within 6 months of natalizumab discontinuation[94,95] so SPAQI recommend continuing natalizumab perioperatively with input from the prescribing neurologist.[24]

Gastroenterology

Perioperative continuation of vedolizumab did not increase postoperative infectious complications following colectomy in UC patients in smaller studies,[96-98] so ECCO recommend continuation,[36] but larger studies are needed to validate this. SPAQI recommend withholding vedolizumab and natalizumab for at least one dosing interval prior to surgery, however this recommendation was based on the ACR recommendations on ustekinumab.[23]

SLE

Patients with well controlled, non-severe SLE are sometimes permitted to cease biologic treatments such as belimumab, with close monitoring for disease flare, but for patients with poorly controlled or severe SLE, it is often recommended to continue biologic treatment, in consultation with the patient's rheumatologist.[9,22,39]

Should rituximab be withheld in patients who have severe SLE, there are concerns regarding risk of disease flare and organ damage, particularly as the medication has a long dosing interval. Therefore, rituximab should not be withheld in patients with severe SLE, and instead, surgery should be scheduled towards the end of the dosing cycle in month five or six.[9,22]

Inhibition of the complement system

Finally, eculizumab, an inhibitor of complement protein C5 is used in neuromyelitis optica and some variants of myasthenia gravis.

SPAQI recommend continuing eculizumab perioperatively,[24] based mostly on expert opinion.

TARGETED SYNTHETIC DMARDS

The third category of DMARDs are targeted synthetic drugs which inhibit intracellular enzymes that form part of the transduction pathway for the proinflammatory response, in particular the cytokine inflammatory response. While fewer in number than the biologic agents, categories of synthetic DMARDs are presented below, in Table 5.

Table 5. Categories of targeted synthetic DMARDs

JAK inhibitors	baracitinib, tofacitinib, upadacitinib, deucravacitinib
PDE4 inhibitor	apremilast

DMARDs: disease-modifying antirheumatic drugs; JAK: Janus kinase; PDE4: phosphodiesterase-4.

JAK inhibitors

Janus kinases (JAK) are intracellular tyrosine kinases that act as second messengers from the cell surface cytokine receptors. JAK inhibitors (JAKi) are simple chemical structures with highly specific targets, effectively acting as inhibitors of cytokine pathways and, unlike biologics, can be given orally. They have relatively quick onset times and short half-lives, meaning they are often taken once or twice daily. JAK inhibitors are used in patients with rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, ulcerative colitis and atopic dermatitis.

Guidelines suggest ceasing JAK inhibitors at least three days prior to surgery to allow for washout[9,17-19,22,73] Previously, guidelines recommended withholding tofacitinib for seven days prior to surgery due to concerns about the long duration of immunosuppression, despite its short serum half-life[21,39,99]. However, recent evidence has shown a more rapid reversal of tofacitinib's immunosuppressive effects following interruption of therapy, resulting in a change in recommendation.[100] If JAK inhibitors are not withheld, these agents may diminish or eliminate the acute phase response, so it is important to closely monitor for infection, even if inflammatory markers remain within normal limits.

PDE4 inhibitors

Apremilast is a phosphodiesterase-4 (PDE4) inhibitor that leads to an increase in intracellular cyclic adenosine monophosphate (cAMP), and subsequent decrease in both immune cell activation and proinflammatory cytokines. It is used in patients with psoriatic arthritis, plaque psoriasis and oral ulcers associated with Behcet's disease.

Of the 25 reviewed guidelines, five discuss the perioperative management of apremilast. One guideline is not able to make any firm recommendations,[17] stating there is insufficient evidence. The remaining four guidelines recommend continuation of apremilast perioperatively, unless the patient's past history indicates an increased risk of postoperative infection.[9,18,19,22]

RECOMMENCEMENT OF THERAPY

Following surgery, all guidelines are conservative in recommencing biologic and JAK inhibitor therapy. For example, the American College of Rheumatology recommends that biologics should only be restarted "once the wound shows evidence of healing, any sutures/staples are out, there is no significant swelling, erythema, or drainage, and there is no ongoing nonsurgical site infection, which is typically ~14 days after surgery".[9] These recommendations are however, based on low quality studies and expert opinion.

While there is likely an optimal duration of interruption to therapy that provides a balance between a lower risk of infection, good wound healing, and reducing the risk of disease flare, the current literature provides insufficient evidence to make definitive recommendations.

CONTROVERSIES

Research into the optimal perioperative management of biologic and targeted synthetic DMARDs significantly lags against the pace of their rapid development and widespread therapeutic adoption. The knowledge gap is reflected by the paucity of available evidence and the varied recommendations seen between guidelines and indications.

For example, the American College of Rheumatology recommends that patients with conditions other than SLE, undergoing total hip or knee replacement surgery, should have surgery scheduled at the end of a biologic DMARD dosing cycle, with the next dose of the biologic withheld. This recommendation is based on low quality studies and expert opinion.

However, the European Crohn's and Colitis Organisation (ECCO) guidelines do not recommend cessation of biologic DMARDs for patients with Crohn's disease having abdominal surgery, based on a meta-analysis of 18 non-randomised studies and a prospective cohort study.[52]

These guidelines are both disease-specific and surgery-specific. It remains unclear whether the patient taking infliximab for rheumatoid arthritis having abdominal surgery should follow the rheumatology advice to stop infliximab, or the gastroenterology advice to continue infliximab, or conversely, which guideline the patient taking infliximab for Crohn's disease having a joint replacement should follow. Since both guidelines are based on low quality evidence, it is difficult for the perioperative medicine practitioner to make much sense of the current evidence base.

Management of these patient cohorts have not featured prominently in the emerging field of perioperative medicine. This is likely due to a combination of factors, including the perceived complexity of these patients, lack of familiarity with novel immune medications, and perhaps because other comorbidities (such as cardiovascular issues) command more attention. Regardless of the reasons, raising the profile of these patient groups is important to ensure that the perioperative risks they face can be minimised through individualised perioperative management and promotion of new research to investigate best practice.

SURGICAL PROCEDURES

The risk of infection and poor wound healing varies with the surgical procedure being undertaken. There is a clear difference in risk between a patient undergoing a gastroscopy or small bowel biopsy, compared to a patient having an oesophagectomy or bowel resection. Yet, most guidelines that advocate for perioperative cessation of DMARDs, do not clearly outline which surgical procedures constitute major surgery with a substantial risk of postoperative infection and/or wound breakdown. There is certainly no high-quality evidence to guide these decisions. Three guidelines have attempted to define high surgical risk with statements such as “surgical procedures during which the respiratory, gastrointestinal, or genitourinary tract is entered” or where “there is a major break in sterile technique, pillage from the gastrointestinal tract, or an active infection or devitalised tissue”.[15,17,68] One guideline recommends the consideration of prophylactic antibiotics should the patient undergo high-risk or emergency surgery.[71] Another guideline recommends prophylactic antibiotics in oral surgery due to the increased risk of bacterial contamination.[18] However, mitigation strategies against postoperative infection when immunomodulatory drugs are continued (such as prolonged antibiotic use, using an alternative surgical approach, or selectively improving the immune response to infection) have not been investigated, to our knowledge.

The guidelines discuss patients who are generally at an increased risk of infection, however, do not further stratify against specific factors such as age, active disease, tobacco exposure, obesity, nutritional statues, diabetes, vascular disease, or other comorbidities. These factors also need to be taken into consideration when deciding whether to continue or withhold their DMARDs.

PATIENT-CENTRED, MULTIDISCIPLINARY, PERIOPERATIVE MANAGEMENT

Given the uncertainty about best practice in DMARD management, and the potential significance of outcomes relating to underlying disease control or surgical risk, it is important that perioperative decision-making involves the patient and their treating specialists. Patients taking these medications may have experienced life-altering changes in their chronic and often debilitating disease and are likely to be motivated and engaged with their healthcare providers.

Decisions should consider the severity of their underlying disease and any comorbidities that may increase the risk of infection or wound breakdown including diabetes, vascular disease, obesity, and tobacco exposure. Informed consent should consider the potential risk of disease flare, postoperative infection and poor wound healing, as well as a presentation of the limited evidence base and expert opinions about optimal medication management and timing of surgery. Patients and practitioners may benefit from the use of tools such as a likelihood-consequence matrix to develop a shared understanding, not only of technical risks, but outcomes that each party considers important.

The specific input of treating specialists for the underlying disease should be sought, especially for complex patients, as they likely have unique knowledge of the individual patient, their disease course over an extended period, and likely have experience managing similar patients in the perioperative period. These discussions are best had early in the perioperative journey, ideally at the time that surgery is first contemplated, providing sufficient time to optimise, plan and consider the implications of changes to the management of these complex chronic conditions, including timing of surgery in relation to drug administration cycles.

CONCLUSION

In summary, **conventional** DMARDs can be continued perioperatively for most patients, with a small number of exceptions (e.g. a history of poor wound healing). For **targeted** synthetic DMARDs, apremilast can be continued in the perioperative period for most patients, whilst JAK inhibitors should be ceased three days prior to surgery, for most patients.

Perioperative management of **biologic** DMARDs remains an area with large knowledge gaps and significant disagreement between expert groups. Rheumatology and dermatology guidelines lean towards withholding biologics perioperatively, neurology guidelines advise continuation, and gastroenterology guidelines are conflicting.

As we have highlighted, the conflicting advice between guidelines can be attributed to the heterogeneity of patient populations, wide variety of therapeutics being studied, range of surgical procedures being studied, and the paucity of high-quality data to guideline decision making. In this context, individualised decisions made in consultation with treating specialists that consider the unique circumstances of the patient, the severity of their underlying condition and the specifics of the surgical intervention will remain paramount.

Additional studies are needed to investigate the optimal management of biologic DMARDs in the perioperative period, however, we acknowledge the challenges of conducting research on this heterogeneous group of drugs, patients and pathologies. While existing guidelines typically reflect the interests of specific cohorts of patients with unique disease pathologies, it is hoped that accumulated observational and trial data will create the opportunity to undertake a more systematic review and develop broader multidisciplinary consensus guidelines to inform the perspective of the perioperative medicine practitioner.

REFERENCES

1. Buer JK. A history of the term “dmard”. Inflammopharmacology. 2015; 23:163-71.
2. Upchurch KS, Kay J. Evolution of treatment for rheumatoid arthritis. Rheumatology. 2012; 51(suppl_6):vi28-vi36.
3. Reid C, Griffiths CE. Psoriasis and treatment: Past, present and future aspects. Acta dermato-venereologica. 2020; 100(3):69-79.
4. Fassmer AM, Garbe E, Schmedt N. Frequency and trends of disease-modifying antirheumatic drug (dmard) use in germany. Pharmacology research & perspectives. 2016; 4(5):e00254.
5. Muddasani S, Fleischer Jr AB. United states systemic psoriasis treatments: Increases in the use of biologic agents and plateau of methotrexate and oral small molecule inhibitors. Journal of Dermatological Treatment. 2022; 33(1):143-5.
6. Hyndman IJ. Rheumatoid arthritis: Past, present and future approaches to treating the disease. Wiley Online Library; 2017. p. 417-9.
7. Actis GC, Pellicano R, Fagoonee S, Ribaldone DG. History of inflammatory bowel diseases. Journal of clinical medicine. 2019; 8(11):1970.
8. PBS Analytics and Strategic Insight Section Pricing, PBS Policy Branch Technology Assessment and Access Division. Pbs expenditure and prescriptions report 1 july 2021 to 30 june 2022 [internet]. Canberra, Department of Health and Aged Care; 2022
9. Goodman SM, Springer BD, Chen AF, Davis M, Fernandez DR, Figgie M, et al. 2022 american college of rheumatology/ american association of hip and knee surgeons guideline for the perioperative management of antirheumatic medication in patients with rheumatic diseases undergoing elective total hip or total knee arthroplasty. The Journal of Arthroplasty. 2022; 37(9):1676-83.
10. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British society of gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019; 68(Suppl 3):s1-s106.
11. Nielsen O, Vainer B, Rask-Madsen J. The treatment of inflammatory bowel disease with 6-mercaptopurine or azathioprine. Alimentary pharmacology & therapeutics. 2001; 15(11):1699-708.
12. Neurath M. Thiopurines in ibd: What is their mechanism of action? Gastroenterology & hepatology. 2010; 6(7):435.
13. Choi YM, Debbaneh M, Weinberg JM, Yamauchi PS, Van Voorhees AS, Armstrong AW, et al. From the medical board of the national psoriasis foundation: Perioperative management of systemic immunomodulatory agents in patients with psoriasis and psoriatic arthritis. Journal of the American Academy of Dermatology. 2016; 75(4):798-805. e7.
14. Warren R, Weatherhead S, Smith C, Exton L, Mohd Mustapa M, Kirby B, et al. British association of dermatologists’ guidelines for the safe and effective prescribing of methotrexate for skin disease 2016. British Journal of Dermatology. 2016; 175(1):23-44.
15. Ledingham J, Gullick N, Irving K, Gorodkin R, Aris M, Burke J, et al. Bsr and bhpr guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatology. 2017; 56(6):865-8.
16. Bombardier C, Hazlewood GS, Akhavan P, Schieir O, Dooley A, Haraoui B, et al. Canadian rheumatology association recommendations for the pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs: Part ii safety. The Journal of rheumatology. 2012; 39(8):1583-602.
17. Tsai T-F, Hsieh T-Y, Chi C-C, Chou C-T, Hsieh L-F, Chen H-H, et al. Recommendations for psoriatic arthritis management: A joint position paper of the taiwan rheumatology association and the taiwanese association for psoriasis and skin immunology. Journal of the Formosan Medical Association. 2021; 120(3):926-38.
18. Albrecht K, Poddubnyy D, Leipe J, Sewerin P, Iking-Konert C, Scholz R, et al. Perioperative management of patients with inflammatory rheumatic diseases: Updated recommendations of the german society for rheumatology. Zeitschrift für Rheumatologie. 2023; 82(Suppl 1):1-11.
19. Axford JS, Schmerling R, Jones S. Preoperative evaluation and perioperative management of patients with rheumatic diseases [Internet]. UpToDate; 2022 [updated Oct 12]. Available from: https://www.uptodate.com/contents/preoperative-evaluation-and-perioperative-management-of-patients-with-rheumatic-diseases.
20. Glennon V. An australian living guideline for the pharmacological management of inflammatory arthritis [Internet]. 2023 [updated Jan 11]. Available from: https://app.magicapp.org/#/guideline/LqRV3n.
21. Management of rheumatoid arthritis 2019 clinical practice guidelines. In: Malaysia MoH, editor. Putrajaya, Malaysia: Malaysia Health Technology Assessment Section; 2021.
22. Russell LA, Craig C, Flores EK, Wainaina JN, Keshock M, Kasten MJ, et al. Preoperative management of medications for rheumatologic and hiv diseases: Society for perioperative assessment and quality improvement (spaqi) consensus statement. Mayo Clinic Proceedings [Internet]: Elsevier; 2022. p. 1551-71.

23. Pfeifer KJ, Selzer A, Whinney CM, Rogers B, Naik AS, Regan D, et al. Preoperative management of gastrointestinal and pulmonary medications: Society for perioperative assessment and quality improvement (spaqi) consensus statement. Mayo Clinic Proceedings [Internet]: Elsevier; 2021. p. 3158-77.
24. Oprea AD, Keshock MC, O'Glasser AY, Cummings III KC, Edwards AF, Hunderfund AL, et al. Preoperative management of medications for neurologic diseases: Society for perioperative assessment and quality improvement consensus statement. Mayo Clinic Proceedings [Internet]: Elsevier; 2022. p. 375-96.
25. Subramanian V, Pollok R, Kang J, Kumar D. Systematic review of postoperative complications in patients with inflammatory bowel disease treated with immunomodulators. Journal of British Surgery. 2006; 93(7):793-9.
26. Sany J, Anaya J, Canovas F, Combe B, Jorgensen C, Saker S, et al. Influence of methotrexate on the frequency of postoperative infectious complications in patients with rheumatoid arthritis. The Journal of rheumatology. 1993; 20(7):1129-32.
27. Murata K, Yasuda T, Ito H, Yoshida M, Shimizu M, Nakamura T. Lack of increase in postoperative complications with low-dose methotrexate therapy in patients with rheumatoid arthritis undergoing elective orthopedic surgery. Modern rheumatology. 2006; 16(1):14-9.
28. Grennan D, Gray J, Loudon J, Fear S. Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. Annals of the rheumatic diseases. 2001; 60(3):214-7.
29. Borgas Y, Gülfe A, Kindt M, Stefánsdóttir A. Anti-rheumatic treatment and prosthetic joint infection: An observational study in 494 elective hip and knee arthroplasties. BMC Musculoskeletal Disorders. 2020; 21(1):1-8.
30. Ren Y, Yang Q, Luo T, Lin J, Jin J, Qian W, et al. Better clinical outcome of total knee arthroplasty for rheumatoid arthritis with perioperative glucocorticoids and disease-modifying anti-rheumatic drugs after an average of 11.4-year follow-up. Journal of Orthopaedic Surgery and Research. 2021; 16(1):1-9.
31. Visser K, Katchamart W, Loza E, Martinez-Lopez J, Salliot C, Trudeau J, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: Integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3e initiative. Annals of the rheumatic diseases. 2009; 68(7):1086-93.
32. Afzali A, Park CJ, Zhu K, Hu JK, Sharma P, Sinanan MN, et al. Preoperative use of methotrexate and the risk of early postoperative complications in patients with inflammatory bowel disease. Inflammatory bowel diseases. 2016; 22(8):1887-95.
33. Jain A, Witbreuk M, Ball C, Nanchahal J. Influence of steroids and methotrexate on wound complications after elective rheumatoid hand and wrist surgery. The Journal of hand surgery. 2002; 27(3):449-55.
34. Pieringer H, Stuby U, Biesenbach G. The place of methotrexate perioperatively in elective orthopedic surgeries in patients with rheumatoid arthritis. Clinical Rheumatology. 2008; 27:1217-20.
35. Loza E, Martinez-Lopez J, Carmona L. A systematic review on the optimum management of the use of methotrexate in rheumatoid arthritis patients in the perioperative period to minimize perioperative morbidity and maintain disease control. Clinical & Experimental Rheumatology. 2009; 27(5):856.
36. Adamina M, Bonovas S, Raine T, Spinelli A, Warusavitarne J, Armuzzi A, et al. Ecco guidelines on therapeutics in crohn's disease: Surgical treatment. Journal of Crohn's and Colitis. 2020; 14(2):155-68.
37. Ali UA, Martin ST, Rao AD, Kiran RP. Impact of preoperative immunosuppressive agents on postoperative outcomes in crohn's disease. Diseases of the colon & rectum. 2014; 57(5):663-74.
38. Aberra FN, Lewis JD, Hass D, Rombeau JL, Osborne B, Lichtenstein GR. Corticosteroids and immunomodulators: Postoperative infectious complication risk in inflammatory bowel disease patients. Gastroenterology. 2003; 125(2):320-7.
39. Moreira PM, Correia AM, Cerqueira M, Gil MF. Perioperative management of disease-modifying antirheumatic drugs and other immunomodulators. Perioperative management of disease-modifying antirheumatic drugs and other immunomodulators ARP Rheumatology. 2022; 3:218-24.
40. Tanaka N, Sakahashi H, Sato E, Hirose K, Ishima T, Ishii S. Examination of the risk of continuous leflunomide treatment on the incidence of infectious complications after joint arthroplasty in patients with rheumatoid arthritis. JCR: Journal of Clinical Rheumatology. 2003; 9(2):115-8.
41. Fuerst M, Möhl H, Baumgärtel K, Rüther W. Leflunomide increases the risk of early healing complications in patients with rheumatoid arthritis undergoing elective orthopedic surgery. Rheumatology international. 2006; 26(12):1138-42.
42. Jenks KA, Stamp LK, O'Donnell JL, Savage RL, Chapman PT. Leflunomide-associated infections in rheumatoid arthritis. The Journal of rheumatology. 2007; 34(11):2201-3.
43. Lacaille D, Guh DP, Abrahamowicz M, Anis AH, Esdaile JM. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. Arthritis care & research. 2008; 59(8):1074-81.
44. Shippey EA, Wagler VD, Collamer AN. Hydroxychloroquine: An old drug with new relevance. Cleveland Clinic journal of medicine. 2018; 85(6):459-67.
45. Cheifetz AS, Cullen GJ. Sulfasalazine and 5-aminosalicylates in the treatment of inflammatory bowel disease [Internet]. UpToDate; 2015 [updated Dec 08]. Available from: https://www.uptodate.com/contents/sulfasalazine-and-5-aminosalicylates-in-the-treatment-of-inflammatory-bowel-disease.
46. Therapeutic Goods Administration. What is regulated as a biological: Australian regulatory guidelines for biologicals. In: Department of Health, editor. ACT: Commonwealth of Australia,; 2020.
47. Food and Drug Administration. What are "biologics" questions and answers [Internet]. 2018 [updated Jun 02 2018]. Available from: https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers.
48. Burmester GR. Overview of biologic agents in the rheumatic diseases [Internet]. UpToDate; 2023 [updated Apr 27]. Available from: https://www.uptodate.com/contents/overview-of-biologic-agents-in-the-rheumatic-diseases#H1.
49. Melsheimer R, Geldhof A, Apaolaza I, Schaible T. Remicade®(infliximab): 20 years of contributions to science and medicine. Biologics: Targets and Therapy. 2019:139-78.

50. Therapeutic Goods Administration. Remicade infliximab 100mg powder for injection vial (73827) [Internet]. Commonwealth of Australia,. Available from: https://www.tga.gov.au/resources/artg/73827.
51. Cessak G, Kuzawińska O, Burda A, Lis K, Wojnar M, Mirowska-Guzel D, et al. Tnf inhibitors–mechanisms of action, approved and off-label indications. Pharmacological Reports. 2014; 66(5):836-44.
52. Cohen BL, Fleshner P, Kane SV, Herfarth HH, Palekar N, Farraye FA, et al. Prospective cohort study to investigate the safety of preoperative tumor necrosis factor inhibitor exposure in patients with inflammatory bowel disease undergoing intra-abdominal surgery. Gastroenterology. 2022; 163(1):204-21.
53. Xu Y, Yang L, An P, Zhou B, Liu G. Meta-analysis: The influence of preoperative infliximab use on postoperative complications of crohn's disease. Inflammatory bowel diseases. 2019; 25(2):261-9.
54. Rosenfeld G, Qian H, Bressler B. The risks of post-operative complications following pre-operative infliximab therapy for crohn's disease in patients undergoing abdominal surgery: A systematic review and meta-analysis. Journal of Crohn's and Colitis. 2013; 7(11):868-77.
55. Billioud V, Ford AC, Tedesco ED, Colombel J-F, Roblin X, Peyrin-Biroulet L. Preoperative use of anti-tnf therapy and postoperative complications in inflammatory bowel diseases: A meta-analysis. Journal of Crohn's and Colitis. 2013; 7(11):853-67.
56. Waterland P, Athanasiou T, Patel H. Post-operative abdominal complications in crohn's disease in the biological era: Systematic review and meta-analysis. World Journal of Gastrointestinal Surgery. 2016; 8(3):274.
57. Kopylov U, Ben-Horin S, Zmora O, Eliakim R, Katz LH. Anti-tumor necrosis factor and postoperative complications in crohn's disease: Systematic review and meta-analysis. Inflammatory bowel diseases. 2012; 18(12):2404-13.
58. Narula N, Charleton D, Marshall J. Meta-analysis: Peri-operative anti-tnf α treatment and post-operative complications in patients with inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2013; 37(11):1057-64.
59. Yang Z-P, Hong L, Wu Q, Wu K-C, Fan D-M. Preoperative infliximab use and postoperative complications in crohn's disease: A systematic review and meta-analysis. International Journal of Surgery. 2014; 12(3):224-30.
60. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. Acg clinical guideline: Ulcerative colitis in adults. Official journal of the American College of Gastroenterology| ACG. 2019; 114(3):384-413.
61. Na S-Y, Choi CH, Song EM, Bang KB, Park SH, Kim ES, et al. Korean clinical practice guidelines on biologics and small molecules for moderate-to-severe ulcerative colitis. Intestinal Research. 2023; 21(1):61-87.
62. Lau C, Dubinsky M, Melmed G, Vasiliauskas E, Berel D, McGovern D, et al. The impact of preoperative serum anti-tnfα therapy levels on early postoperative outcomes in inflammatory bowel disease surgery. Annals of surgery. 2015; 261(3):487.
63. Zittan E, Milgrom R, Ma GW, Wong-Chong N, O'Connor B, McLeod RS, et al. Preoperative anti–tumor necrosis factor therapy in patients with ulcerative colitis is not associated with an increased risk of infectious and noninfectious complications after ileal pouch–anal anastomosis. Inflammatory bowel diseases. 2016; 22(10):2442-7.
64. Ward S, Mytton J, Henderson L, Amin V, Tanner J, Evison F, et al. Anti-tnf therapy is not associated with an increased risk of post-colectomy complications, a population-based study. Colorectal Disease. 2018; 20(5):416-23.
65. El-Hussuna A, Qvist N, Zangenberg MS, Langkilde A, Siersma V, Hjort S, et al. No effect of anti-tnf-α agents on the surgical stress response in patients with inflammatory bowel disease undergoing bowel resections: A prospective multi-center pilot study. BMC surgery. 2018; 18(1):1-10.
66. Yang Z, Wu Q, Wang F, Wu K, Fan D. Meta-analysis: Effect of preoperative infliximab use on early postoperative complications in patients with ulcerative colitis undergoing abdominal surgery. Alimentary pharmacology & therapeutics. 2012; 36(10):922-8.
67. Smith C, Yiu Z, Bale T, Burden A, Coates L, Edwards W, et al. British association of dermatologists guidelines for biologic therapy for psoriasis 2020: A rapid update. British Journal of Dermatology. 2020; 183(4):628-37.
68. Menter A, Strober BE, Kaplan DH, Kivelevitch D, Prater EF, Stoff B, et al. Joint aad-npf guidelines of care for the management and treatment of psoriasis with biologics. Journal of the American Academy of Dermatology. 2019; 80(4):1029-72.
69. Holroyd CR, Seth R, Bukhari M, Malaviya A, Holmes C, Curtis E, et al. The british society for rheumatology biologic dmard safety guidelines in inflammatory arthritis. Rheumatology. 2019; 58(2):e3-e42.
70. Sanmartí R, García-Rodríguez S, Álvaro-Gracia JM, Andreu JL, Balsa A, Cáliz R, et al. 2014 update of the consensus statement of the spanish society of rheumatology on the use of biological therapies in rheumatoid arthritis. Reumatología Clínica (English Edition). 2015; 11(5):279-94.
71. Goëb V, Ardizzone M, Arnaud L, Avouac J, Baillet A, Belot A, et al. Recommendations for using tnfα antagonists and french clinical practice guidelines endorsed by the french national authority for health. Joint Bone Spine. 2013; 80(6):574-81.
72. Lau CS, Chia F, Dans L, Harrison A, Hsieh TY, Jain R, et al. 2018 update of the aplar recommendations for treatment of rheumatoid arthritis. International journal of rheumatic diseases. 2019; 22(3):357-75.
73. Louthrenoo W, Kasitanon N, Katchamart W, Aiewruengsurat D, Chevaisrakul P, Chiowchanwisawakit P, et al. 2016 updated thai rheumatism association recommendations for the use of biologic and targeted synthetic disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis. International journal of rheumatic diseases. 2017; 20(9):1166-84.
74. Giles JT, Bartlett SJ, Gelber AC, Nanda S, Fontaine K, Ruffing V, et al. Tumor necrosis factor inhibitor therapy and risk of serious postoperative orthopedic infection in rheumatoid arthritis. Arthritis Care & Research: Official Journal of the American College of Rheumatology. 2006; 55(2):333-7.
75. Clay M, Mazouyes A, Gilson M, Gaudin P, Baillet A. Risk of postoperative infections and the discontinuation of tnf inhibitors in patients with rheumatoid arthritis: A meta-analysis. Joint Bone Spine. 2016; 83(6):701-5.
76. Goodman SM, Menon I, Christos PJ, Smethurst R, Bykerk VP. Management of perioperative tumour necrosis factor α inhibitors in rheumatoid arthritis patients undergoing arthroplasty: A systematic review and meta-analysis. Rheumatology. 2016; 55(3):573-82.

77. Mabille C, Degboe Y, Constantin A, Barnetche T, Cantagrel A, Ruyssen-Witrand A. Infectious risk associated to orthopaedic surgery for rheumatoid arthritis patients treated by anti-tnfalpha. Joint Bone Spine. 2017; 84(4):441-5.
78. Ruyssen-Witrand A, Gossec L, Salliot C, Luc M, Duclos M, Guignard S, et al. Complication rates of 127 surgical procedures performed in rheumatic patients receiving tumor necrosis factor alpha blockers. Clin Exp Rheumatol. 2007; 25(3):430-6.
79. Dixon W, Lunt M, Watson K, Hyrich K. Anti-tnf therapy and the risk of serious post-operative infection: Results from the bsr biologics register (bsrbr). Annals of the rheumatic diseases [Internet]: BMJ Publishing Group BMA House, Tavistock Square, London WC1H 9JP, UK; 2007. p. 118.
80. Kawakami K, Ikari K, Kawamura K, Tsukahara S, Iwamoto T, Yano K, et al. Complications and features after joint surgery in rheumatoid arthritis patients treated with tumour necrosis factor-α blockers: Perioperative interruption of tumour necrosis factor-α blockers decreases complications? Rheumatology. 2010; 49(2):341-7.
81. Momohara S, Kawakami K, Iwamoto T, Yano K, Sakuma Y, Hiroshima R, et al. Prosthetic joint infection after total hip or knee arthroplasty in rheumatoid arthritis patients treated with nonbiologic and biologic disease-modifying antirheumatic drugs. Modern rheumatology. 2011; 21(5):469-75.
82. Kubota A, Sekiguchi M, Nakamura T, Miyazaki Y, Suguro T. Does use of a biologic agent increase the incidence of postoperative infection in surgery for rheumatoid arthritis after total joint arthroplasty? Modern rheumatology. 2014; 24(3):430-3.
83. den Broeder AA, Creemers MC, Fransen J, de Jong E, de Rooij D-JR, Wymenga A, et al. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: A large retrospective study. The Journal of rheumatology. 2007; 34(4):689-95.
84. Bibbo C, Goldberg JW. Infectious and healing complications after elective orthopaedic foot and ankle surgery during tumor necrosis factor-alpha inhibition therapy. Foot & ankle international. 2004; 25(5):331-5.
85. Hirano Y, Kojima T, Kanayama Y, Shioura T, Hayashi M, Kida D, et al. Influences of anti-tumour necrosis factor agents on postoperative recovery in patients with rheumatoid arthritis. Clinical Rheumatology. 2010; 29:495-500.
86. Kubota A, Nakamura T, Miyazaki Y, Sekiguchi M, Suguro T. Perioperative complications in elective surgery in patients with rheumatoid arthritis treated with biologics. Modern rheumatology. 2012; 22(6):844-8.
87. Talwalkar S, Grennan D, Gray J, Johnson P, Hayton M. Tumour necrosis factor α antagonists and early postoperative complications in patients with inflammatory joint disease undergoing elective orthopaedic surgery. Annals of the rheumatic diseases. 2005; 64(4):650-1.
88. Wendling D, Balblanc J, Brousse A, Lohse A, Lehuede G, Garbuio P, et al. Surgery in patients receiving anti-tumour necrosis factor α treatment in rheumatoid arthritis: An observational study on 50 surgical procedures. Annals of the rheumatic diseases. 2005; 64(9):1378-9.
89. van Duren BH, Wignall A, Goodman S, Hewitt C, Mankia K, Pandit H. The effect of perioperative biologic disease-modifying anti-rheumatic drugs on the risk of postoperative complications: Surgical site infection, delayed wound healing, and disease flares following orthopaedic surgical procedures. JBJS. 2022; 104(12):1116-26.
90. George MD, Baker JF, Hsu JY, Wu Q, Xie F, Chen L, et al. Perioperative timing of infliximab and the risk of serious infection after elective hip and knee arthroplasty. Arthritis care & research. 2017; 69(12):1845-54.
91. George MD, Baker JF, Winthrop KL, Goldstein SD, Alemao E, Chen L, et al. Immunosuppression and the risk of readmission and mortality in patients with rheumatoid arthritis undergoing hip fracture, abdominopelvic and cardiac surgery. Annals of the rheumatic diseases. 2020; 79(5):573-80.
92. Morel J, Locci M, Banal F, Combe B, Cormier G, Dougados M, et al. Safety of surgery in patients with rheumatoid arthritis treated with tocilizumab: Data from the french (registry-roactemra) regate registry. Clin Exp Rheumatol. 2020; 38(3):405-10.
93. Md Yusof MY, Vital EM, McElvenny DM, Hensor EM, Das S, Dass S, et al. Predicting severe infection and effects of hypogammaglobulinemia during therapy with rituximab in rheumatic and musculoskeletal diseases. Arthritis & Rheumatology. 2019; 71(11):1812-23.
94. O'connor P, Goodman A, Kappos L, Lublin F, Miller D, Polman C, et al. Disease activity return during natalizumab treatment interruption in patients with multiple sclerosis. Neurology. 2011; 76(22):1858-65.
95. Gueguen A, Roux P, Deschamps R, Moulignier A, Bensa C, Savatovsky J, et al. Abnormal inflammatory activity returns after natalizumab cessation in multiple sclerosis. Journal of Neurology, Neurosurgery & Psychiatry. 2014; 85(9):1038-40.
96. Ferrante M, de Buck van Overstraeten A, Schils N, Moens A, Van Assche G, Wolthuis A, et al. Perioperative use of vedolizumab is not associated with postoperative infectious complications in patients with ulcerative colitis undergoing colectomy. Journal of Crohn's and Colitis. 2017; 11(11):1353-61.
97. Novello M, Stocchi L, Steele SR, Holubar S, Duraes L, Kessler H, et al. Case-matched comparison of postoperative outcomes following surgery for inflammatory bowel disease after exposure to vedolizumab vs other biologics. Journal of Crohn's and Colitis. 2020; 14(2):185-91.
98. Law CC, Narula A, Lightner AL, McKenna NP, Colombel J-F, Narula N. Systematic review and meta-analysis: Preoperative vedolizumab treatment and postoperative complications in patients with inflammatory bowel disease. Journal of Crohn's and Colitis. 2018; 12(5):538-45.
99. Goodman SM, Springer B, Guyatt G, Abdel MP, Dasa V, George M, et al. 2017 american college of rheumatology/ american association of hip and knee surgeons guideline for the perioperative management of antirheumatic medication in patients with rheumatic diseases undergoing elective total hip or total knee arthroplasty. The Journal of Arthroplasty. 2017; 32(9):2628-38.
100. Kaine J, Tesser J, Takiya L, DeMasi R, Wang L, Snyder M, et al. Re-establishment of efficacy of tofacitinib, an oral jak inhibitor, after temporary discontinuation in patients with rheumatoid arthritis. Clinical Rheumatology. 2020; 39:2127-37.

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Obstetric anaesthesia in rheumatic heart disease – a unique perspective from the Top End

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INTRODUCTION

Rheumatic heart disease (RHD) is a complex manifestation of social inequity. It is a life-long burden and, in Australia, affects predominantly young First Nations Australians. It is endemic in the Northern Territory (NT), with a rate of disease 26 times higher than the rest of Australia.[1] Despite intensive primary and secondary prevention, it is not a disease of the past, with episodes of acute rheumatic fever (ARF) continuing to increase in the NT. Of those suffering an episode of ARF, 50% will develop rheumatic heart disease within 10 years, of which one-third will be severe. With episodes of ARF occurring almost exclusively in children, this translates to the majority of subsequent heart disease occurring in those aged 15-44. Females are consistently over-represented in this population leading to a disproportionate burden of disease in women of childbearing age.[2]

As the tertiary referral centre in the Northern Territory, the Royal Darwin Hospital is in the unique situation of managing a relatively high volume of obstetric patients with rheumatic heart disease, often from the most remote locations in Australia. Up to 2-3% of First Nations women who become pregnant in the NT have some form of RHD, and many have had previous valve interventions.[3] This presents not only the challenge of managing valvular heart disease in pregnancy and the peripartum period, but also in a way that addresses different concepts of health and the additional complexities of distance, language, and culture.

CARDIOVASCULAR CHANGES IN PREGNANCY AND LABOUR

Pregnancy is a dynamic physiological process with significant alterations to the cardiovascular system. These changes are driven by the endocrine effects of progesterone, the addition of the parallel placental circulation, and the response to flow-metabolism coupling in the presence of increased metabolic demands. There is up to a 50% increase in cardiac output (CO), primarily due to an increase in blood volume, heart rate (HR), and a steady decrease in systemic vascular resistance (SVR).[4] A physiologic anaemia of pregnancy occurs due to an increase in blood volume in excess of the concurrent increase in red-cell mass. This reduces blood viscosity and resistance to blood flow.[5] The predominant haemodynamic state is hypervolaemic, hyperdynamic, and vasodilated. The net effect is decreased systolic blood pressure (SBP). These changes peak in the 28th week of pregnancy.

At the time of first and second-stage labour (unassisted by anaesthesia), there is a sudden additional increase in HR and CO due to the sympathetic activation from pain and autotransfusion of up to 500 ml of blood from each uterine contraction. Valsalva manoeuvres during pushing decrease the preload and increase the afterload.[6] Further autotransfusion occurs in the third stage from the placental circulation and unloading of aortocaval compression. CO then reduces precipitously to pre-pregnancy levels within 24-48 hours.

These changes are often poorly tolerated in patients with rheumatic heart disease, particularly those with stenotic valvular lesions and pulmonary hypertension, who struggle to cope with sudden increases/decreases in the circulatory volume, diastolic filling, SVR, and CO. Anaesthetic interference, such as epidural analgesia, will temper the more acute changes, while other interventions, such as rapid fluid administration or the induction of a general anaesthetic, will add an extra level of complexity.[7]

MATERNAL AND FOETAL OUTCOMES IN RHD

Most of the evidence on outcomes in pregnancy in RHD comes from overseas, from low-income countries, where RHD accounts for a greater proportion of obstetric cardiac disease. One of the largest prospective datasets is from the registry of pregnancy and cardiac disease (ROPAC), which published outcomes for a series of 390 patients with rheumatic mitral disease in pregnancy in 2018. In this series, the mortality rate was 1.9%; however, nearly 50% of patients with severe mitral stenosis (MS) and 23% with severe mitral regurgitation (MR) developed heart failure. In addition, severe MS was an independent risk factor for adverse foetal outcomes.[8] Foetal outcomes in maternal cardiac disease are poor due to reduced uteroplacental flow from obstructive left heart disease. This translates into low birthweight, preterm delivery, and higher rates of neonatal intensive care admissions and stillbirth.[9] A recent 2020 systematic review of 12 studies had similar findings, with mitral stenosis being associated with a 3% mortality rate, 38% rate of heart failure, and independently associated with adverse foetal outcomes.[10] This is consistent with several other recent publications where severe MS and pulmonary hypertension were independent risk factors for maternal morbidity.[9,11,12] It should be noted that these outcomes are more pronounced in low income, low health literacy settings where antenatal care is compromised, and resources are limited.[13,14]

Australian data, limited in numbers, indicates a lower overall mortality rate but still significant morbidity and adverse effects on the foetus. For example, recent retrospective studies in Western Australia (WA) and the NT recorded no maternal mortalities, while two prospective studies recorded a mortality rate of 0.3-0.4%.[9,13,15,16]

A retrospective review of RHD in pregnancy in the NT from 2010 to 2019 indicated at least 13 cases of RHD in pregnancy being managed per year, with up to 25% of patients in the modified World Health Organization (mWHO) class III and IV risk categories (Figure 1).[17] There were no maternal or neonatal mortalities in the study. Ninety-one per cent of patients identified were from remote areas, and interestingly there was a relatively high rate of postpartum haemorrhage (24%) relative to national data (5-15%).[15] In our experience, the total number of cases and representation of critical events are likely to be significantly underestimated due to limitations in retrospective data collection. To our knowledge, we can recall specific patients in the time-period of this review who suffered considerable morbidity, and this review should not give false confidence in the management of these complex patients.

RISK STRATIFICATION OF RHD IN PREGNANCY

Many risk-scoring systems are available to classify the burden of cardiac disease in pregnancy (CARPREG I, CARPREG II, ZAHARA).[12,18,19] Of those available, the mWHO classification[20] is considered to be better at predicting maternal outcomes.[21,22] It classifies maternal risk into four categories, with level I representing the lowest risk of a maternal cardiac event (2.5-5%) and level IV representing the highest (40-100%). For level IV patients, pregnancy is not recommended before surgical or interventional management of their cardiac condition.

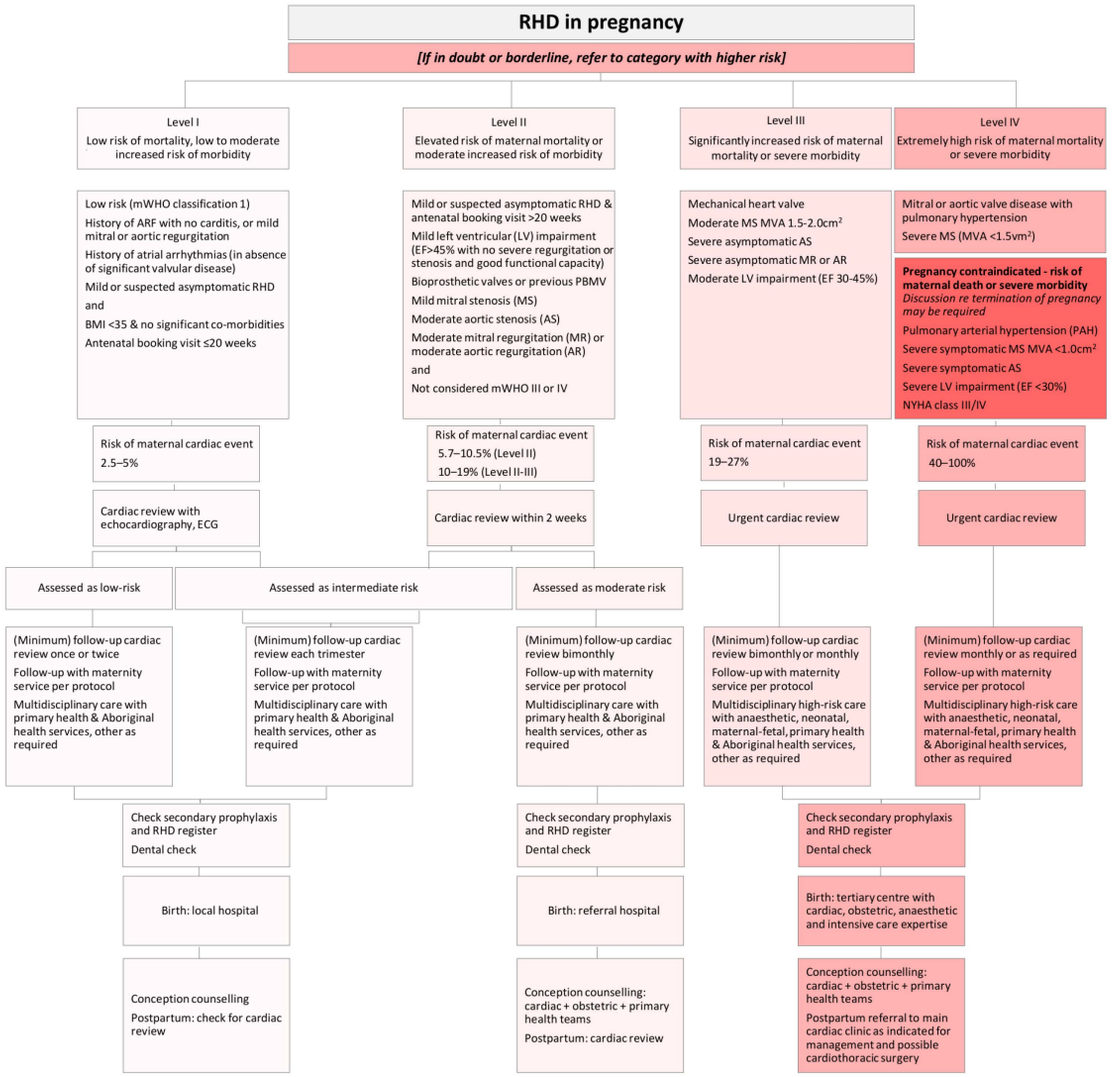
The mWHO classification applies to congenital disorders, aortopathies, and advanced procedures such as heart transplantation. RHD Australia (an Australian government co-ordination unit aimed at controlling RHD/ARF) has adapted the risk stratification to focus on the valvulopathies seen in rheumatic heart disease, particularly the risk posed by differing severities of mitral valve stenosis and pulmonary hypertension.[23]

Management during pregnancy and planning for delivery is guided by the mWHO classification (Figure 1). Level I patients can generally be managed in the community, with a single cardiology review and a local delivery.[21] Patients with a level II classification require follow-up with bimonthly cardiology reviews and delivery in a larger centre. Patients classified as level III and IV (where termination has been declined) need monthly cardiology review and accommodation within easy access to a tertiary centre, where delivery should occur. All patients require some level of multi-disciplinary team (MDT) planning for delivery, which should involve shared

decision-making with the patient and their family. For patients classified as level III and IV, the MDT involves an obstetrician and maternofetal medicine specialist, neonatologist, cardiologist, intensivist, and anaesthetist with assistance from interpreters and Indigenous liaison officers (42% of First Nations patients use English as their second language).[24] The expansion of online platforms and telehealth in the NT has dramatically improved the ability to facilitate these meetings and reviews, reducing unnecessary travel and keeping women in community for longer.

Figure 1. Classification of RHD in pregnancy

Reproduced from the 2020 Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease[25]



Regarding risk stratification, two important clinical caveats are observed.

Firstly, the increase in cardiac output secondary to hypervolaemia will increase the transmitral valve gradient, often without associated changes in mitral valve area (by planimetry).[26] Therefore, it is not unusual for patients with a mitral valve area (MVA) >1.0cm^2 to have a transmitral mean gradient >10mmHg later in pregnancy. For this reason, the mWHO classification considers MVA <1.5cm^2 in pregnancy as severe, rather than using a transmitral gradient classification system. If a mean pressure gradient (MPG) classification system is used, a patient with a MPG >10mmHg in the first trimester of pregnancy is likely to be at a higher risk of complications compared to a patient who starts with a lower gradient and develops an MPG>10mmHg later in pregnancy.[27]

Secondly, the unique weather environment of the Top End of the NT is one of the greatest physiologic stress tests available to anaesthetists and perioperative physicians. Some Top End patients will arrive at the hospital following a pregnancy spent entirely in ≥30°C heat, 80% or more relative humidity, and with a daily step count to parallel professional athletes. Taking time to perform an appropriate functional assessment and understand the day-to-day life of patients often reveals an incredible physiologic reserve, which may weigh in on decision-making. For mWHO class III and IV patients, or where this physiological reserve is unclear, stress echocardiography or a six-minute walk test (6MWT) is frequently performed in the early third trimester to help stratify those who are more likely to decompensate. This is particularly useful to help overcome the limitations of NYHA classification in pregnancy, where shortness of breath can be multifactorial.

BEYOND CLINICAL PRIORITIES

While clinical priorities guide recommendations, for many patients the impact of non-clinical factors (cultural, social, financial) cannot be ignored. These may exacerbate any clinical risk if not appropriately addressed.[28] There are anaesthetists in the Top End currently engaged with communities to explore these factors, the differences in perception of healthcare, and the impact of Western medicine. While eagerly awaiting formal publication of this important work, we can only share our personal experiences and stories to give insight into these factors.

One of the biggest issues faced in the NT is the patient's disposition of where to deliver. For many First Nations patients, the severity of their condition means delivering away from their land and Country. High-risk patients will be transferred to Darwin in the third trimester. Without a local cardiac surgical service, patients will occasionally require transfer >3000km interstate if the need for cardiac intervention or mechanical circulatory support is anticipated. The transfer to Darwin, or especially interstate, can have significant social impacts. The transfer of a patient away from family, culture and Country can be likened to an international relocation, often while critically unwell and preparing to embark on the challenges of motherhood. Also, women may be too unwell to look after their child post-delivery, disrupting the maternal-neonatal connection. A small proportion of patients may require cardiac surgery, affecting their initial ability to breastfeed due to the sternotomy. The impact may be profound, with some women having to leave their babies interstate and return home alone in the face of this adversity. As clinicians, we must be aware of these flow-on effects when making transfer decisions.

We must be aware of how our perception of "good medicine" aligns with the patient's perceptions. Understanding resource limitations and staff expertise, the aim is to make every effort to support the pregnant woman's wishes. The importance of birthing on Country is paramount to many First Nations women, and when this is not possible, the concept should be applied as a metaphor. This requires designing services in collaboration with First Nations women to be inclusive, holistic, and culturally competent.[29,30]

PRECONCEPTION PLANNING

All women of childbearing age with significant rheumatic heart disease should have a pre-pregnancy assessment where patients can be counselled about the risk of pregnancy, have their cardiovascular status optimised, and further therapies planned, for example, mitral valvuloplasty. Where cardiac surgery is being planned, effective, long-term but reversible contraceptive therapies like an intrauterine device can be considered. Oestrogen-based contraceptives pose an added risk of thromboembolism and potentially increase the risk of mechanical valve thrombosis. Tubal ligation is discussed in cases where patients have completed their families.[25] Where pregnancy is contraindicated, patients are appropriately counselled, but the final decision will rest with the patient and should be respected. Cardiovascular disease and the inability to bear children can result in significant social stigma for the patient, and these topics need to be addressed in a multidisciplinary setting with social and cultural sensitivity.

ANTENATAL MANAGEMENT

Screening

Identification of RHD early in pregnancy allows for better risk management and time for intervention planning and implementation. Unfortunately, in low-resource settings, up to 25 per cent of RHD in pregnancy remains unidentified until unmasked by the haemodynamic changes of the second or third trimester.[14] Anecdotally, this is not infrequent in the NT, with patients occasionally presenting in heart failure as their first presentation. Recognising patients at risk starts in primary care, and the NT is currently running a pilot program called "The Two Heart Beats Study", whereby women from remote communities receive a screening echocardiogram with their first-trimester ultrasound. Access to echocardiography is challenging outside of a tertiary centre, and the emphasis is on providing primary care physicians with baseline skills to diagnose subclinical RHD.

Medical optimisation

RHD management in pregnancy involves balancing pharmacotherapy against relative risk(s) of teratogenicity. Hypertension, arrhythmias, anaemia and active infections, which may cause cardiac decompensation, can be addressed early. Heart failure and fluid overload can be managed with diuresis and rate control. This will help manage the risk of acute pulmonary oedema. Volume overload will result in an increase in transmitral gradients without a decrease in the valve area. Significant reductions in transmitral gradients can be achieved with well managed diuresis. A summary is included in Table 1.

Table 1. Medication management of RHD in pregnancy

THERAPIES	CHANGE IN PREGNANCY
Arrhythmia control	Beta blockers: continue (accept an increased rate of IUGR, neonatal hypoglycaemia). Digoxin is safe and routinely loaded.[31]
BP control	Aldosterone antagonists (AA), Angiotensin-converting enzyme inhibitors (ACEi) and Angiotensin II receptor blockers (ARBs) are discontinued due to teratogenicity. Alternative: hydralazine, labetalol, methyldopa as per non-cardiac pregnancy.[32]
Anticoagulation	Warfarin is teratogenic in the first trimester due to its effects on organogenesis, although both European and ASA guidelines allow warfarin up to 5 mg in the first trimester. RHD Australia also recommends changing to bi-daily LMWH only in the first trimester, then switching back to Warfarin from the 13th to the 35th week.[25,33,34] Change to heparin or Low Molecular Weight Heparin (LMWH) peripartum (around the 36th week) in preparation for neuraxial techniques. There is no consensus on optimal anticoagulation. Although LMWH has better foetal outcomes, it has higher rates of thrombogenicity. The fluctuating fluid states of pregnancy mean that weight-based dosing alone will not be accurate in achieving therapeutic levels so anti-Xa levels are recommended.

In remote communities, access to frequent testing can be problematic, and any change in therapeutic anticoagulation exposes the woman to an increased risk of thrombogenic complications. Local services aim to continue warfarin up until the 36th week, then switch to LMWH in the peripartum period. High risk patients (mechanical valves, thrombophilia or active thrombotic disease) are transferred to Darwin in the third trimester to have anticoagulation managed and monitored.

Surgical intervention

Percutaneous balloon mitral valvuloplasty (PBMV) is safe and results in good foetal outcomes in patients with severe stenotic lesions.[27,35,36] However, it carries the risk of acute severe mitral regurgitation and pericardial tamponade and is not always appropriate for patients with mixed valvular lesions. As there is no cardiothoracic surgical service in the NT to manage the complications of PBMV, patients needing cardiac intervention require interstate transfer to Adelaide.

DELIVERY

Planning

In the absence of obstetric indications for lower uterine segment Caesarean section (LUSCS), normal vaginal delivery is preferred due to lower rates of postpartum haemorrhage, infection, and thromboembolism.[37,38] Planned LUSCS can avoid emergent delivery and allow expert multidisciplinary input in the highest-risk cases. Spontaneous labour is reasonable for patients classified as mWHO II risk if they reside within close proximity to the hospital. For remote patients, this entails hotel-style accommodation, which can be provided in the weeks leading up to delivery. As mentioned previously, this often results in the displacement of many First Nations women from their support networks at a time of high stress. In patients classified as mWHO III and IV risk, the preferred approach is planned labour induction in the intensive care unit (ICU). This allows optimisation of timing, personnel, equipment, and resources with continuous monitoring during the dynamic stages of labour and the postpartum period. It also aids in the inpatient optimisation of volume status, rate control and management of anticoagulation before a neuraxial technique.

Anaesthetic considerations

Established RHD often presents as a mixed valvular disorder. Table 2 delineates the most common anaesthetic considerations for each valvular disorder. Haemodynamic aims are generally targeted to the most severe lesion; however, care must be taken not to underestimate the additive effects of moderate lesions in series (that is, aortic regurgitation and mitral regurgitation). Left-sided valve disease, stenotic lesions, and pulmonary hypertension carry the highest risk of patient morbidity and mortality.[20,27,39] Pulmonary hypertension due to obstructive left ventricular disease such as mitral or aortic stenosis is associated with a 30-56% risk of maternal mortality.[39] If these lesions are associated with right ventricular dysfunction or a poor functional score, the risk increases exponentially. In addition, the hypercoagulable state of pregnancy increases the probability of pulmonary emboli, which can, in turn, worsen pulmonary hypertension. A small pulmonary embolus may result in acute right ventricular failure in a patient who is maximally compensated.

Regurgitant lesions, in comparison, are generally well tolerated during labour, delivery and anaesthesia in the absence of heart failure and pulmonary hypertension.[12]

Many patients will have required previous valve interventions before becoming pregnant. In women of childbearing age, it is standard to offer a bioprosthetic valve replacement with subsequent surgery to convert to a mechanical valve after the completion of their family. Bioprosthetic valves do not require therapeutic anticoagulation like their mechanical counterparts but are at risk of structural degeneration and may need reoperation as early as within the first five years. This option is not always selected due to the requirement to return interstate for redo surgery. As a result, many women in the NT present in pregnancy with previous mechanical valve replacements, requiring therapeutic anticoagulation. It is not uncommon for patients to present in the NT with restenosis, obstruction of valve replacements, or failure of previous valve repairs.

Due to the complexity of valvular disorders and the rate of unexpected “moderate to severe” findings, all diagnostic transoesophageal echocardiography performed in Darwin is done in the operating theatre complex with a consultant anaesthetist.

Table 2: Anaesthetic goals and considerations in common RHD lesions and sequelae

Valvular lesion	Pathophysiologic processes	Anaesthetic goals (HR, preload, afterload, contractility)
Mitral stenosis	Fixed preload to the left ventricle (LV) impairs the ability to increase CO in demand to the effective vasodilated state of pregnancy. Hypervolaemia and tachycardia of pregnancy lead to an increased gradient across the mitral valve, left atrial (LA) dilation and increased pulmonary artery pressures. If severe pulmonary hypertension develops, right ventricular failure may also occur.	Heart rate: Prevent tachycardias and aggressively treat dysrhythmias (adequate analgesia, avoid terbutaline, defibrillation pads on). Normovolaemia: pre-emptive diuresis if evidence of pulmonary oedema or right ventricular failure before induction of labour. Preferential use of vasopressors over volume for hypotension management. Percutaneous balloon valvuloplasty (see surgical management below).
Aortic stenosis	Decreased SVR of pregnancy associated with the vascular changes and vasodilation of neuraxial anaesthesia decreases coronary perfusion pressures. Tachycardia decreases LV diastolic filling time and LV perfusion time. Often associated with LV diastolic function.	Gentle initiation of neuraxial analgesia and anaesthesia with concurrent management of the vasoplegia. Low threshold to treat haemorrhage with volume resuscitation. Transcatheter aortic valve replacement in specific cases may be warranted, safe, and effective.[40]
Regurgitant lesions – **MR and AR**	Forward regurgitant fraction is improved with a low SVR and a higher HR. Neuraxial will reduce the SVR which improves the regurgitant fraction. MR is associated with an enlarged LA and an increased risk of arrhythmias. APO may result from increases in LA and pulmonary pressures, particularly when there is an acute regurgitant change with increased SVR or acute ischaemia with chordae rupture.	Avoid increases in SVR. Avoid bradycardia – use ephedrine and chronotropic agents. Avoid arrhythmias – digoxin loading is commonly used in Darwin on patient admission. Acceptance of lower blood pressure may be an appropriate technique as patients will have increased forward flow. However, at some point hypotension will reduce placental circulation flow as this is a pressure-passive circulation.
Mechanical prosthetic valve	High risk of valvular thrombosis with hypercoagulable state of pregnancy.	Vitamin K antagonist continued in pregnancy and changed to LMWH in the peripartum period (as above). Higher risk of intra and postpartum haemorrhage. Consider early surgical management of postpartum haemorrhage. GA LUSCS if the anticoagulation cannot be stopped. Mechanical valve thrombosis is a life-threatening emergency (due to acute stenosis, regurgitation and heart failure) and requires urgent transfer to a cardiothoracic centre to provide (TOE-guided) thrombolysis or surgery to extract the clot.

Pulmonary hypertension/ right ventricular dysfunction	Increased circulating blood volume and venous return results in acute right heart dysfunction in the face of elevated pulmonary vascular resistance or poor RV reserve. Hypercoagulable state of pregnancy increases the risk of pulmonary emboli. Decreased SVR leading to decreased coronary perfusion to a hypertrophic RV reliant on diastolic perfusion. Placental blood autotransfusion postpartum may result in acute pulmonary hypertension and right ventricular failure.	Regular volume status tracking with diuresis where necessary. Maintain strict fluid balance and make haemodynamic decisions using invasive monitoring. Maintain right ventricular perfusion by maintaining SVR using vasopressor support. Invasive monitoring and pre-emptive vasopressor therapy is recommended when instituting neuraxial analgesia/anaesthesia. Careful incremental initiation of neuraxial analgesia and anaesthesia. Reduce PVR using nebulised milrinone or additionally inhaled nitric oxide or nebulised prostacyclin if intubated. Sildenafil is also a safe option in pregnancy. Prevent increases in PVR: avoid over sedation causing hypercarbia, administer supplemental oxygen. Limit oxytocic use. Oxytocin boluses in 0.5-1 unit increments with vasopressor support to offset hypotension. Ergometrine and carboprost are contraindicated as they can increase pulmonary pressures. Therefore, early surgical management is the mainstay of treatment of PPH. Under GA: Avoid over or under ventilation to maintain normocarbia and high intrathoracic pressure, and use TOE to monitor RV and cardiac output.

Monitoring

All parturients should have standard ANZCA monitoring, including a five-lead electrocardiogram to allow early detection of arrhythmias and subendocardial ischaemia.

Arterial line monitoring with or without pulse contour analysis is utilised to guide vasopressor management in the face of haemodynamic insults like neuraxial analgesia and postpartum haemorrhage. However, arterial waveform analysis has limited application in cases of rapid haemodynamic disturbances such as during a LUSCS.

The use of a central venous access line is indicated in high-risk cases where the use of vasoactive medications is expected; however, there is no proven utility of central venous pressure (CVP) monitoring in this patient population. Pulmonary artery catheters are generally not required.[41,42]

Defibrillation pads are placed pre-emptively in case of unstable arrhythmias, and fluid balance is monitored with an indwelling urinary catheter.

Peripartum sequential transthoracic echocardiography (TTE) can help guide management, and if the patient is intubated, a TOE provides more detailed information due to improved windows.

Continuous cardiotocography (CTG) for foetal monitoring is indicated prior to any intervention.

Anticoagulation

For patients on regular anticoagulation, Vitamin K antagonists have usually been ceased in the peripartum period and changed to LMWH. Therapeutic anticoagulation with LMWH must be ceased at least 24 hours before any attempted neuraxial technique.[43] A neuraxial technique may be required earlier than anticipated if spontaneous labour is induced by the insertion of the balloon for cervical ripening on the day prior to induction. This needs to be considered when deciding on the timing of cessation. Overall, therapeutic anticoagulation in the peripartum period will increase the risk of peripartum haemorrhage and needs to be weighed against the risk of valvular or systemic thrombosis, which is made worse by the hypercoagulable state of pregnancy.

Fluid management

Preload to the right ventricle is increased in the immediate postpartum period due to autotransfusion from the uterus and decompression of the IVC from the non-gravid uterus. This can precipitate acute pulmonary oedema, especially in patients with stenotic valvular lesions. Thus, little fluid is administered during delivery and caesarean sections (100-200ml at a time), and a degree of postpartum haemorrhage (PPH) is tolerated depending on the state of right ventricular filling on repeated echocardiograms. With minimal fluid administration, the autotransfusion of 400-500mL of blood is often nicely balanced by 400-500mL of bleeding to maintain a state of compensated normovolaemia.

Arrhythmias

Parturients will often already be started on anti-arrhythmic therapies, which can be loaded again in the peripartum period. Modification of the ALS algorithm for the pregnant patient (manual uterine displacement, perimortem LUSCS) remains unchanged, and there is a low threshold for cardioversion for any unstable rhythm.

Oxytocics and postpartum haemorrhage

The haemodynamic consequences of postpartum haemorrhage can be significant, but oxytocics themselves carry substantial risks, particularly in patients with mitral stenosis. Ergometrine increases cardiac afterload through vasoconstriction, increases pulmonary arterial pressures (PAP) and can lead to coronary vasospasm.[44] Carboprost can also lead to increases in PAP, and they are both avoided.[45] In patients with pre-existing pulmonary hypertension, a sudden increase in PAP can precipitate a pulmonary hypertensive crisis and acute right heart failure. Oxytocin causes hypotension and tachycardia through vasodilatation and has been associated with coronary vasospasm. This combination of effects is particularly deleterious in patients with stenotic lesions, where diastolic filling is paramount in maintaining cardiac output. Therefore, oxytocin must be carefully titrated in 0.5 to 1 unit doses and balanced with vasopressors based on real-time arterial monitoring. If required, a low volume infusion can be commenced.[46] Carbetocin carries similar risks to oxytocin but is less titratable and, therefore, omitted.[47] Misoprostol can be given rectally or orally because it has no cardiac side effects but is a weaker oxytocic.

Tranexamic acid is given prophylactically at the time of delivery to mitigate the risk of PPH. In the event of significant bleeding, early surgical management is required and haemostasis can often be achieved in the setting of a well-working epidural. Minor suturing or placement of a Bakri balloon can be performed quickly in intensive care, whereas other procedures may require transfer to the operating theatre.

Obstetric emergencies and other drugs

Respect for a fragile haemodynamic state should be observed with any drug given during the peripartum period. Seemingly benign drugs can have significant haemodynamic effects. This includes drugs used in the management of obstetric emergencies, such as terbutaline, which can cause tachycardia. There should be a clearly documented plan for how to manage such situations should they occur. Other anecdotal examples include significant hypotension with metoclopramide and nausea-related tachycardia from systemic absorption of neuraxial opioids.

Post-delivery management

Patients remain at high risk of decompensation and should be observed in a high dependency area with invasive lines left in situ in case of a return to theatre.[48] In addition to the risk of postpartum haemorrhage, there is a high risk of decompensated cardiac failure with a decrease in CO, an increase in SVR, and a significant shift in fluid balance. Postpartum pain can also lead to sympathetic activation, and the epidural can be left in situ for analgesia if anticoagulation is not required. Intrathecal and epidural morphine can minimise the need for ongoing epidural infusions postoperatively. Breastfeeding should also be observed in the initial postpartum period as endogenous oxytocin release can have haemodynamic effects. Cardiology review and planning for potential surgery happen in the following weeks. Where possible, surgery is deferred for six months to allow for breastfeeding. This delay is often possible in the context of a return to a non-pregnant circulation and a reduction in transmitral pressures.

Anaesthetic techniques

Preoperative consultation with an anaesthetist should occur as early as possible. Unfortunately, this is often challenging due to the constraints of distance and also social and cultural barriers, which may not be readily apparent. Anaesthetic techniques are discussed with the patient and their family, in the presence of interpreters and Indigenous Liaison Officers, when required. Opportunistic review of patients is often necessary to align multiple assessments during a single visit (antenatal clinic, cardiology clinic, pre-anaesthetic clinic). Ideally, patients and their families have the opportunity to meet their multidisciplinary team well before delivery to build rapport and trust, and to ensure adequate time for questioning and understanding.

Labour in the intensive care unit

An early and well-organised arrival to ICU can ensure prompt insertion of invasive lines and an epidural and help facilitate early induction. This will maximise the chances of delivery during regular operating hours when staff and resources are optimised.

Arterial lines are placed for all patients and central lines for patients where vasoactive medications may be required (severe mitral stenosis, pulmonary hypertension, decompensated heart failure, arrhythmia). This is done before the insertion of the epidural to allow careful loading and titration. It also facilitates prompt emergency management during labour should a trip to the operating theatre be required. In our patient population, a small amount of sedation is frequently required to offset the tachycardia and sympathetic response from discomfort and anxiety associated with an unfamiliar environment and uncomfortable procedures. This can be in the form of remifentanil (0.1-0.2mcg/kg/min, similar to an obstetric PCA dose), which is easily titratable, reversible, safe and has favourable haemodynamic effects and small doses of midazolam (0.025mg/kg) once continuous CTG is placed.[49-51] Care must be taken to minimise the time in Trendelenburg position for central line insertion to prevent a sustained increase in venous return and acute pulmonary oedema.

An epidural is placed as normal to ablate the sympathetic response to labour. It is tested with low-dose local anaesthetic (5mL of 0.125% bupivacaine or 0.2% ropivacaine in 1mL increments). Further doses are given via a programmed intermittent epidural bolus or a patient-controlled epidural analgesia (PIEB/PCEA) regime utilising ultra-low dose concentrations of local anaesthetics to minimise motor block and haemodynamic effects (0.0625% bupivacaine or 0.1% ropivacaine). We use a PIEB with PCEA regimen as it has been shown to have a lower incidence of breakthrough pain, lower overall local anaesthetic dosing and minimal haemodynamic effects in the dilute concentration compared to continuous epidural infusion techniques.[52,53] Any vasodilation is counteracted by vasopressor support with real-time monitoring. Beta-blockade may be acutely necessary to curtail the reflex tachycardia associated with vasodilation from the epidural (or, in the case of a failed epidural). Both intravenous esmolol and metoprolol are safe and effective agents.

Artificial rupture of membranes (ARM) and induction are then performed with a reduced dose of oxytocin, followed by an intrapartum echo. Labour proceeds in the dependent position and passive descent is allowed at full dilation to minimise the undesirable effects of pushing. Instrumental lift-out is used with limited pushing if haemodynamics are favourable. Delivery ideally occurs in the presence of an anaesthetist and intensivist, with theatre notified in case of emergent transfer. While attempts are made to have a dedicated anaesthetic team available, the unpredictable nature of obstetrics and a small anaesthetic department dictates that all of our perioperative staff are prepared to manage these patients.

Management of the third stage and PPH is described previously above.

Caesarean section

Elective caesarean deliveries are performed with a slowly loaded epidural or a combined spinal epidural (CSE) technique. Where CSE is performed for high-risk patients, the spinal component contains only intrathecal morphine and no local anaesthetic. Intrathecal morphine is used to prevent postpartum sympathetic activation from incisional pain. The neuraxial technique is performed after invasive line insertion with or without sedation as described above. For patients with pulmonary hypertension, a pre-operative dose of nebulised milrinone 5mg can be given to vasodilate the pulmonary circulation. Epidural loading can be achieved with incremental 0.5% bupivacaine or 2% lignocaine with adrenaline 1:200,000, 1-2mL at a time, coinciding with slow increases in vasopressor support to offset any drop in SVR. For patients with pulmonary hypertension, vasopressin may be preferred to noradrenaline as a first-line option as it has no effect on pulmonary vascular resistance.

A semi-emergent LUSCS is possible with a titrated load of the epidural together with invasive monitoring and vasopressor support where time allows.

Elective caesarean sections under a general anaesthetic are recommended in cases where anticoagulation cannot be stopped, or the patient needs an emergent delivery (for maternal decompensation or foetal distress), where a slowly titrated epidural is not feasible.

While opioids are not globally utilised in GA LUSCS, in the cardiac patient, haemodynamic stability is prioritised over foetal sedation at induction. The use of remifentanil or alfentanil may provide the best balance between sympatholysis and prolonged foetal sedation. A general anaesthetic has its own risk, but it allows the use of a TOE and the delivery of inhaled nitric oxide, milrinone or nebulised prostacyclin in an intubated and ventilated patient.[41]

CONCLUSION

The perioperative management of rheumatic heart disease in the Top End falls upon the shoulders of a small group of dedicated and experienced obstetricians, midwives, cardiologists, intensivists, and anaesthetists. The management of this condition requires a comprehensive understanding of obstetric physiology, cardiac pathophysiology, and cultural awareness. As a result of ongoing social inequity we are likely to continue to encounter a high level of complicated obstetric RHD in the future. As a general tertiary hospital without cardiac surgical services, we continue to learn from our patients, colleagues, and experiences to improve and develop a service that fits the complex needs of patients in the Top End.

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REFERENCES

1. Welfare AIoHa. Acute rheumatic fever and rheumatic heart disease in Australia 2017-2021. Government A; 2023 March 2023. Report No.: CVD 99.
2. Zühlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). 2015.
3. Vaughan G, Tune K, Peek MJ, Jackson Pulver L, Remenyi B, Belton S, et al. Rheumatic heart disease in pregnancy: strategies and lessons learnt implementing a population-based study in Australia. International health. 2018;10(6):480-9.
4. Soma-Pillay P, Nelson-Piercy C, Tolppanen H, Mebazaa A. Physiological changes in pregnancy: review articles. Cardiovascular journal of Africa. 2016;27(2):89-94.
5. Ramsay M. Normal hematological changes during pregnancy and the puerperium. The obstetric hematology manual Cambridge University Press, Cambridge. 2010:1-11.
6. Nishimura RA, Tajik AJ, editors. The Valsalva maneuver and response revisited. Mayo Clinic Proceedings; 1986: Elsevier.
7. Bedson R, Riccoboni A. Physiology of pregnancy: clinical anaesthetic implications. Continuing Education in Anaesthesia, Critical Care and Pain. 2014;14(2):69-72.
8. Van Hagen IM, Thorne SA, Taha N, Youssef G, Elnagar A, Gabriel H, et al. Pregnancy outcomes in women with rheumatic mitral valve disease: results from the registry of pregnancy and cardiac disease. Circulation. 2018;137(8):806-16.
9. Owens A, Yang J, Nie L, Lima F, Avila C, Stergiopoulos K. Neonatal and maternal outcomes in pregnant women with cardiac disease. Journal of the American Heart Association. 2018;7(21):e009395.
10. Ducas RA, Javier DA, D'Souza R, Silversides CK, Tsang W. Pregnancy outcomes in women with significant valve disease: a systematic review and meta-analysis. Heart. 2020;106(7):512-9.
11. Baghel J, Keepanasseril A, Pillai AA, Mondal N, Jeganathan Y, Kundra P. Prediction of adverse cardiac events in pregnant women with valvular rheumatic heart disease. Heart. 2020;106(18):1400-6.

12. Silversides CK, Grewal J, Mason J, Sermer M, Kiess M, Rychel V, et al. Pregnancy outcomes in women with heart disease: the CARPREG II study. Journal of the American College of Cardiology. 2018;71(21):2419-30.
13. Rémond MG, Li Z, Vaughan G, Frawley J, Peek MJ, Carapetis JR, et al. The spectrum, severity and outcomes of rheumatic mitral valve disease in pregnant women in Australia and New Zealand. Heart, Lung and Circulation. 2022;31(4):480-90.
14. Suri V, Sikka P, Singla R, Aggarwal N, Chopra S, Vijayvergiya R. Factors affecting the outcome of pregnancy with rheumatic heart disease: an experience from low-middle income country. Journal of Obstetrics and Gynaecology. 2019;39(8):1087-92.
15. Begley CM, Gyte GM, Devane D, McGuire W, Weeks A, Biesty LM. Active versus expectant management for women in the third stage of labour. Cochrane database of systematic reviews. 2019(2).
16. Sullivan E, Vaughan G, Li Z, Peek M, Carapetis JR, Walsh W, et al. The high prevalence and impact of rheumatic heart disease in pregnancy in First Nations populations in a high-income setting: a prospective cohort study. BJOG: An International Journal of Obstetrics & Gynaecology. 2020;127(1):47-56.
17. Lam CK, Thorn J, Lyon X, Waugh E, Piper B, Wing-Lun E. Rheumatic heart disease in pregnancy: Maternal and neonatal outcomes in the Top End of Australia. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2023;63(1):74-80.
18. Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier L-A, Morton BC, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation. 2001;104(5):515-21.
19. Drenthen W, Boersma E, Balci A, Moons P, Roos-Hesselink JW, Mulder BJ, et al. Predictors of pregnancy complications in women with congenital heart disease. European heart journal. 2010;31(17):2124-32.
20. Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in heart disease. Heart. 2006;92(10):1520-5.
21. Sartain J, Anderson N, Barry J, Boyd P, Howat P. Rheumatic heart disease in pregnancy: cardiac and obstetric outcomes. Internal medicine journal. 2012;42(9):978-84.
22. Balci A, Sollie-Szarynska KM, van der Bijl AG, Ruys TP, Mulder BJ, Roos-Hesselink JW, et al. Prospective validation and assessment of cardiovascular and offspring risk models for pregnant women with congenital heart disease. Heart. 2014;100(17):1373-81.
23. Sliwa K, Libhaber E, Elliott C, Momberg Z, Osman A, Zühlke L, et al. Spectrum of cardiac disease in maternity in a low-resource cohort in South Africa. Heart. 2014;100(24):1967-74.
24. Statistics ABo. 2016 Census reveals the changing face of the Northern Territory. 2017.
25. RHDAustralia (ARF/RHD) writing group. The 2020 Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease. Medical Journal of Australia. 2021;214(5):220-7.
26. Franklin WJ, Gandhi M. Congenital heart disease in pregnancy. Cardiology Clinics. 2012;30(3):383-94.
27. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomström-Lundqvist C, Cifkova R, De Bonis M, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy: the task force for the management of cardiovascular diseases during pregnancy of the European Society of Cardiology (ESC). European heart journal. 2018;39(34):3165-241.
28. Barclay L, Kornelsen J, Longman J, Robin S, Kruske S, Kildea S, et al. Reconceptualising risk: Perceptions of risk in rural and remote maternity service planning. Midwifery. 2016;38:63-70.
29. Cousins S. Birthing on Country: improving maternal care in Australia. The Lancet. 2023;401(10372):184-5.
30. Kildea S, Gao Y, Hickey S, Nelson C, Kruske S, Carson A, et al. Effect of a Birthing on Country service redesign on maternal and neonatal health outcomes for First Nations Australians: a prospective, non-randomised, interventional trial. The Lancet Global Health. 2021;9(5):e651-e9.
31. Kugamoorthy P, Spears DA. Management of tachyarrhythmias in pregnancy–A review. Obstetric Medicine. 2020;13(4):159-73.
32. Podymow T, August P. Update on the use of antihypertensive drugs in pregnancy. Hypertension. 2008;51(4):960-9.
33. D'Souza R, Ostro J, Shah PS, Silversides CK, Malinowski A, Murphy KE, et al. Anticoagulation for pregnant women with mechanical heart valves: a systematic review and meta-analysis. European heart journal. 2017;38(19):1509-16.
34. Yarrington CD, Valente AM, Economy KE. Cardiovascular management in pregnancy: antithrombotic agents and antiplatelet agents. Circulation. 2015;132(14):1354-64.
35. Sreerama D, Surana M, Moolchandani K, Chaturvedula L, Keepanasseril A, Keepanasseril A, et al. Percutaneous balloon mitral valvotomy during pregnancy: A systematic review and meta-analysis. Acta Obstetricia et Gynecologica Scandinavica. 2021;100(4):666-75.
36. Mehta LS, Warnes CA, Bradley E, Burton T, Economy K, Mehran R, et al. Cardiovascular considerations in caring for pregnant patients: a scientific statement from the American Heart Association. Circulation. 2020;141(23):e884-e903.
37. Lindley KJ, Conner SN, Cahill AG. Adult congenital heart disease in pregnancy. Obstetrical & Gynecological Survey. 2015;70(6):397-407.
38. Easter SR, Rouse CE, Duarte V, Hynes JS, Singh MN, Landzberg MJ, et al. Planned vaginal delivery and cardiovascular morbidity in pregnant women with heart disease. American journal of obstetrics and gynecology. 2020;222(1):77. e1-. e11.
39. Bedard E, Dimopoulos K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? European heart journal. 2009;30(3):256-65.
40. Hodson R, Kirker E, Swanson J, Walsh C, Korngold EC, Ramelli S. Transcatheter aortic valve replacement during pregnancy. Circulation: Cardiovascular Interventions. 2016;9(10):e004006.
41. Arendt K, Lindley K. Obstetric anesthesia management of the patient with cardiac disease. International journal of obstetric anesthesia. 2019;37:73-85.
42. Meng M-L, Arendt KW. Obstetric anesthesia and heart disease: practical clinical considerations. Anesthesiology. 2021;135(1):164-83.

43. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines. Regional Anesthesia & Pain Medicine. 2010;35(1):64-101-64-.
44. Lin Y-H, Seow K-M, Hwang J-L, Chen H-H. Myocardial infarction and mortality caused by methylergonovine. Acta obstetricia et gynecologica Scandinavica. 2005;84(10):1022-.
45. Secher N, Andersen L. Changes in the pattern of regional pulmonary blood flow after PGF2α infusion in pregnant women. Cardiovascular Research. 1977;11(1):26-30.
46. Langesaeter E, Rosseland L, Stubhaug A. Haemodynamic effects of repeated doses of oxytocin during Caesarean delivery in healthy parturients. British journal of anaesthesia. 2009;103(2):260-2.
47. Archer T, Knape K, Liles D, Wheeler A, Carter B. The hemodynamics of oxytocin and other vasoactive agents during neuraxial anesthesia for cesarean delivery: findings in six cases. International Journal of Obstetric Anesthesia. 2008;17(3):247-54.
48. Safdar Z. Pulmonary arterial hypertension in pregnant women. Therapeutic Advances in Respiratory Disease. 2013;7(1):51-63.
49. Oliveira PSC, Sant'Anna BC, Seixas NB, Mendonça JA. Low-dose midazolam for anxiolysis for pregnant women undergoing cesarean delivery: a randomized trial. Brazilian Journal of Anesthesiology. 2022;72:450-6.
50. Senel AC, Mergan F. Premedication with midazolam prior to caesarean section has no neonatal adverse effects. Revista Brasileira de Anestesiologia. 2014;64:16-21.
51. Wilson MJ, MacArthur C, Hewitt CA, Handley K, Gao F, Beeson L, et al. Intravenous remifentanil patient-controlled analgesia versus intramuscular pethidine for pain relief in labour (RESPITE): an open-label, multicentre, randomised controlled trial. The lancet. 2018;392(10148):662-72.
52. Roofthooft E, Barbé A, Schildermans J, Cromheecke S, Devroe S, Fieuws S, et al. Programmed Intermittent Epidural Bolus vs. Patient-controlled Epidural Analgesia for Maintenance of Labour Analgesia: A 2-Center, Double-blind, Randomized Study. Obstetric Anesthesia Digest. 2021;41(4):199.
53. Xu J, Zhou J, Xiao H, Pan S, Liu J, Shang Y, et al. A systematic review and meta-analysis comparing programmed intermittent bolus and continuous infusion as the background infusion for parturient-controlled epidural analgesia. Scientific reports. 2019;9(1):1-11.

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Radiation safety and the anaesthetist

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INTRODUCTION

Background ionising radiation exposure in the general population is a combination of environmental and artificial radiation. According to the International Commission for Radiation Safety 'medical procedures make up most of the manufactured dose, by far'.[1] This does not include the therapeutic uses of ionising radiation, but rather radiation used for diagnostic purposes. Given the proximity of healthcare personnel to medical procedures utilising radiation on a day-to-day basis, limiting and measuring occupational radiation exposure is a necessary safety measure that should be present in all healthcare systems and hospitals. The anaesthetist is frequently involved in such medical procedures, whether in operating theatres or in remote procedure rooms, and previous research has identified poor baseline knowledge and practice of radiation protection in anaesthetists. This article will outline the basic science of radiation effects on the body (radiobiology) and identify the potential risks of occupational radiation exposure for anaesthetists. We will then set out the current best practices to reduce exposure to the lowest possible occupational risk.

BASIC SCIENCES OF RADIOBIOLOGY

Ionising radiation

Radiation is energy travelling through space in the form of subatomic particles or electromagnetic waves. Ionising radiation, the type than can cause tissue damage, can be defined as radiation with the ability to displace electrons from atoms. Ionising radiation can be divided into photons of the electromagnetic spectrum (gamma rays, X-rays) and subatomic particles (alpha and beta particles).[2] Table 1 summarises the types of ionising radiation and its relevance to the general population.

Table 1. Types of ionising radiation

Type	Composition	Penetration	Radiation weighting factor
Alpha particles	Helium nucleus (two neutrons & two protons)	Very low (will not penetrate skin)	20
Beta particles	Electron or positron	Low (may penetrate skin, absorbed by clothing)	1
X-rays	Photon	Penetrates body	1
Gamma rays	Photo	Penetrates body	1

Ionisation of a molecule may lead to the breakage of chemical bonds and production of highly reactive free radicals. It is by these processes that the adverse effects of ionising radiation occur. The biological effectiveness (or destructive ability of ionising radiation against living tissue) of different types of ionising radiation is measured by the dimensionless factor Wr (radiation weighting factor). X-rays have a Wr of 1, while alpha particles have a Wr of 20.

Stochastic versus deterministic effects

The adverse effects of radiation fall into two categories:

- Stochastic effects are those where the probability of an event is dose-related, with no lower threshold. Stochastic effects in humans include cancer induction.
- Deterministic effects (tissue reactions) are those where the severity of an event is dose-related, with a lower threshold below which an event will not occur.[3] Deterministic effects include cataract formation, hair loss, radiation burns, radiation pneumonitis, sterility, and death.

While this classification of radiation effects has recently been challenged,[4] for the purposes of the article we will focus mostly on the stochastic effects of radiation, namely the risk of cancer induction. Cancer induction is the major concern in occupational radiation exposure outside of radiation accidents and disasters.

Cancer induction

It is important to understand that as a stochastic effect, there is no safe dose below which cancer induction will not occur. This linear no-threshold model suggests that any exposure to ionising radiation will increase the risk, but not the severity, of cancer induction. Ionising radiation causes DNA damage directly, via an interaction between ionising particles and DNA, and indirectly, by production of reactive oxygen species. Double-stranded DNA damage from radiation often results in cellular apoptosis, however lesser damage may lead to altered function and potentially malignant proliferation.

While there are no radiation-specific cancers, some cancers are more commonly associated with radiation exposure than others.[5] The Law of Bergoiné and Tribondeau states that the radiosensitivity of biological tissue is directly proportional to the mitotic activity and inversely proportional to the degree of differentiation of its cells.[6] This is why haematopoietic, reproductive, gastrointestinal, and foetal cells are among the most radiosensitive cells, and associated malignancies are seen more commonly in radiation exposure. Radiation has been implicated in all steps of carcinogenesis: from initiation, promotion, and progression of a tumour. As a result, radiotherapy itself can increase the risk of developing further malignancy. For example, retinoblastoma patients have a higher risk of developing osteosarcoma of the orbit following radiotherapy. Given that the same tumour suppressor gene has been implicated in both cancers, radiation provides the 'second hit' required to induce cancer transformation in the bone.[7]

BACKGROUND AND OCCUPATIONAL EXPOSURE

Dosing scalars, for the purposes of quantifying background and radiation exposure, are traditionally described in units of Gray (Gy) and Sieverts (Sv) although these are very large amounts of radiation so mSv and mGy are often used. Commonly utilised units, and their means of calculation, are presented in Table 2.

Table 2. Dosing scalars for ionising radiation

Dosing	Unit	Calculation
Absorbed dose	Gray (Gy)	joule/kg deposited
Equivalent dose	Seivert (Sv)	absorbed dose (Gy) x radiation weighting factor (Wr)
Effective dose	Seivert (Sv)	equivalent Dose (Sv) x Σ Wt (tissue weighting factor)

The *absorbed dose* is the amount of energy deposited. This is the unit radiation oncologists use to prescribe treatment in cancer.

The *equivalent dose* takes into account the type of ionising radiation being deposited, and its relative biological effectiveness (see radiation weighting factor above).

The effective dose further corrects the dose by the various body tissues that have been irradiated. The organs and tissue in the body have different sensitivities to ionising radiation, and therefore the effects of partial irradiation on the body can be calculated using the effective dose. The sum of all tissue weighting factors will add up to one, and therefore if the entire body has been irradiated, the effective dose will equal the equivalent dose.[8] Organs such as the gonads and bone marrow will have a much higher tissue weighting factor than bone and skin.

Total annual background radiation exposure in the population is variable, differing from region to region. A report by the UK Centre for Radiation, Chemical and Environmental Hazards Radiation Protection Division concluded that the average background radiation exposure in the UK population was 2.7 mSv per year. Of this, 16 per cent was artificial radiation exposure, mostly medical radiation.[9] The United Nations Scientific Committee on the Effects of Atomic Radiation report in 2008 found an approximate yearly exposure of 3 mSv, of which 0.6 mSv was due to artificial exposure, mostly medical radiation.[10] Therefore, by far the greatest source of artificial ionising radiation worldwide is related to diagnostic medical procedures.

Occupational radiation dosing limits are set out by the International Commission for Radiation Protection (ICRP). Outside of rescue operations and catastrophic incidents, occupational radiation dose is limited to 20 mSv/year effective dose, averaged over five years (to a total 100 mSv), with no single year exceeding 50 mSv effective dose.[11] The ICRP recommends that all pregnant women should have exposure levels similar to that of the general population and limit the dose to the fetus to 1 mSv for the remainder of the pregnancy. To put this in context, the effective dose of a chest X-ray (antero-posterior and lateral views) is 0.1 mSv, and for a CT abdomen-pelvis, 8 to 14 mSv.[12]

HOW MUCH RADIATION IS THE ANAESTHETIST EXPOSED TO?

To answer the question of how much radiation an anaesthetist is exposed to, it is important to consider individual differences in workplace practice. The environments of potential exposure include:

- operating theatres - X-rays, fluoroscopy via C-Arm
- interventional radiology suite
- diagnostic radiology
- endoscopy - endoscopic retrograde cholangiopancreatography (ERCP)
- cardiac catheterisation suite
- nuclear medicine suite - brachytherapy, external beam radiotherapy
- emergency departments

The specific areas of increased risk have been highlighted as endoscopy (ERCP), cardiac catheterisation suite, interventional radiology suite, vascular and neurointerventional fluoroscopy.[13]

In the past two decades, there has been an increase in interest in radiation safety for the anaesthetist, with several studies published measuring longitudinal exposure in anaesthetists. Individual exposure is quite easy to measure with the aid of a personal radiation monitor (dosimeter). These monitors should be used in all medical facilities where medical ionising radiation is present, and provided to all staff who are at risk of regular exposure. They should be worn on the outside of lead aprons as they are intended to measure the radiation staff are exposed to, not that which they receive. The Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) code on radiation protection stipulates that a dosimeter 'is provided to each occupationally exposed person who is likely to be exposed to ionising radiation in excess of 1mSv in any one year'.[14] One millisievert is defined as the average accumulated background radiation dose to an individual for 1 year, exclusive of radon, in the United States, or the dose produced by exposure to 1 milligray (mGy) of radiation. Pragmatic examples of clinical exposures (for a patient) are summarised in Table 3.

Table 3. Common clinical radiation dose exposures

Radiological technique	Estimated average radiation exposure (mSv)
Chest x-ray (PA film)	0.02
Lumbar spine	1.5
I.V. urogram	3
Upper G.I. exam	6
Barium enema	8
CT head	2
CT chest	7
CT abdomen	8
Coronary artery calcification CT	3
Coronary CT angiogram	16
Cross-country airplane flight	0.04

Extracted from: Average effective dose in millisieverts (mSv) from McCollough CH, et al[37]

The challenge, therefore, is to identify which anaesthetists are likely to be exposed to this level of radiation. Unsurprisingly, given the utility and simplicity of the dosimeter, there have been a number of studies measuring anaesthetists' longitudinal exposure to radiation in their workplace using these dosimeters. A review of the literature shows that some anaesthetists may well cross this annual threshold of 1 mSv. Although, 1mSv is the threshold for recommending the utilisation of a dosimeter. Occupational exposure limits are set as less than 20 mSv per year, averaged over 5 years, with no single year being greater than 50 mSv.

A 2006 paper from Charles Gairdner Hospital followed 29 fulltime anaesthetists over a period of one month.[15] The casemix could be described as typical of a large adult tertiary referral centre, where 'IR exposure could occur'. A dosimeter was placed behind a lead apron, and a second on the exposed collar to enable estimates of whole-body exposure. Of the 29 anaesthetists, seven exceeded the threshold for radiation detection. These numbers were extrapolated to obtain estimated annual exposure, of which the highest effective dose was 2.14 mSv/year, although most were much lower.

A similar trainee-led project from the United States in 2017 followed 41 anaesthesiology trainees over periods of three months wearing thermoluminescent dosimeters to measure shallow, deep and eye exposure.[16] Mean shallow dose (exposure at tissue depth of 0.007cm) was 0.214 mSv over three months. The highest deep dose recorded (exposure at a tissue depth of 1 cm, estimating internal organ exposure) was 0.52 mSv. Extrapolating this dose over a year would yield a maximal exposure of 2.08 mSv.

These numbers are reassuring as they fall well below the 50 mSv maximum and 20 mSv averaged yearly dose limits set by the ICRP. To put this into perspective, the Centers for Disease Control and Prevention states that 'commercial airline crew have the largest annual effective dose of radiation (3.07 mSv) of all US radiation exposed workers',[17] with exposure ranging from 0.2 to 5 mSv per year. The UK National Radiological Protection Board Survey estimated average annual air crew doses of 4.6 mSv per year, higher than nuclear workers (3.6 mSv).[18]

There are particular areas of the hospital where ionising radiation exposure is potentially higher. A report from Yonsei University College of Medicine, Korea, tracked the exposure to ionising radiation of three senior anaesthesiology trainees over three months through a combined 363 procedures in the ERCP room.[19] Dosimeters were worn on the neck and wrist. Over three months the highest deep dose measured at the neck was 0.59 mSv and 1.27 mSv at the wrist. Of note, the anaesthetist who had the highest exposure at the wrist also performed the greatest amount of jaw thrusts. Mayr et al in 2019 placed a lead-lined cap on the head of an anaesthetist who assisted in 32 transcatheter aortic valve implantation procedures in the space of 15 days. Dosimeters were placed on the inside and outside of the cap. The maximum dose recorded on the outside of the cap over this period was 0.55 mSv.[20]

Finally, it is often thought that the proceduralists, with their close proximity to the patient and therefore the X-ray beam would naturally be at risk of highest exposure. In a comparison of exposure between the proceduralist and anaesthetists in a neurointerventional suite, dosimeters were placed on the foreheads of staff over the course of 31 diagnostic and interventional procedures.[21] The anaesthetist was found to have a three-fold greater exposure than the radiologist/proceduralist. The authors proposed that this surprising finding was likely due to theatre design, especially C-arm spatial configuration favouring protection of the proceduralist and not the anaesthetist. Another publication showed that the location receiving the highest dose of radiation in an endovascular suite during thoracoabdominal aortic aneurysm repairs was the anaesthetic machine, higher than the proceduralist, scrub nurse or radiographer.[22] This was attributed to there being no protective equipment around the anaesthetic machine.

Cataracts and occupational radiation exposure: stochastic or deterministic?

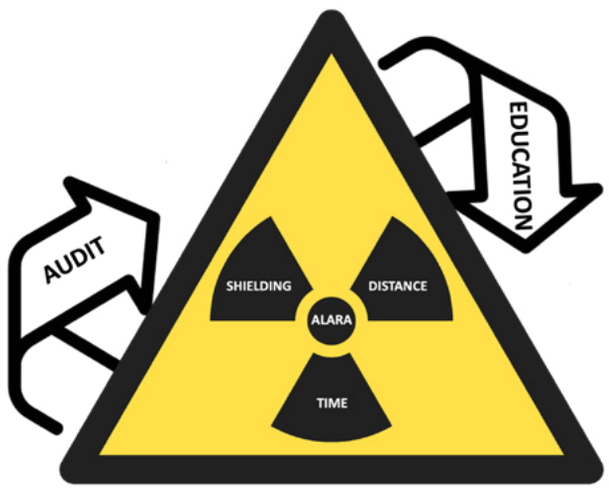
Those regularly anaesthetising for interventional radiology procedures or in the cardiac catheter laboratory may have noticed fellow radiologists and cardiologists wearing an extra piece of equipment over their eyes in addition to the standard lead apron and thyroid shield. Radiation protection eyewear or lead glasses are increasingly being recommended for radiation-exposed workers, and the evidence suggests that eye exposure to ionising radiation in anaesthetists is increasing.[23] Veno et al, in 2010, found the incidence of posterior lens opacities in interventional cardiologists to be significantly higher than in age-matched controls (38% versus 12%).[24] A subsequent systematic review in 2020 included 21 eligible studies, the vast majority of which involved radiologists, radiology technicians and interventional cardiologists, and found an increased incidence of cataracts, especially posterior subcapsular cataracts.[25] Ionising radiation exposure is strongly associated with posterior lens opacities, as shown from data investigating cataracts and atomic bomb survivors and nuclear accident clean-up workers.[26] In 2012 the ICRP reviewed and reduced the acceptable occupational equivalent dose to the lens from 150 mSv to 20 mSv,[27] with the proviso that this would continue to be reviewed. While the risk of cataracts has historically been seen as deterministic, this has been challenged in the literature, and it may indeed follow a non-linear model with no apparent threshold below which radiation-induced cataracts will not occur.[28]

Overall, the results from the literature are reassuring. Most anaesthetists are unlikely to reach yearly occupational safety limits outside of accidents and disasters. Anaesthetists are, however, radiation-exposed workers, potentially to a greater degree than many other healthcare colleagues and this may indeed be underrecognised.

PRINCIPLES OF RADIATION PROTECTION

The ALARA principle – as low as reasonably achievable – is the guiding principle of radiation safety. The principle is to utilise the smallest dose possible to produce the desired effect (e.g. adequate imaging) and reduce exposure to unwanted radiation. This principle can further be broken down into the 'big three' of radiation safety: time, distance, protection. We would like to add 'regular education' and 'audit' to these principles. This is graphically represented in Figure 1.

Figure 1. Radiation safety principles: As low as reasonably achievable (ALARA)



Time

Minimising exposure to radiation, either through reducing the total time the radiation source is active (e.g. screening time), or reducing the time spent near the active source (e.g. leaving the room during screening).

Distance

The amount of radiation exposure from a source is inversely proportional to the square of the distance. Known as the inverse square law, this implies that doubling the distance from the radiation source will effectively reduce exposure four-fold. X-ray exposure in the operating theatre (such as from a C-arm) is a combination of scatter (from the patient, equipment, floor) and direct beam exposure. Distancing oneself from the source and the beam is therefore very important.

In practice then, how far is safe enough? A systematic review looking at radiation doses received at certain distances from a C-arm found that the dose received decreased significantly with increasing distance, and that at distances of 1.5 metres or greater, either no dose or insignificant doses were recorded. This article even went so far as to question the need for lead protection for anaesthetists who are routinely at 1.5 metres or more away from a fluoroscopy unit.[29] Looking at one particular study analysed in the review, investigators placed dosimeters in certain locations of a fluoroscopy room, labelled by distance and with surrogate names of clinicians and their probable location in the room. The fluoroscopy unit was then turned on continuously for ten minutes. The surgeon's dosimeter was placed at 30 cm, and the anaesthetist's at 1.5 metres. While the surgeon recorded a total dose exposure of 0.2 mSv/min of fluoroscopy time, the anaesthetist's dosimeter did not register any positive readings.[30]

It is a recommendation of the ARPANSA that if staff are required to be present in the room during active use of X-ray/CT, they should try to stand at least two metres away from the X-ray tube, and also outside the primary beam. The operator should also, at the very least, be wearing a lead apron.[31]

Shielding

Standing a certain distance from the patient may not be achievable or practical in certain conditions, and certainly not something that can be assured in the practice of general anaesthesia. The third foundation of radiation safety is the use of protective equipment. Structural shielding in the form of mobile lead shields and lead drapes offer protection but may not protect from scatter. Personal protective equipment includes lead aprons, thyroid shields, leaded glasses, and gloves. Lead-free and lead-composite garments are also used. It is recommended that lead aprons have a minimum of 0.25 mm lead thickness.[32] There is a recommendation that staff with higher levels of exposure should consider thicker lead gowns, of the order of 0.50 mm. The garments should regularly be inspected for cracks or defects and should be stored on hangers with minimal folds.

Education and audit

Despite 50 to 70 per cent of orthopaedic surgeons or anaesthesia trainees indicating a concern regarding the potential adverse effects of radiation in surveys of radiation safety, only one-fifth wore adequate personal protective equipment, indicating a discrepancy between concerns and practice.[33]

In our own department, we audited the dosimeter use of 108 anaesthesia trainees and consultants. From 72 respondents, 85% were regularly assigned to lists involving potential radiation exposure but only eight (11%) staff members were in possession of a personal radiation monitor, two of whom declared to have checked their radiation exposure results. Eighty-eight per cent of respondents without dosimeters declared being interested in obtaining one for future use. We are currently in the process of obtaining dosimeters and hope to measure the yearly exposure to assess the risk. Suggested audit questions for anaesthesia departments are given in Table 4.

A before-and-after study of a single education session on radiation safety given to anaesthetists and surgeons identified that, while knowledge improved (e.g. 'what is an effective dose'), good radiation safety practice did not (e.g. the use of protective equipment).[34] Although there may have been a response bias to this study, it suggested that repeated education may be needed to improve department wide practice.

Table 4. Suggested questionnaire for auditing purposes

Questions	Potential responses (*Italics* = correct where applicable)
Knowledge	
What knowledge level do you think you have about radiation safety?	Excellent, good, adequate, inadequate, minimal
What are the annual occupational dose limits for radiation-exposed workers?	10, 20, 50, 100 mSv per year
What is the ALARA principle?	Free text
If you double your distance from a radiation source, how will your dose change?	same, 75% less, 50% less, *25% less*
What is the maximum occupational dose limit allowed in a given year for a radiation-exposed worker?	10, *20*, 50, 75 mSv
Is there a dose limit below which cancer induction will not occur with ionising radiation?	TRUE or *FALSE*
Where should the dosimeter be worn?	Under radiation PPE to estimate the dose received, *Outside of PPE to measure the radiation exposed to.*
A staff member becomes pregnant. Their annual occupational dose limit as a radiation exposed worker is now	20 mSv for the rest of the pregnancy. *They are not to be considered a radiation-exposed worker during their pregnancy*
Good radiation safety knowledge has been shown to translate into good radiation safety practice.	TRUE / *FALSE*
Practice	
How often are you exposed to ionising radiation at work?	Daily, weekly, monthly, rarely/never
Are you concerned about your radiation exposure at work?	Y or N
What concerns you the most regarding radiation exposure?	Cancer induction, cataracts, effects during pregnancy
Which radiation protective equipment do you wear at work?	Lead apron, thyroid shield, glasses, cap
Have you been provided with a personal radiation monitor?	Y or N
If yes, do you wear it regularly?	Y or N
If yes, where do you wear it?	In a position that it is under a lead PPE, In a position that is outside of lead PPE
If yes, do you check your radiation exposure results?	Y or N
If no, would you like to have a dosimeter provided to you?	Y or N

In addition to ALARA, other important principles include adequate signage (e.g. visible warning signs), regular monitoring of personnel and area exposure, and appointment of a radiation safety officer. The function of a radiation safety officer will depend on their employer, but essentially the role is to protect employees and members of the public from unnecessary exposure to radiation and ensure that employers fulfill their obligations under the Radiation Control Act (1990).[35] These would include ensuring radiation doses to employees and members of the public are as low as reasonably achievable, ensuring the safety and quality control of existing and new procedures where radiation or radioactive material is involved, ensuring regular training of all radiation-exposed workers, and reviewing and reporting incidents and accidents. Qualifications of the radiation safety officer should be appropriate to their workplace – a large teaching hospital's radiation safety officer would likely be assumed by a medical physicist or similar.

Radiation and pregnancy

It is important to stress that occupational safety limits in place for radiation exposed workers do not apply to pregnant members of the workforce. This is because, unlike radiation-exposed workers who have acceptable exposure limits, pregnant staff members' exposure to radiation should be minimised and ideally avoided. While very high doses of radiation (>500 mGy) have very significant deleterious effects on the foetus, such as death, miscarriage, growth retardation, severe intellectual disability, and other malformations, it is unclear if lower doses of absorbed radiation (<10 mGy) increase the risk of childhood leukaemia and cancer.[36] Therefore, once the member of staff has declared their pregnancy, the staff member should not receive a dose greater than 1 mSv for the remainder of the pregnancy. Not surprisingly, the highest risk period for stochastic and deterministic effects of radiation occurs in the first trimester during organogenesis, emphasising the need for routine good radiation safety practice.

CONCLUSION

Anaesthetists support patients through both diagnostic and interventional procedures which require utilisation of radiation, and as such can be classified as radiation-exposed workers. While the overall risks posed to anaesthetists remain low, the exposure of anaesthetists to ionising radiation may be underappreciated compared to other specialties. Infrastructure and safety measures should be built into every healthcare setting and regularly audited and appraised to ensure stringent measures are in place to monitor patients' and workers' exposure. It is important to emphasise that the stochastic effects of radiation, namely cancer induction, have no threshold below which an increase in risk will not occur. Utilising the principles of time, distance and shielding is effective in reducing overall exposure. Ongoing education is likely needed for these principles to be reliably put into practice.

REFERENCES

1. ICRPaedia. International Commission for Radiation Protection: Sources of Radiation Exposure (updated 8 March 2019). Available from: http://icrpaedia.org/Sources_of_Radiation_Exposure
2. Australian Radiation Protection and Nuclear Safety Agency: What is ionising radiation? Available from: https://www.arpansa.gov.au/understanding-radiation/what-is-radiation/ionising-radiation
3. Bushberg JT, Seibert JA, Leidholdt EM Jr, Boone JM. The Essential Physics of Medical Imaging, Third Edition, 2012. Lippincott Williams & Wilkins, Philadelphia, PA, USA.
4. Hamada N and Fujimichi Y. Classification of radiation effects for dose limitation purposes: history, current situation and future prospects. J Radiat Res July 2014; 55(4):629-640. Available from: https://academic.oup.com/jrr/article/55/4/629/930449
5. Shah DJ, Sachs RK, and Wilson DJ. Radiation-induced cancer: a modern view. Br J Radiol, 2012; 85 (1020): e1166-e1173. Available from https://www.birpublications.org/doi/10.1259/bjr/25026140
6. Radiopaedia. Law of Bergonié and Tribondeau: Radiopaedia; 2019. Available from: https://radiopaedia.org/articles/law-of-bergonie-and-tribondeau
7. National Research Council (US) Committee on the Biological Effects of Ionizing Radiation (BEIR V). Health Effects of Exposure to Low Levels of Ionizing Radiation: Beir V. Washington (DC): National Academies Press (US); 1990. Available from: https://www.ncbi.nlm.nih.gov/books/NBK218704/ doi: 10.17226/1224
8. ICRP. Occupational Intakes of Radionuclides: Part 1. London, UK: ICRP Publications; 2015. 190 p. Available from https://journals.sagepub.com/doi/pdf/10.1177/ANIB_44_2
9. Watson S, Jones A, Oatway W and Hughes J. Ionising Radiation Exposure of the UK Population: 2005 Review. UK: HPA Radiation Protection Division; 2005. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/340209/HpaRpd001.pdf
10. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and Effects of Ionizing Radiation. Report to the General Assembly with Scientific Annexes. New York, USA; 2008. 179p. Available from: https://www.unscear.org/unscear/en/publications/2008_1.html
11. ICRP. The 2007 Recommendations of the International Commission on Radiological Protection. London, UK: ICRP Publication 103; 2007. Available from: https://www.icrp.org/publication.asp?id=ICRP%20Publication%20103
12. Skinner S. Radiation Safety. Australian Family Physician. 2014 Jun; 42(6):387-389. Available from: https://www.racgp.org.au/afp/2013/june/radiation-safety
13. World Federation of Societies of Anaesthesiologists. Ionising Radiation and the Anaesthetist. Hong Kong: WFSA; 2020. Available from: https://resources.wfsahq.org/atotw/ionising-radiation-and-the-anaesthetist/
14. ARPANSA. Radiation Protection in the Medical Applications of Ionizing Radiation. Canberra: Radiation Protection Series Publication; 2008 May. 44 p. Available from: https://www.arpansa.gov.au/sites/default/files/legacy/pubs/rps/rps14.pdf
15. Durack DP, Gardner AI, Trang A. Radiation Exposure During Anaesthetic Practice. Anaesth Intensive Care. 2006 Apr; 34(2):216-217
16. Wang R, Kumar A, Tanaka P, Macario A. Occupational Radiation Exposure of Anesthesia Providers: A Summary of Key Learning Points and Resident-Led Radiation Safety Projects. Seminars in Cardiothoracic and Vascular Anesthesia. 2017 Feb 12; 21(2):165-171.

17. The National Institute for Occupational Safety and Health. Aircrew Safety & Health. USA: CDC; 2017 May. Available from: https://www.cdc.gov/niosh/topics/aircrew/cosmicionizingradiation.html#fn01
18. Lim MK. Cosmic Rays: are air crews at risk? Occup Environ Med. 2002; 59:428-433.
19. Lee B, Kim MS, Eum D et al. The radiation environment of anaesthesiologists in the endoscopic retrograde cholangiopancreatography room. Sci Rep. South Korea: 2019 Jun; 9, 9124. Available from: https://doi.org/10.1038/s41598-019-45610-4
20. Mayr NP, Wiesner G, Kretschmer A, et al. Assessing the level of radiation experienced by anesthesiologists during transfemoral transcatheter aortic valve implantation and protection by a lead cap. PLOS ONE, Germany. 2019 Jan;14(1). E0210872. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6353158/
21. Anastasian ZH, Strozyk D, Meyers PM et al. Radiation Exposure of the Anesthesiologist in the Neurointerventional Suite. Anesthesiology 2011 Mar; 114(3):512-520. Available from: https://pubs.asahq.org/anesthesiology/article/114/3/512/11001/Radiation-Exposure-of-the-Anesthesiologist-in-the
22. Mohapatra A, Greenburg RK, Mastracci TM et al. Radiation exposure to operating room personnel and patients during endovascular procedures. J Vasc Surg 2013 Sep; 58(3):702-709. Available from: https://www.jvascsurg.org/article/S0741-5214(13)00330-3/fulltext.
23. Sharkey A, Gambhir P, Saraskani S, et al. Occupational radiation exposure in doctors: an analysis of exposure rates over 25 years. British J Radiol. 2021 Sep; 94(1127). Available from: https://www.birpublications.org/doi/full/10.1259/bjr.20210602
24. Vano E, Kleiman NJ, Duran A, et al. Radiation cataract risk in interventional cardiology personnel. Radiat Res 2010 Oct; 174(4):490-495. Available from: https://bioone.org/journals/radiation-research/volume-174/issue-4/RR2207.1/Radiation-Cataract-Risk-in-Interventional-Cardiology-Personnel/10.1667/RR2207.1.short
25. Della Vecchia E, Modenese A, Loney T, et al. Risk of cataract in health care workers exposed to ionizing radiation: a systematic review. Med Lav 2020 Aug; 111(4):269-284. Available from: https://www-ncbi-nlm-nih-gov.ezproxy.anzca.edu.au/pmc/articles/PMC7809955
26. Chodick G, Bekiroglu N, Hauptmann M, et al. Risk of cataract after exposure to low doses of ionizing radiation: a 20-year prospective cohort study among US radiologic technologists. Am J Epidemiol. 2008 Jul]; 168(6). 620-631. Available from: https//www.ncbi.nlm.nih.gov/pmc/articles/PMC2727195/
27. Clement CH, Stewart FA, Akleyev AV, et al. ICRP PUBLICATION 118: ICRP Statement on Tissue Reactions and Early and Late Effects of Radiation in Normal Tissues and Organs — Threshold Doses for Tissue Reactions in a Radiation Protection Context. Annals of the ICRP. 2012;41(1-2):1-322. Available from: https://journals.sagepub.com/doi/10.1016/j.icrp.2012.02.001
28. Ainsbury EA, Bouffler SD, Dorr W, et al. Radiation cataractogenesis: A review of recent studies. Radiation Research 2009 Jul 1; 172(1):1-9. Available from: https://bioone.org/journals/radiation-research/volume-172/issue-1/RR1688.1/Radiation-Cataractogenesis-A-Review-of-Recent-Studies/10.1667/RR1688.1.short
29. Rhea EB, Rogers TH, and Riehl JT. Radiation safety for anaesthesia providers in the orthopaedic operating room. Anaesthesia 2016 Apr: 71(4):455-461. Available from: https://associationofanaesthetists-publications.onlinelibrary.wiley.com/doi/10.1111/anae.13400
30. Mehlman CT and DiPasquale TG. Radiation exposure to the orthopaedic surgical team during fluoroscopy: "how far away is far enough?". J Orthop Trauma 1997 Aug; 11(6):392-398. Available from: https://journals.lww.com/jorthotrauma/Abstract/1997/08000/Radiation_Exposure_to_the_Orthopaedic_Surgical.2.aspx
31. Australian Radiation Protection and Nuclear Safety Agency: Radiation Protection in Diagnostic and Interventional Radiology. Canberra, Australia: ARPANSA; 2008 Jul. 77p. Available from: https://www.arpansa.gov.au/sites/default/files/legacy/pubs/rps/rps14_1.pdf
32. Cheon BK, Kim CL, Kim KR, et al. Radiation safety: a focus on lead aprons and thyroid shields in interventional pain management. Korean J Pain 2018 Oct; 31(4):244-252. Available from: https://www.epain.org/journal/view.html?volume=31&number=4&spage=244
33 Joeris A, Goldhahn S, Kalampoki V and Gebhard F. Intraoperative Radiation Exposure of Orthopaedic Surgeons – Mismatch Between Concerns and Protection. Occup Med Health Aff 2018 May; 6(2):273. Available from: https://www.omicsonline.org/open-access/intraoperative-radiation-exposure-of-orthopaedic-surgeonsmismatch-between-concerns-and-protection-2329-6879-1000273-101233.html.
34. Brun A, Alcaraz Mor R, Bourelly et al. Radiation Protection for surgeons and anesthetists: practice and knowledge before and after training. J Radiol Prot 2018 Mar; 38(1):175-188. Available from: https://iopscience.iop.org/article/10.1088/1361-6498/aa9dbd
35. NSW Environment Protection Authority (EPA). Radiation Guideline 5 - Recommendations for Radiation Safety Officers and Radiation Safety Committees. NSW EPA; 2022. Available from: https://www.epa.nsw.gov.au/your-environment/radiation/management-licence/info-radiation-management/rad-safety-officers#:~:text=The%20function%20of%20an%20RSO,the%20harmful%20effects%20of%20radiation.
36. ICRP. Annals of the ICRP: Publication 84. Pregnancy and Medical Radiation. Annals of the ICRP. 2000 (1): 9-13. Available from: https://journals.sagepub.com/doi/pdf/10.1177/ANIB_30_1
37. Average effective dose in millisieverts (mSv) from McCollough CH, Bushberg JT, Fletcher JG, Eckel LJ. Answers to common questions about the use and safety of CT scans. Mayo Clin Proc. 2015;90(10):1380-92

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100 years of insulin: Everything old is new again

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INTRODUCTION

2023 is the centenary of the commercial introduction of insulin for the treatment of diabetes. Along with paracetamol and aspirin, it is one of few drugs that remains a mainstay of modern medicine following more than 100 years of use. Insulin is frequently prescribed, or its administration modified, by anaesthetists in everyday practice. Furthermore, based on estimates of population data, 0.44% of people reading this chapter are likely to be type 1 diabetics, 3.1% of those over age 50 are type 2 diabetics requiring insulin, and on retirement, 3.8% may require insulin.[1-3] As a drug, insulin has a history that makes it significant and relevant to all clinicians; its development, introduction into clinical practice, changes in pharmaceutics (and therefore pharmacodynamics), and method of delivery have all evolved to ensure its continued use. In addition to that, it is one of the few drugs that resulted in a remarkable decrease in morbidity and mortality. In this chapter we review the development of the drug and the unusual circumstances surrounding its commercial release. We will also be looking at the changes made to insulin over time, allowing it to serve as an example of the value in continual reassessment of the pharmacology of commonly used drugs to enable optimal usage.

THE DEVELOPMENT OF INSULIN

Although the first recorded clinical description of diabetes occurs in the Ebers Papyrus (c 1550 BCE), it was the development of histology, made possible by improvement in microscope technology in the 1850s, that allowed for the discovery of pancreatic islets by Langerhans in 1869.[4] By 1901 Eugene Opie had demonstrated a connection between islet damage and diabetes, and by 1920 several scientists had managed to develop pancreatic extracts to reduce hyperglycaemia, these developments were however not easily translated into clinical practice.[5]

In Toronto, in the northern hemisphere summer of 1921, the successful extraction and administration of insulin occurred. There are several factors that led to this success, among others the sheer determination of those in the Toronto Laboratory. This well-funded laboratory was equipped with senior staff offering their guidance that led to significant improvements in the measurement of blood glucose.[6] The last mentioned allowed for a more accurate determination of the effects of proposed treatments for hyperglycaemia, a significant advantage over previous researchers. The discovery was a true team effort; in the efforts of orthopaedic surgeon Frederick Banting and Charles Best (laboratory assistant and medical student) to produce animal pancreatic extracts, the advice of Professor of Physiology John McLeod for preservation techniques, and biochemist James Collip in the purification of insulin. Although the chemical structure was yet to be determined, McLeod called the substance insulin, derived from the Latin word for island *insula*, referencing the islets of Langerhans.

Unfortunately, the relationships between the senior researchers Banting and McLeod became strained to the extent of great hostility, which is well documented.[6] This peaked when the Nobel Prize was awarded to them, and Banting originally refused to accept the award as Best was not acknowledged. Fortunately, this animosity did not prevent the discovery of insulin.

THE RAPID CLINICAL RELEASE OF INSULIN – A GIFT TO THE WORLD

Two days after the successful isolation of insulin in January 1921, the University of Toronto's wholly owned Connaught Institute signed an agreement with Banting, Best, Collip and Macleod for the production of insulin. The increasing need for a large-scale production however saw this arrangement unable to provide the amount of insulin required.[6] This necessitated a commercial agreement with a commercial manufacturer, but this agreement was for one year only. With the significant prevalence of diabetes, the discovery of insulin had the potential to reap large financial benefits for its discoverers. It has been documented that two of the physicians involved in its development, Banting and Macleod, were concerned that patenting insulin may reduce the availability of insulin worldwide.[7] However, in the absence of a patent, others would be free to patent and manufacture the discovery, with potential significant financial gains at the expense of widespread availability. Banting famously declared that "insulin does not belong to me, it belongs to the world".[8]

Banting, Best and Collip transferred their patent rights for the purification method to the University of Toronto for one dollar each, after which the university filed the application for the patent, which prevented the discovery's exploitation by a single entity. The University of Toronto then licensed the sale of insulin in North America and granted the patent rights to non-profit organisations in other countries.[7]

The discovery, rapid release and widespread availability of insulin, "gift to the world", stands in stark contrast to the situation surrounding the patent for early HIV (human immunodeficiency virus) infection therapy. In the era of the COVID-19 pandemic, there has been continued discussion of the role of patents in diagnosis and therapy, as well as the need for the widespread availability of medications that includes economically developing nations.[9]

INSULIN PRESCRIPTION – THE CHALLENGE OF DOSING

Unlike many other pharmacological agents used to manipulate physiological parameters, insulin may be challenging to prescribe and administer effectively. Normal physiology dictates that insulin is secreted by pancreatic islet beta cells in response to elevated blood glucose levels. This process is highly regulated by a multitude of complex biological systems including transcription factors, autonomic innervation, and other hormones (such as glucagon-like peptide-1, adrenaline and insulin itself).[10] Insulin is stored and stabilised in the pancreas in the form of hexamers – units of six insulin molecules connected with hydrogen bonds and zinc ions – which readily dissociate into biologically active, rapidly-absorbed monomers for use in cellular glucose uptake upon release.

Both hyper- and hypoglycaemia are associated with a variety of medical complications, the use of insulin as a treatment for diabetes mellitus thus aims to target near-normal blood glucose levels – approximately 4-10 mmol/L. Monitoring blood glucose as an indicator for effective treatment is, however, a challenge in itself. Traditional finger-prick testing can only be undertaken a few times a day in a practical manner, each requiring a separate blood lancet and sample. These discrete readings may pose a challenge to the clinician to accurately predict glucose trends and thus difficulties in safely prescribing insulin doses. Likewise, many variables affect how a patient processes exogenous insulin at any particular time: dietary intake, physical activity, concurrent illnesses, body temperature, blood flow to the injection site, lipodystrophy and the development of insulin resistance, to name a few.[11]

Prior to the development of accurate home and hospital glucose monitoring systems, a large margin of error existed when it came to insulin prescriptions. This was detrimental given the hazardous consequences of hypo- and hyperglycaemia. Insulin dosing had to err on the side of safety (avoiding hypoglycaemic episodes), which naturally gravitated towards sub-optimal management of diabetes. This necessitated the improvement in glucose monitoring systems, insulin formulations and delivery systems to refine the ability to mimic physiological endogenous insulin secretion.

INITIAL CHANGES IN INSULIN PREPARATIONS

Initial insulin preparations were crude by today's standards, being prepared from bovine and porcine pancreases. Although there are amino acid differences between the above mentioned animal and human insulin, the pharmacodynamic and pharmacokinetic effects are remarkably similar. However, animal insulins are exogenous, and long-term insulin administration was associated with the development of anti-insulin antibodies, insulin resistance and lipoatrophy in a significant proportion of patients.[12]

In the 1970s and 1980s, improvements in processing and chemical techniques allowed for the development of modified animal insulins. The modifications resulted in insulins which were free of proinsulin and other immunogenic polypeptides, also more closely resembling the amino acid sequencing of human insulin.[13] By 1982 the discovery of the gene for human insulin and the development of recombinant DNA technology

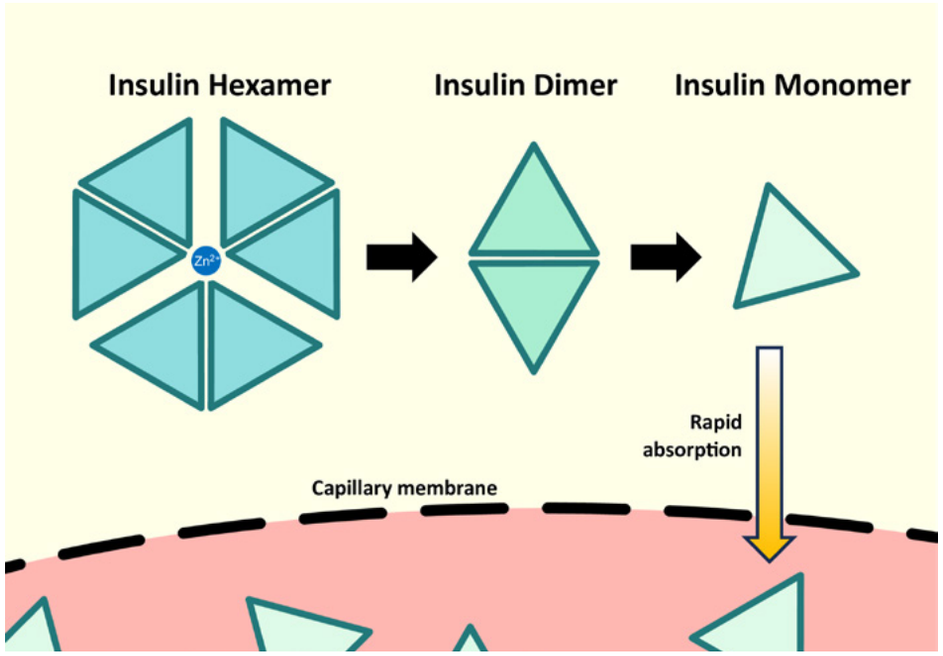
allowed for the production of biosynthetic insulin, which has superseded animal insulin. Interestingly, human insulin is also associated with development of anti-insulin antibodies, but these are generally in low titres and are clinically insignificant.[5,13]

INSULIN ANALOGUES

Insulin analogues are insulin molecules in which, by means of recombinant DNA and genetic engineering technology, changes are made to the amino acid structure to result in pharmacokinetic and pharmacodynamic properties that differ from the original molecule. The biological properties and stability of the insulin molecule is however preserved.[14] The development of different analogues had made it possible for the development of intermittent insulin dosing allowing for a closer imitation of the normal physiological variability in insulin secretion.

As mentioned before, insulin is stored as hexamers which dissolve into active molecules in the blood stream upon release (see Figure 1). The time effects of rapid acting insulins are facilitated either by altering the molecule by one or two amino acids to reduce the strength of the interactions that hold insulin molecules together, or by formulating the molecule in a monomeric/dimeric state, removing the time delay associated with hexamer dissolution.[14] Varying the insulin formulation and thus the molecule to affect hexamer formation is the key to speeding or slowing the absorption of injected insulin into the circulation. Examples of currently prescribed insulin analogues include intermediate acting insulin glargine (an example being Optisulin®), and rapid acting insulin lispro (Humalog®), and insulin aspart (Novorapid®).

Figure 1. Dissociation of insulin hexamers into rapidly-absorbed monomers



INNOVATIVE DELIVERY SYSTEMS

Traditionally, exogenous insulin has been administered via subcutaneous injection – a reliable technique that is still used commonly today. Subcutaneous insulin can be considered the gold-standard route of insulin delivery. Plunger syringes were associated with inaccurate dosing (due to syringe dead space) and a negative psychological impact, thus modern insulin pens were developed with smaller needles to provide a more convenient, precise and flexible way to administer specific doses.[15,16] Subcutaneous administration however is associated with adverse effects including lipodystrophy, scar formation, oedema and allergy symptoms, leading to investigations for improved methods of delivery.

Oral insulin has shown to be an ineffective alternative due to issues with poor absorption and enzymatic proteolysis leading to low bioavailability.[17] Although pulmonary delivery of insulin was first unsuccessfully trialled in 1924, modern development of inhaled insulin was made possible by improvements in aerosolised delivery systems and particle pharmacology.[18] Inhaled insulin is associated with faster absorption, peak concentration,

and more rapid metabolism. It is licensed in the US and has been used in the UK in select patient subgroups (but not in Australia or New Zealand), albeit with a shaky start. The first approved product (Exubera®) was withdrawn from the market in 2007 due to risks of hypoglycaemia, and the only remaining product (Afrezza®) faces limitations in acceptance when compared to the more established subcutaneous insulin.[19] Despite the theoretical benefits of this route of administration, inhaled insulin has not penetrated the commercial insulin market to a significant extent. The reasons are multifactorial; the perceived risks of altered respiratory function, the lack of insurance coverage in the US, and the concurrent development of continuous delivery systems that allow for insulin administration to more closely match that of normal physiology. Despite the low uptake, there is continued research into this mode of delivery, including the potential for vibrating mesh technology (nebulisers), especially for type 2 diabetics.[20]

Insulin pumps are portable devices that provide an uninterrupted infusion of insulin, reducing the need for repeated injections. This is termed "Continuous Subcutaneous Insulin Infusion" (CSII), and the initially introduced systems supplied insulin at a steady basal rate with additional user-initiated bolus doses. Introduced in the 1960s, they broadly are comprised of an insulin reservoir and infusion set.[16] Pumps often take on the form of a wearable electronic device (which stores the insulin and controls the rate of infusion) connected to a subcutaneous cannula within the infusion set. However, patch pumps (such as the Omnipod DASH® or Accu-Chek® Solo available in Australian and New Zealand markets) combine the two components into a single unit that eliminates the need for connective tubing, attaching to the skin with an adhesive and improving freedom of movement for patients.[21]

By themselves, pumps rely entirely on user input to determine the rate and timing of insulin doses, especially mealtime boluses. The development of continuous glucose monitoring (CGM) systems has opened up the possibility of allowing pumps to auto-regulate insulin dosing by providing ongoing blood glucose level feedback, helping to alleviate the issues associated with individual finger-prick testing. Dexcom, Medtronic and Abbott are among some of the medical technology companies that offer CGM devices that attach externally for 1-2 weeks and transmit data wirelessly to smartphones through Bluetooth scanning (or other similar digital connection).[22] While not approved in Australia or New Zealand as yet, long-term implantable devices in the upper arm or abdominal fascia that stay in situ for over six months provide a glimpse into the future of CGM, and have been introduced into clinical practice in other countries.[23]

Automated insulin delivery systems have been a breakthrough in the management of type 1 diabetes, aiming to function as an "artificial pancreas" that responds intelligently to blood glucose levels. They incorporate three components: an insulin pump, a CGM, and an algorithm that communicates information between the two. The first commercial device emerged in the late 1970s in the form of the Biostator – a bulky ventilator-sized machine that was for inpatient use that relied on intravenous glucose sensing and insulin infusion.[24] Since then, many refinements have been made over the years, both to the equipment as well as the algorithms, improving their ability to extrapolate glucose patterns and predict hypoglycaemia. A true closed-loop system that requires no external input is still in only trial-stage technology, but several hybrid closed-loop (HCL) devices exist that are partially automated, they still require user input for factors such as insulin-carbohydrate ratio and insulin action time. Examples of portable HCL devices currently commercially available in Australia and New Zealand are the Medtronic MiniMed™ 780G and the Tandem t:slim X2™ pump. Trials have demonstrated effective glycaemic control with these systems, and they remain popular options for type 1 diabetics to this day.[25,26]

Automated insulin delivery (AID) systems are recommended for all type 1 diabetics. They are associated with significant improvements in quality of life, a reduced diabetes management burden to patients and their families and are safe and effective in helping patients achieve their long-term glycaemic goals while reducing hypoglycaemia risk.[27] Despite the improved technology and advantages, patients still require basic diabetic management skills to ensure optimal results, and it may not be suitable for all patients.

CHANGES IN PERIOPERATIVE GLYCAEMIC MANAGEMENT

In an intraoperative setting, anaesthetists aim to regulate blood glucose levels between 5-10 mmol/L^{-1} (depending on various protocols) to avoid the increased morbidity and mortality associated with hypoglycaemia, and the risk of nosocomial infection associated with higher blood glucose levels.[28] While more liberal intraoperative glucose control ranging up to 12 mmol/L^{-1} allows anaesthetists to err on the side of safety and lowers the medication burden on the patient, it is associated with higher short-term mortality and postoperative complications in both diabetic and non-diabetic patients.[29] Tighter control is therefore desirable, this however requires more attentive glucose monitoring to avoid hypoglycaemia.

The relatively recent introduction of AID systems into society has significant potential to change our approach to perioperative glycaemic management. As detailed above, they can autonomously monitor blood glucose and self-initiate insulin administration, theoretically making it easier to maintain tight glycaemic control

intraoperatively. While research is still somewhat limited, initial trials on the perioperative use of AID systems have been promising by demonstrating their ability to maintain patients in a safe glucose range.[30,31]

Current approaches to CSII (which also apply to AID systems) suggest re-siting the infusion set the day before surgery in an area away from the operative field but still accessible to the anaesthetist, such as the abdomen or thigh (depending on the operation). There are still limitations to insulin pumps intraoperatively though. They are not appropriate for every procedure: emergency and protracted surgeries provide logistical barriers in managing glucose with the pump's supply of insulin, and radiological intervention may alter the device's ability to function. In these cases, disconnection is recommended with reversion to the 'intraoperative gold standard' of intravenous insulin infusion.[32] However, the possibility of continuing the use of AID systems for shorter and/or elective procedures provides an exciting area for further investigation in the future.

CONCLUSION

Compared with other medical specialties, anaesthesia makes use of a relatively narrow spectrum of medications, many of which have had a long history of use in the specialty. As one of the few medical specialties in which extensive postgraduate education in clinical pharmacology occurs, anaesthetists have the unique opportunity to consider new and alternate methods of delivery of the drugs that we administer. That a drug such as insulin has retained its place in clinical practice through these changes is a reminder that there is always room for improvement and that change is necessary in our pursuit to improve the quality of life of patients. In the absence of a functioning crystal ball, it is difficult to make predictions about the long-term future of drugs, but in the absence of a cure for diabetes, it is likely that in another one hundred years insulin will continue to be in use, albeit in different molecular forms and with delivery systems that will continue to have evolved.

REFERENCES

1. Australian Institute of Health and Welfare. Diabetes: Australian facts [Internet] Canberra (ACT): Australian Institute of Health and Welfare; 2023 [cited 28 May 2023] Available from: https://www.aihw.gov.au/reports/diabetes/diabetes/contents/about
2. Australian Bureau of Statistics. Diabetes [Internet] Canberra (ACT): Australian Bureau of Statistics; 2022 [cited 28 May 2023] Available from: https://www.abs.gov.au/statistics/health/health-conditions-and-risks/diabetes/latest-release
3. Ministry of Health. Diabetes Data and Stats [Internet] Wellington NZ: Ministry of Health; 2022 [cited 28 May 2023] Available from: https://www.health.govt.nz/nz-health-statistics/health-statistics-and-data-sets/diabetes-data-and-stats
4. King KM, Rubin G. A history of diabetes: from antiquity to discovering insulin. Br J Nurs. 2003 Oct 9-22;12(18):1091-5.
5. Vecchio I, Tornali C, Bragazzi NL, Martini M. The Discovery of Insulin: An Important Milestone in the History of Medicine. Front Endocrinol (Lausanne). 2018 Oct 23; 9:613.
6. Tan SY, Merchant J. Frederick Banting (1891-1941): Discoverer of insulin. Singapore Med J. 2017 Jan; 58(1):2-3.
7. Hoen E, Berger J, Calmy A, Moon S. Driving a decade of change: HIV/AIDS, patents and access to medicines for all. J Int AIDS Soc. 2011 Mar 27; 14:15.
8. Canadian Medical Hall of Fame. Sir Frederick Banting, M [Internet] London Canada. Canadian Medical Hall of Fame. Date Unknown [Cited 29 May 2023] Available from: https://cdnmedhall.ca/laureates/frederickbanting
9. Alpha Lee, John Chodera and Frank von Delft Why we are developing a patent-free COVID antiviral therapy. [Internet] Rockville MD American Society for Biochemistry and Molecular Biology. 2021 Dec 19 [cited 28 May 2023] Available from: https://www.asbmb.org/asbmb-today/opinions/121921/a-patent-free-covid-antiviral
10. Tokarz VL, MacDonald PE, Klip A. The cell biology of systemic insulin function. J Cell Biol. 2018 Jul 2; 217(7):2273-2289.
11. Binder C, Lauritzen T, Faber O, Pramming S. Insulin pharmacokinetics. Diabetes Care. 1984 Mar-Apr; 7(2):188-99.
12. Richter B, Neises G. 'Human' insulin versus animal insulin in people with diabetes mellitus. Cochrane Database Syst Rev. 2005 Jan 25; 2005(1):CD003816.
13. Fineberg SE, Kawabata TT, Finco-Kent D, Fountaine RJ, Finch GL, Krasner AS. Immunological responses to exogenous insulin. Endocr Rev. 2007 Oct; 28(6):625-52.
14. Hirsch IB, Juneja R, Beals JM, Antalis CJ, Wright EE. The Evolution of Insulin and How it Informs Therapy and Treatment Choices. Endocr Rev. 2020 Oct 1; 41(5):733–55.
15. Hall GH, Thompson CJ, Palmer A. Danger of dead space in U100 insulin syringes. Br Med J (Clin Res Ed). 1984; 288(6413):284-5.
16. Kesavadev J, Saboo B, Krishna MB, Krishnan G. Evolution of Insulin Delivery Devices: From Syringes, Pens, and Pumps to DIY Artificial Pancreas. Diabetes Ther. 2020; 11(6):1251-69.
17. Wong CY, Martinez J, Dass CR. Oral delivery of insulin for treatment of diabetes: status quo, challenges and opportunities. J Pharm Pharmacol. 2016; 68(9):1093-108.
18. Cunningham SM, Tanner DA. A Review: The Prospect of Inhaled Insulin Therapy via Vibrating Mesh Technology to Treat Diabetes. Int J Environ Res Public Health. 2020 Aug 10; 17(16):5795.
19. Oleck J, Kassam S, Goldman JD. Commentary: Why Was Inhaled Insulin a Failure in the Market? Diabetes Spectr. 2016; 29(3):180-4.

20. Santos Cavaiola T, Edelman S. Inhaled insulin: a breath of fresh air? A review of inhaled insulin. Clin Ther. 2014; 36(8):1275-89.
21. Ginsberg BH. Patch Pumps for Insulin. J Diabetes Sci Technol. 2019; 13(1):27-33.
22. Olczuk D, Priefer R. A history of continuous glucose monitors (CGMs) in self-monitoring of diabetes mellitus. Diabetes Metab Syndr. 2018; 12(2):181-7.
23. Chen C, Zhao XL, Li ZH, Zhu ZG, Qian SH, Flewitt AJ. Current and Emerging Technology for Continuous Glucose Monitoring Sensors (Basel). 2017; 17(1): 182.
24. Clemens AH, Chang PH, Myers RW. The development of Biostator, a Glucose Controlled Insulin Infusion System (GCIIS). Horm Metab Res. 1977; Suppl 7:23-33.
25. Silva JD, Lepore G, Battelino T, Arrieta A, Castañeda J, Grossman B, Shin J, Cohen O. Real-World Performance of the MiniMed™ 780G System: First Report of Outcomes from 4120 Users. Diabetes Technol Ther. 2022 Feb; 24(2):113-119.
26. Berget C, Lange S, Messer L, Forlenza GP. A clinical review of the t:slim X2 insulin pump. Expert Opin Drug Deliv. 2020 Dec;17(12):1675-1687.
27. Burnside MJ, Lewis DM, Crocket HR, Meier RA, Williman JA, Sanders OJ, Jefferies CA, Faherty AM, Paul RG, Lever CS, Price SKJ, Frewen CM, Jones SD, Gunn TC, Lampey C, Wheeler BJ, de Bock MI. Open-Source Automated Insulin Delivery in Type 1 Diabetes. N Engl J Med. 2022 Sep 8; 387(10):869-881.
28. Crowley K, O Scanaill P, Jermanades J, Buggy DJ. Current practice in the perioperative management of patients with diabetes mellitus: a narrative review. Br J Anaes 2023; Advance online publication.
29. Kang ZQ, Huo JL, Zhai XJ. Effects of perioperative tight glycemic control on postoperative outcomes: a meta-analysis. Endocr Connect. 2018 Dec 1; 7(12):R316-R327.
30. Kaddoum R, Khalili A, Shebbo FM, Ghanem N, Daher LA, Ali AB, Chehade NEH, Maroun P, Aouad MT. Automated versus conventional perioperative glycemic control in adult diabetic patients undergoing open heart surgery. BMC Anesthesiol. 2022 Jun 16; 22(1):184.
31. Becker D, Eshmuminov D, Keller R, Mueller M, Bautista Borrego L, Hagedorn C, Duskabilova M, Tibbitt MW, Onder C, Clavien PA, Rudolf von Rohr P, Schuler MJ, Hefti M. Automated Insulin Delivery - Continuous Blood Glucose Control During Ex Situ Liver Perfusion. IEEE Trans Biomed Eng. 2021 Apr; 68(4):1399-1408.
32. Partridge H, Perkins B, Mathieu S, Nicholls A, Adeniji K. Clinical recommendations in the management of the patient with type 1 diabetes on insulin pump therapy in the perioperative period: a primer for the anaesthetist. Br J Anaesth. 2016 Jan; 116(1):18-26.

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Adult perioperative risk stratification

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BACKGROUND

Risk tools can help quantify risk and guide informed decision making for patients, anaesthetists, perioperative physicians and surgeons. They can be used to estimate both mortality and morbidity. There is an ethical imperative to provide patients with an estimation of risk of adverse outcomes during the surgical and anaesthesia consent process. Risk tools can also help to identify high risk patients that may benefit from increased postoperative surveillance and monitoring, allowing appropriate allocation of limited hospital resources with the potential benefit of mitigating morbidity and mortality.[1]

An international prospective study as part of the Sprint National Anaesthesia Project, SNAP-2 collaborative, showed that clinician judgement was commonly used as the only means to predict surgical risk. In this study of 22,631 patients, it was the sole documented tool for risk assessment in 79% of patients.[2] The study showed that the use of a risk prediction tool in conjunction with clinical judgement can improve estimation of perioperative risk.[2]

Numerous surgical risk assessment tools primarily focus on predicting 30-day mortality following surgery. However, there is a growing recognition that evaluating risk beyond this timeframe is crucial, particularly in terms of long-term quality of life outcomes. For instance, the New Zealand based nzRisk tool goes beyond 30-day mortality and incorporates the risk of mortality up to two years postoperatively.[3] Further, informing patients about likely short and long-term quality of life is paramount. Although the American College of Surgeons National Surgical Quality Improvement Program Surgical risk calculator (ASA NSQIP ACS) offers valuable insights into mortality and morbidity outcomes in the US health system, there are limitations when applying this risk tool to the Australian and New Zealand population. Additionally, there is also a lack of data linking risk tools to a reduction in morbidity and mortality and to improvements in patient centred outcomes. Further research is therefore imperative in this area to provide an evidence base upon which healthcare providers can appropriately address the quality of life outcomes that may hold greater importance for many high risk patients. Further research is also needed to determine the relationships between risk quantification tools and specific modifications of care to reduce morbidity and mortality.

THE IDEAL RISK TOOL

An ideal surgical risk prediction tool would have a number of properties, including:

Statistical properties

1. High accuracy – The tool should be able to accurately predict the likelihood of the outcome.[4]
2. Good discrimination – Discrimination is a combined measure of the sensitivity and the specificity of a risk prediction tool. It indicates that a tool can accurately distinguish between patients who do and do not experience the outcome of interest. Discrimination is measured by the area under the receiver operating curve (AUROC) or c-statistic.[4]

3. Good calibration – The tool should be well calibrated, meaning that the predicted probabilities of the outcome match the observed outcomes over a range of values. This is commonly measured by the Hosmer-Lemeshow test or Brier score.[4]
4. Locally validated – The tool should be validated in the population (country or health system) of interest.[4]

Further properties

5. Wide applicability – The ideal tool would be applicable to a wide range of surgical procedures and patient populations.
6. Versatile – In addition to mortality prediction, the tool should be able to stratify risk of major morbidity.
7. Simple and easy to use – The tool should be easy to use, with a clear and intuitive interface.[5]
8. Parsimonious – The ideal tool would require the user to input the smallest number of variables that will provide an accurate prediction of the outcome.
9. Transparent and explainable – The tool should be transparent, with the ability to provide information on how it arrived at a particular prediction.
10. Regularly updated – The tool should be recalibrated with the most recent population data to ensure it remains accurate and reliable.[5]
11. Compliance with data privacy and security regulations – The tool should comply with any relevant regulations, data security and privacy policies.

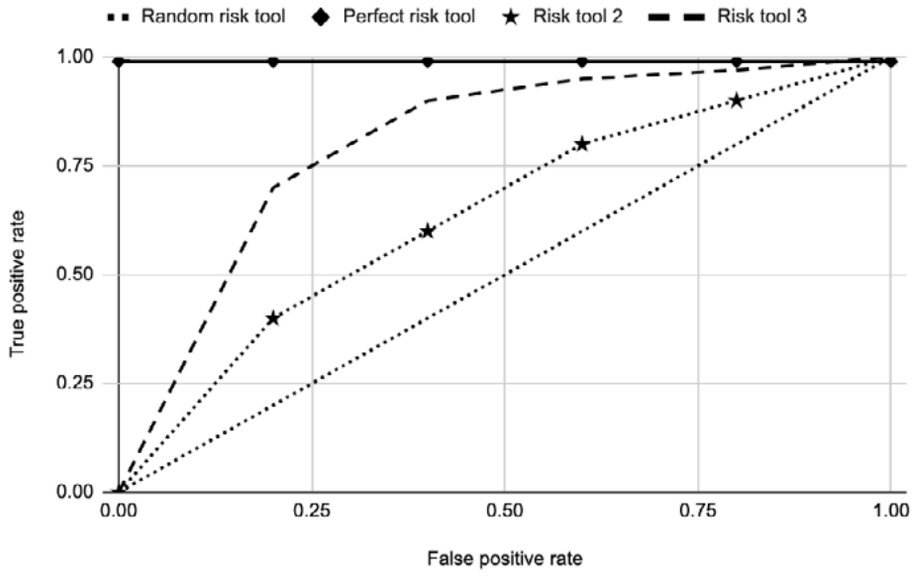
DISCRIMINATION VERSUS CALIBRATION

Discrimination is the ability of a risk prediction tool to differentiate between patients who do or do not get the outcome of interest (for example, death within 30 days postoperatively). It is a combined measure of the sensitivity and the specificity of a risk prediction tool. When sensitivity, or the true positive rate (y-axis) and 1-specificity or the false positive rate (x-axis), are plotted on a graph, the area under this curve is called the area under the receiver operating curve (AUROC). The c-statistic is an alternative term for the same metric.

An AUROC or c-statistic of greater than 0.9 is considered to be excellent.[6] A value of 0.7 - 0.89 is considered good[6], while a value of less than 0.7 is considered poor.[6] High performing surgical risk prediction tools have an AUROC or c-statistic of around 0.9 (for example, Surgical Outcomes Risk Tool (SORT) (0.91[7]), nzRISK (0.921[3]). A visual representation emphasising variations in calibration is provided in Figure 1.

Figure 1. Graph showing different models and discrimination

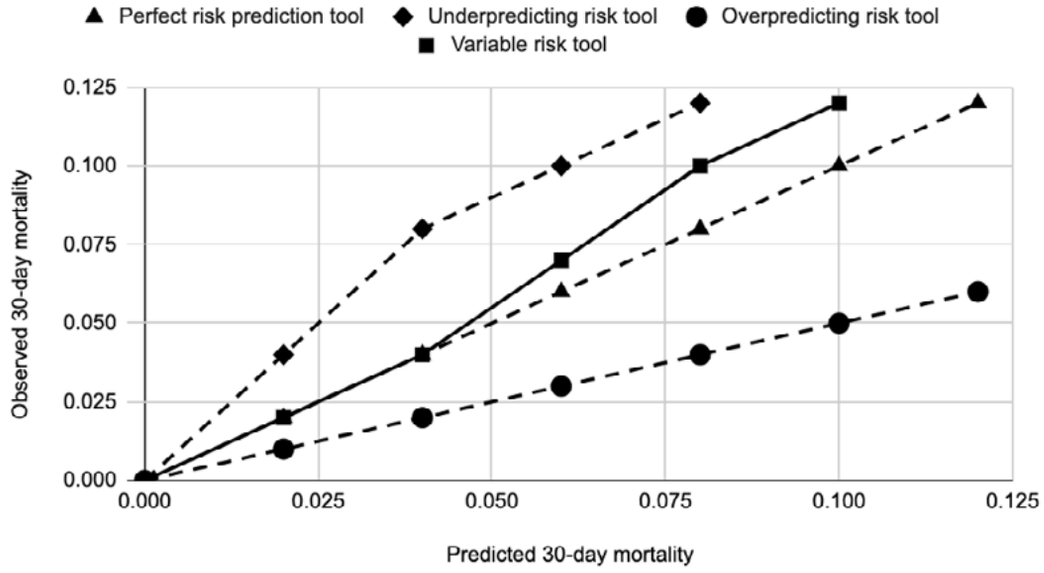
Calibration compares the expected outcomes predicted by the prediction tool to the observed outcomes from the statistical model development data set. A perfect prediction tool would have identical predicted and



observed outcomes. Calibration curves therefore show how predicted risk differs from the observed risk over the range of different risk levels. For example a risk tool may consistently over predict or under-predict mortality. Alternatively, it may predict mortality well in low risk but underestimate risk in high risk surgical patients. A visual representation emphasising variations in calibration is provided in Figure 2.

Figure 2. Graph showing different risk models and calibration

When a risk prediction tool is developed, the data set is split randomly into a model development dataset and



a test dataset. The statistical model is developed on the development dataset, then applied to the test dataset in a process called internal validation. Internal validation confirms that the model is valid in the population from which the dataset originated. Model validity is strengthened by external validation, which may be temporal or geographic. In temporal external validation, the model is applied to the same or a similar dataset at a future point in time. In geographical external validation, the model is applied to a different geographical region which may have different underlying population or healthcare system characteristics. Risk prediction tools should undergo external validation. Models should be externally validated before use in a different geographical or healthcare setting.[3]

COMMONLY USED PERIOPERATIVE RISK TOOLS

There is a plethora of perioperative risk tools which have been used and are currently used.[8] The most commonly used tools in the Second National Anaesthesia Project: Epidemiology of Critical Care provision after Surgery (SNAP-2: epiCCS) study were American Society of Anaesthesiologists – Physical Status (ASA-PS) (38.1%), Portsmouth Physiological and Operative Severity Score for the Enumeration of Morbidity and Mortality (P-POSSUM) (6.2%) and Surgical Outcome Risk Tool (SORT) (3.3%).[2] This article will aim to introduce some of these risk tools including their evidence basis for use in the Australia and New Zealand population. A comprehensive systematic review can provide further information on a wider range of risk tools for interested readers.[8]

American Society of Anesthesiologists – Physical Status (ASA-PS)

While the ASA-PS was not designed as a risk prediction score it is commonly used amongst those involved in the perioperative care of patients to convey risk.[2,9] A two-centre study[10] showed ASA-PS alone to have reasonable discrimination for mortality (AUROC 0.810 SE 0.044 confidence interval 0.792 - 0.828).

ASA-PS forms a part of many risk scoring systems that will be discussed in this article including SORT and nzRISK.

The American College of Surgeons National Surgical Quality Improvement Program Surgical Risk Calculator (ACS NSQIP SRC)

The ACS NSQIP SRC (NSQIP) was originally created in 2013[11] and subsequently updated with improved calibration in 2016[12] and 2021[13]. It has been developed from nearly 400 hospitals across the United States of America, based on data from 1,414,006 patients. The algorithm behind the risk calculator is not publicly available. Twenty-one variables are required to predict 30-day mortality and morbidity. The calculator requires the specific surgery to be entered. This tool does allow the medical practitioner to adjust the risk score if it is thought to have underpredicted the risk.

In the initial development, based on the population data described above, the model had excellent performance for mortality (AUROC = 0.944, Brier score = 0.011), and morbidity (AUROC = 0.816, Brier score = 0.069).[11]

A number of studies have been performed to investigate the accuracy of the NSQIP risk calculator in the Australian and New Zealand population with a range of results. A recent retrospective study of 200 patients undergoing plastic and reconstructive surgery at a public tertiary referral centre in New South Wales concluded that the NSQIP risk calculator was a poor predictor of postoperative complications (AUROC 0.699, Brier score = 0.087).[14] A retrospective study of 2321 patients undergoing all surgical procedures, performed at another public tertiary referral centre in New South Wales, showed the NSQIP risk calculator performed well at predicting mortality (AUROC 0.93) but performed less well at other morbidity outcomes (AUROC 0.71), calibration was not reported.[15] In a different public tertiary referral centre, again in New South Wales, a study involving a small cohort of 58 patients who met the selection criteria of high risk (mortality risk >5%) general surgical emergency procedures demonstrated that the NSQIP risk calculator held reasonable discrimination for mortality (c-statistic 0.835 95% confidence interval 0.654 - 0.977). Overall, the study found the risk tool overpredicted mortality (Brier score = 0.125). Analysis of secondary outcomes found the risk tool to be inaccurate. The authors ultimately concluded that there was "insufficient evidence to reject the ACS model."[16]

It is clear that NSQIP, in its current iteration, is not perfect for the Australian and New Zealand population given its inaccuracies both in broader surgical specialities and specific surgical specialties.

Surgical Outcome Risk Tool

The Surgical Outcome Risk Tool (SORT) is a risk prediction tool developed in the United Kingdom on a cohort of surgical patients undergoing inpatient non-cardiac and non-neurosurgery. The cohort also excluded obstetrics and transplant surgical patients. It was created as a result of data from the National Confidential Inquiry into Patient Outcome and Death (NCEPOD) audit "knowing the risk"[17]. It provides a risk of mortality based on 10 preoperative variables.

There are many advantages of the SORT. It is easily accessible online[18], it has a smartphone app[19] and it utilises preoperative variables. The ease of access and functionality allow it to be used by a range of perioperative physicians.

A number of international external validation studies of SORT have been conducted, including the Second National Anaesthesia Project: Epidemiology of critical care after surgery (SNAP-2: EpiCCS) study, the nzRISK study, and Australian external validation studies.

SNAP-2: EpiCCS (SNAP-2)

The SORT was evaluated in a cohort of 22,631 patients, encompassing individuals from the United Kingdom, Australia, and New Zealand, as part of the SNAP-2 project.[2] SNAP-2 was a prospective study conducted over a one-week duration, investigating mortality in patients undergoing inpatient surgery. The study involved 274 hospitals. Ethical approval was obtained to enrol all eligible patients during the designated week in the United Kingdom and New Zealand, as well as numerous regions of Australia. Comparative analysis was performed between clinical judgement, P-POSSUM, surgical risk score (SRS), and SORT. Table 1 presents the findings of this investigation. Notably, the combined utilisation of clinical judgement and SORT demonstrated superior discriminatory ability. It is important to note that all the assessed methods exhibited a tendency to overestimate risk of mortality within the study population.

Table 1. Area under the receiver operating curve (AUROC) adapted from results for different risk prediction tools in the SNAP-2: EpiCCS study[2]

Assessment tool	Discrimination (AUROC) for mortality
Clinical judgement alone	0.89
SORT	0.9
P-POSSUM	0.89
Surgical risk score	0.85
Clinical judgement and SORT	0.92

SORT = Surgical Outcomes Risk Tool
P-POSSUM = Portsmouth Physiological and Operative Severity Score for the Enumeration of Morbidity and Mortality

NEW ZEALAND

When the SORT was applied to the New Zealand population it provided good discrimination for 30-day predicted mortality but poor calibration.[3]

In the nzRISK validation study, data from the New Zealand National Minimum Data Set for patients having surgery between January 2013 and December 2014 was used. External validation of SORT was conducted on a cohort of 360,140 patients who underwent surgery during the study period. The findings revealed satisfactory discrimination with an AUROC of 0.906. Calibration was found to be poor, with calibration slope of 5.32. These results suggest that SORT may not be valid for use in this national surgical population.[3] A random 75% split of the New Zealand Minimum Data Set data was then used to develop the nzRISK model, which was validated in the remaining 25% of the data set.[3]

During internal validation of nzRISK, incorporation of sex and ethnicity variables, in addition to those used in SORT, was performed to assess 1-month, 1-year, and 2-year mortality outcomes. The results demonstrated excellent discrimination, with AUROC values of 0.921, 0.904, and 0.895, respectively. Furthermore, the calibration improved to 1.12, 1.02, and 1.02, respectively.[3] The ability to calculate mortality beyond 30 days is an additional benefit of this tool.

When nzRISK was tested on a Western Australian retrospective patient cohort it performed well for discrimination (AUROC 0.909) but was inferior to the SORT for calibration in this cohort of patients.[20]

AUSTRALIA

Further work has been conducted looking at the validity of the SORT at assessing 30-day mortality risk in Australia. An Australian external validation study looking retrospectively at 161,277 private healthcare patients[21] showed good discrimination (c-statistic 0.96). The SORT showed good calibration over the prediction range 0-10% but over-estimated mortality in the small cohort above 10% 30-day predicted mortality risk. The authors comment that the confidence interval did approach the calibration line. It should be noted that this private healthcare cohort had a low mortality rate of 0.2% indicating that this cohort of patients may not represent the general Australian population due to selection bias and classification bias. It may be prudent to include covariables such as private health insurance status and hospital setting in a risk prediction tool, considering the potential variations in perioperative mortality. Another retrospective study with over 44,000 patients looking at a tertiary hospital in Western Australia from 2014-2021 showed SORT to have the highest discrimination (AUROC 0.922). SORT also exhibited good calibration but consistently overpredicted 30-day mortality risk which increased with age of the patients. This study interestingly showed thresholds for the top decile (>3.92%) and second highest decile (1.52-3.92%) of predicted 30-day mortality risk. These deciles contributed 76% and 13% of the deaths respectively.[20]

These papers highlight how important it can be to ensure external validation of a risk prediction tool outside of its original population. Risk prediction tools may be internally valid but may not be externally valid. There is currently a risk prediction tool specific to the Australian population under development.

RISK TOOLS IN SPECIFIC SURGICAL POPULATIONS

Patients undergoing emergency laparotomy

Patients undergoing emergency laparotomy represent a high risk cohort. In the United Kingdom the national emergency laparotomy audit (NELA) has been running for nine years.

The NELA risk adjustment model was developed to enable hospitals to compare their outcomes in patients undergoing emergency laparotomies, taking into account the differences in patient risk profiles between hospitals. It recognises that one hospital may be treating a sicker cohort of patients compared to another hospital within a specific time frame. Consequently, the model allows for a fair assessment by adjusting for these differences, as higher mortality rates would be anticipated in the hospital with more high risk patients. The initial audit led to a drop in perioperative mortality for this high risk cohort[22], therefore the NELA risk tool has been adjusted using more recent data. Mortality from emergency laparotomies has dropped from 11.8% to 9.2%.[23] The current risk tool utilises data from almost 74,000 patients undergoing emergency laparotomies performed from 2016-2019. The risk tool has good discrimination (c-statistic 0.863) and adequate calibration.[24]

The risk tool is easily accessed with a website[25] and a free smartphone app[26]. Thirteen variables are required for the calculation. Compared to other tools, SORT requires 10, nzRisk requires 9 and ACS NSQIP SRC requires 21 variables.

Several Australian and New Zealand studies have examined the validity of the NELA score in Australasian patients, with variable results. The Australia and New Zealand Emergency Laparotomy (ANZELA) group investigated mortality among 2,799 patients across 26 hospitals in Australia and New Zealand. Mortality was found to be 7% in this cohort of patients. The NELA score predicted a 9% mortality rate (27,28). A smaller single centre study at University Hospital Geelong involving 285 patients observed a mortality rate of 6% compared to a NELA predicted mortality of 11%.[28,29]

A retrospective study performed at four Australian centres[30] identified 562 patients undergoing emergency laparotomies. The cohort had a 30-day mortality rate of 10.5%. The study found NELA to be sensitive (88.1%) at identifying high risk emergency laparotomy patients. The risk score managed to identify 52 of these patients who died as being high risk (defined as greater than 10% risk of 30-day mortality). The study found NELA to be comparable to ACS NSQIP SRC ($p = 0.18$) and P-POSSUM ($p = 0.07$).

A retrospective cohort study[31] performed at a single centre in Auckland, New Zealand, showed the NELA score compared favourably to other assessed risk scores (P-POSSUM, Acute Physiology and Chronic Health Evaluation (APACHE) and ACS NSQIP). The authors examined 758 cases retrospectively. They found a 30-day mortality in this cohort of 7.9%. The NELA score showed the highest discrimination with AUROC of 0.83. The NELA score was also found to be the best calibrated scoring system (7.4% v 7.9%, $p = 0.95$). The study found the other risk scores significantly overpredicted (P-POSSUM 13.4% and APACHE-II 14.2%, $p<0.001$) and underpredicted mortality (ACS NSQIP 5.4%, $p = 0.0023$). The study also showed that the addition of modified frailty index and nutritional status improved the discrimination of all the risk scores.

Patients with a hip fracture

The Nottingham Hip Fracture Score (NHFS) was developed in 2008 to predict 30-day mortality[32] in patients undergoing surgery for fractured hips. The tool was developed using a cohort of almost 5,000 patients from a single centre in Nottingham, United Kingdom. The original risk tool used seven preoperative variables and had an AUROC of 0.719. Subsequently the risk tool was updated in 2015. A 2011 study showed that the NHFS was useful at delineating low risk (NHFS less than or equal to 4) or high risk (NHFS greater than or equal to 5) and predicted an increased risk of 30-day and one year mortality.[33] The NHFS has been further updated following subsequent studies in other centres.[34] The risk tool has had variable success when externally validated.[35-37]

One systematic review of different risk tools in patients with hip fractures showed the NHFS compared well with other tools analysed.[38] One study examined the use of the NHFS in an Australian population. This single centre, public hospital, retrospective cohort study showed an AUROC of 0.760 (95% confidence interval 0.631 - 0.888) in a cohort of 195 patients.[39] The advantages of this risk tool are that it is easy to access online[40], is quick to perform and all variables are objective and can be obtained preoperatively.

ENCOURAGING THE USE OF PERIOPERATIVE RISK TOOLS

Although there is currently no evidence that the use of risk tools improves perioperative outcomes, utilisation of perioperative risk prediction tools combined with clinical judgement, can be useful in identifying high risk patients.[2] It can also have a benefit in initiating conversations between specialties and improve shared decision making.[7]

Risk scoring adds objectivity to referrals and may improve communication about urgency of operations especially in the emergency setting. Finally risk scoring can help improve the consent process in both the elective and emergency setting.[7] Despite these advantages, risk tools were only used by 11% of clinicians in the SNAP2-EpiCCS study.[2]

Some strategies to increase the use of perioperative risk tools include:

Education

This can include quality improvement projects.[41] A quality improvement project undertaken in 15 Irish hospitals aimed to develop a nationwide surgical trainee-led quality improvement (QI) program to increase the use of perioperative risk scoring in patients undergoing emergency laparotomies. There was a successful increase in the use of perioperative risk scoring in emergency laparotomy patients (using NELA or P-POSSUM) from 0 to 11% during the initial exploratory phase and then 35 to 100% in the full implementation phase. Various strategies including regular emails, posters, instant messaging, and education via grand rounds were used to increase uptake.[41]

Changing attitudes of clinicians would also be an important element. A survey performed in the United States of America examining surgeons' use of perioperative risk tools found that attending surgeons were less likely to use risk tools and rely more on experience and literature. Resident surgeons were more likely to use a perioperative risk tool.[42]

Improving access to tools

In practice, integration into the electronic medical record and utilisation of portable electronic devices to access risk scoring apps (for example SORT) or websites such as MDCalc[43], may improve access to these tools in the perioperative period.

Mandatory risk scoring in documentation

Other strategies that could be used include a requirement for some objective documentation of risk assessment for all patients undergoing emergency surgery at the time of booking, allocation of space in the anaesthetic preassessment form for risk scoring and the use of risk scoring in perioperative high dependency/intensive care unit referrals.

RE-CALIBRATION

Postoperative mortality generally improves over time.[44] A Western Australian study[20] demonstrated how calibration of a risk prediction tool can degrade over time, moving from being very accurate in the development cohort to gradually over-predicting risk by increasing amounts as time passes. This study demonstrates the importance of regularly recalibrating risk prediction tools to ensure they remain valid in the target population.

THE FUTURE

The use of surgical risk prediction models is expected to continue to grow and evolve in the future, as advancements in data analytics, artificial intelligence and machine learning increasingly play a role in improving the development and application of these tools. With increasing amounts of perioperative data being collected and analysed, it is expected that their performance and applicability will continue to improve, helping to identify patients who are at a higher risk for complications and mortality. While the hope is that identifying high risk patients will enable healthcare providers to take steps to mitigate these risks, there is currently little evidence that identification of high risk patients can directly change perioperative outcomes. While it is relatively straightforward to develop or update a risk prediction model, the far greater challenge is to demonstrate that these models can impact outcomes, including patient centred outcomes. There is a need for national and international collaborations to investigate the impact of data-driven, risk stratified, perioperative care to improve perioperative outcomes, and this should be a priority for healthcare providers, payers, and patients.

REFERENCES

1. Swart M, Carlisle JB, Goddard J. Using predicted 30 day mortality to plan postoperative colorectal surgery care: a cohort study†. BJA Br J Anaesth. 2017 Jan 1;118(1):100–4.
2. Wong DJN, Harris S, Sahni A, Bedford JR, Cortes L, Shawyer R, et al. Developing and validating subjective and objective risk-assessment measures for predicting mortality after major surgery: An international prospective cohort study. PLOS Med. 2020 Oct 15;17(10):e1003253.
3. Campbell D, Boyle L, Soakell-Ho M, Hider P, Wilson L, Koea J, et al. National risk prediction model for perioperative mortality in non-cardiac surgery. BJS Br J Surg. 2019;106(11):1549–57.
4. Towards better clinical prediction models: seven steps for development and an ABCD for validation - PubMed [Internet]. [cited 2023 May 30]. Available from: https://pubmed.ncbi.nlm.nih.gov/24898551/
5. Clinical risk assessment tools in anaesthesia - PubMed [Internet]. [cited 2023 May 30]. Available from: https://pubmed.ncbi.nlm.nih.gov/33456869/
6. Sr M, Mg M, P D, Km R, Mp G. Risk stratification tools for predicting morbidity and mortality in adult patients undergoing major surgery: qualitative systematic review. Anesthesiology [Internet]. 2013 Oct [cited 2023 May 30];119(4). Available from: https://pubmed.ncbi.nlm.nih.gov/24195875/
7. Protopapa KL, Simpson JC, Smith NCE, Moonesinghe SR. Development and validation of the Surgical Outcome Risk Tool (SORT). Br J Surg. 2014 Dec;101(13):1774–83.
8. Reilly JR, Gabbe BJ, Brown WA, Hodgson CL, Myles PS. Systematic review of perioperative mortality risk prediction models for adults undergoing inpatient non-cardiac surgery. ANZ J Surg. 2021;91(5):860–70.
9. Horvath B, Kloesel B, Todd MM, Cole DJ, Prielipp RC. The Evolution, Current Value, and Future of the American Society of Anesthesiologists Physical Status Classification System. Anesthesiology. 2021 Nov 1;135(5):904–19.
10. Donati A, Ruzzi M, Adrario E, Pelaia P, Coluzzi F, Gabbanelli V, et al. A new and feasible model for predicting operative risk. Br J Anaesth. 2004 Sep;93(3):393–9.
11. Bilimoria KY, Liu Y, Paruch JL, Zhou L, Kmiecik TE, Ko CY, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. J Am Coll Surg. 2013 Nov;217(5):833-842.e1-3.
12. Liu Y, Cohen ME, Hall BL, Ko CY, Bilimoria KY. Evaluation and Enhancement of Calibration in the American College of Surgeons NSQIP Surgical Risk Calculator. J Am Coll Surg. 2016 Aug;223(2):231–9.
13. ACS Risk Calculator - Home Page [Internet]. [cited 2023 Jun 6]. Available from: https://riskcalculator.facs.org/RiskCalculator/
14. Yung AE, Wong G, Pillinger N, Wykes J, Haddad R, McInnes S, et al. Validation of a risk prediction calculator in Australian patients undergoing head and neck microsurgery reconstruction. J Plast Reconstr Aesthet Surg. 2022 Sep 1;75(9):3323–9.
15. Richardson A, Pang T, Hitos K, Toh JWT, Johnston E, Morgan G, et al. Comparison of administrative data and the American College of Surgeons National Surgical Quality Improvement Program data in a New South Wales Hospital. ANZ J Surg. 2020;90(5):734–9.
16. Parkin CJ, Moritz P, Kirkland O, Doane M, Glover A. Utility of the American College of Surgeons National Surgical Quality Improvement Program surgical risk calculator in predicting mortality in an Australian acute surgical unit. ANZ J Surg. 2020;90(5):746–51.
17. NCEPOD - Peri-operative Care: Knowing the Risk Report (2011) [Internet]. [cited 2022 Sep 2]. Available from: https://www.ncepod.org.uk/2011poc.html
18. Surgical Outcome Risk Tool (SORT) - SOuRCe / NCEPOD [Internet]. [cited 2023 Jun 8]. Available from: http://sortsurgery.com/
19. The Surgical Outcome Risk Tool (SORT) – a preoperative risk prediction tool on the App Store [Internet]. [cited 2023 Jun 7]. Available from: https://apps.apple.com/gb/app/the-surgical-outcome-risk-tool-sort-a-preoperative/id1078747046
20. Torlot F, Yew CY, Reilly JR, Phillips M, Weber DG, Corcoran TB, et al. External validity of four risk scores predicting 30-day mortality after surgery. BJA Open. 2022 Sep;3:100018.
21. External validation of a surgical mortality risk prediction model for inpatient noncardiac surgery in an Australian private health insurance dataset - Reilly - ANZ Journal of Surgery - Wiley Online Library [Internet]. [cited 2022 Sep 2]. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/ans.17946
22. Reports - National Emergency Laparotomy Audit [Internet]. [cited 2023 Jun 7]. Available from: https://www.nela.org.uk/reports
23. Reports - The National Institute of Academic Anaesthesia [Internet]. [cited 2022 Aug 14]. Available from: https://www.nela.org.uk/reports
24. Eugene N, Oliver CM, Bassett MG, Poulton TE, Kuryba A, Johnston C, et al. Development and internal validation of a novel risk adjustment model for adult patients undergoing emergency laparotomy surgery: the National Emergency Laparotomy Audit risk model. Br J Anaesth. 2018 Oct 1;121(4):739–48.
25. NELA risk calculator [Internet]. [cited 2023 Jun 6]. Available from: https://data.nela.org.uk/riskcalculator/
26. Perioperative Risk Calculator on the App Store [Internet]. [cited 2023 Jun 6]. Available from: https://apps.apple.com/au/app/perioperative-risk-calculator/id1443388402
27. Does NELA accurately predict mortality in Australia? [Internet]. [cited 2022 Sep 9]. Available from: https://asc.surgeons.org/talks/does-nela-accurately-predict-mortality-in-australia
28. Kefalianos DJ, Stupart D, Yung-Hsin D, Guest G, Watters D. How predictive is NELA in Victoria and Australia?
29. Mortality Risk for Emergency Laparotomies Overestimated by NELA scores in an Australian Regional Hospital [Internet]. [cited 2022 Sep 9]. Available from: https://asc.surgeons.org/talks/mortality-risk-for-emergency-laparotomies-overestimated-by-nela-scores-in-an-australian-regional-hospital

30. Hunter Emergency Laparotomy Collaborator Group, Hunter Emergency Laparotomy Collaborator Group. High-Risk Emergency Laparotomy in Australia: Comparing NELA, P-POSSUM, and ACS-NSQIP Calculators. J Surg Res. 2020 Feb;246:300–4.
31. Barazanchi A, Bhat S, Palmer-Neels K, Macfater WS, Xia W, Zeng I, et al. Evaluating and improving current risk prediction tools in emergency laparotomy. J Trauma Acute Care Surg. 2020 Aug;89(2):382–7.
32. Maxwell MJ, Moran CG, Moppett IK. Development and validation of a preoperative scoring system to predict 30 day mortality in patients undergoing hip fracture surgery. Br J Anaesth. 2008 Oct;101(4):511–7.
33. Wiles MD, Moran CG, Sahota O, Moppett IK. Nottingham Hip Fracture Score as a predictor of one year mortality in patients undergoing surgical repair of fractured neck of femur. Br J Anaesth. 2011 Apr 1;106(4):501–4.
34. Moppett IK, Parker M, Griffiths R, Bowers T, White SM, Moran CG. Nottingham Hip Fracture Score: longitudinal and multi-centre assessment. BJA Br J Anaesth. 2012 Oct 1;109(4):546–50.
35. Doherty WJ, Stubbs TA, Chaplin A, Reed MR, Sayer AA, Witham MD, et al. Prediction of Postoperative Outcomes Following Hip Fracture Surgery: Independent Validation and Recalibration of the Nottingham Hip Fracture Score. J Am Med Dir Assoc. 2021 Mar 1;22(3):663-669.e2.
36. Rijckevorsel VA van, Roukema GR, Klem TM, Kuijper TM, Jong L de. Validation of the Nottingham Hip Fracture Score (NHFS) in Patients with Hip Fracture: A Prospective Cohort Study in the Netherlands . Clin Interv Aging. 2021 Aug 21;16:1555–62.
37. Olsen F, Lundborg F, Kristiansson J, Hård Af Segerstad M, Ricksten SE, Nellgård B. Validation of the Nottingham Hip Fracture Score (NHFS) for the prediction of 30-day mortality in a Swedish cohort of hip fractures. Acta Anaesthesiol Scand. 2021 Nov;65(10):1413–20.
38. Marufu TC, Mannings A, Moppett IK. Risk scoring models for predicting peri-operative morbidity and mortality in people with fragility hip fractures: Qualitative systematic review. Injury. 2015 Dec 1;46(12):2325–34.
39. Nelson MJ, Scott J, Sivalingam P. Evaluation of Nottingham Hip Fracture Score, Age-Adjusted Charlson Comorbidity Index and the Physiological and Operative Severity Score for the enumeration of Mortality and morbidity as predictors of mortality in elderly neck of femur fracture patients. SAGE Open Med. 2020 Apr 28;8:2050312120918268.
40. Nottingham Hip Fracture Score - www.riskprediction.org.uk [Internet]. [cited 2023 May 30]. Available from: http://www.riskprediction.org.uk/index-nhfs.php
41. Nally DM, Lonergan PE, O'Connell EP, McNamara DA, SURGical Improvement Network (SURGIN). Increasing the use of perioperative risk scoring in emergency laparotomy: nationwide quality improvement programme. BJS Open. 2022 Jul 7;6(4):zrac092.
42. Pradhan N, Dyas AR, Bronsert MR, Lambert-Kerzner A, Henderson WG, Qiu H, et al. Attitudes about use of preoperative risk assessment tools: a survey of surgeons and surgical residents in an academic health system. Patient Saf Surg. 2022 Mar 17;16(1):13.
43. POSSUM for Operative Morbidity and Mortality Risk [Internet]. MDCalc. [cited 2023 Jun 7]. Available from: https://www.mdcalc.com/calc/3927/possum-operative-morbidity-mortality-risk
44. Watters DA, Babidge WJ, Kiermeier A, McCulloch GAJ, Maddern GJ. Perioperative Mortality Rates in Australian Public Hospitals: The Influence of Age, Gender and Urgency. World J Surg. 2016 Nov;40(11):2591–7.

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Intravenous heparin and non-cardiac anaesthesia

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INTRODUCTION

Heparin is documented as being discovered in 1916,[1] and is the oldest anticoagulant[2] used for the prevention and treatment of venous and arterial thrombosis. In anaesthesia, heparin is commonly given for the prevention of thromboembolic complications (TEC) during cardiac and vascular surgery. It is also used as an anticoagulant for extracorporeal circulations, whole blood transfusion, dialysis, cell salvage, and as an anticoagulant in laboratory blood samples. Although unfractionated heparin has greater inter-individual variation in pharmacodynamic effects compared to low molecular weight heparin, its low cost, short half-life, and rapid reversibility with protamine makes it the anticoagulant of choice when careful perioperative control of anticoagulation is needed. This article will focus on non-cardiopulmonary bypass uses of heparin in anaesthesia, as its application in cardiopulmonary bypass has recently been covered in depth.[3]

Pharmacology of heparin

Heparin sodium contains a heterogeneous mixture of negatively charged, sulphated glycosaminoglycan molecules ranging from 3000 to 30,000 Da in molecular weight (mean ~15kDa), which corresponds to approximately 45 saccharide units.[4-6] Due to this heterogeneity, the bioactivity and physiologic action of unfractionated heparin (UFH) can be broad and unpredictable.[7] The WHO standard for UFH has a potency of 122IU/mg of heparin, and since 2008 this has been adopted by the United States Pharmacopeia (which previously used its own standard of 150 IU/mg).[8] This reduced potency is worth noting when looking at heparin doses from older resources. Heparin is prepared from porcine lung and intestinal mucosa (bovine, porcine, or sheep, although porcine is the predominant source worldwide), but it is acceptable to most Jewish and Islamic patients due to its non-enteral route and its medical necessity.[9]

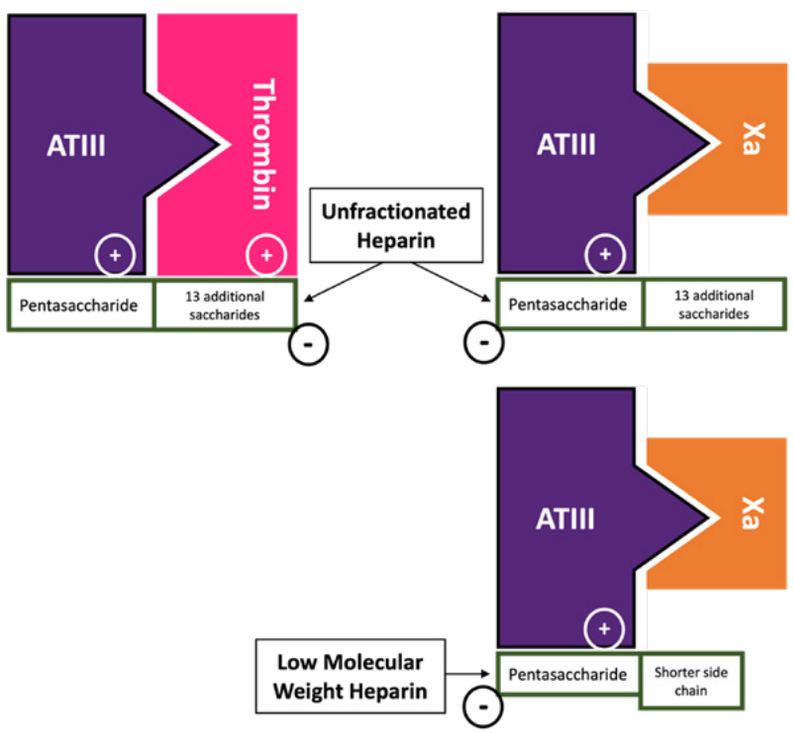
Low molecular weight heparin (LMWH), such as enoxaparin, is prepared via controlled enzymatic cleavage of UFH to produce smaller molecules (mean ~5kDa) with shorter chains (~15 saccharide units) and more predictable actions. LMWH is thus usually the preferred heparin for outpatient and ward-based administration due to its improved bioavailability, lower protein binding, more precise pharmacokinetics, and thus lower requirement for monitoring.[7] Ultra-low molecular weight heparins (ULMWH) have subsequently been developed, but have not gained widespread use due to their lower benefit-to-cost ratio.

The presence of a unique five-sugar sequence (i.e., pentasaccharide) is required for any type of heparin to bind to antithrombin and exert its anticoagulant activity.[10] Binding of this pentasaccharide to Antithrombin III (AT) induces a conformational change, converting it from a slow to a rapid inhibitor of serine proteases and thus enhancing its anticoagulant activity 1000-4000-fold.[10] However, the pentasaccharide-bound AT inhibits only factor Xa. A longer polymeric chain containing 18 or more polysaccharide units is required to bind both antithrombin and thrombin to form a ternary heparin/AT/thrombin complex (Figure 1) in order to inhibit thrombin activity.[2,10,11] This explains why LMWH preferentially inhibits factor Xa than thrombin in a 2:1 to 4:1 ratio, depending on the composition of the chain lengths in a given preparation. Whereas UFH inhibits both factor Xa and thrombin, with its overwhelming effect on thrombin.

Approximately one-third of UFH molecules in the usual clinically administered dose possess the unique pentasaccharide sequence responsible for its anticoagulant effect described above.

However, at concentrations higher than those administered clinically, heparin chains with or without the pentasaccharide sequence start to catalyse thrombin inhibition by a second plasma cofactor, heparin cofactor II.[12] At even higher concentrations, low-affinity heparin impairs factor Xa generation through AT- and heparin cofactor II (HCII)-independent mechanisms.[13] By inactivating thrombin or attenuating its generation, heparin not only prevents fibrin formation from fibrinogen but also inhibits thrombin-induced activation of platelets and thrombin-induced activation of factors V, VIII, and XI.[14,15] Heparin also prevents the formation of a stable clot by inhibiting the activation of fibrin stabilising factor (XIII). The primary locations of common clinically used anticoagulants are presented in a simplified form in Figure 2.

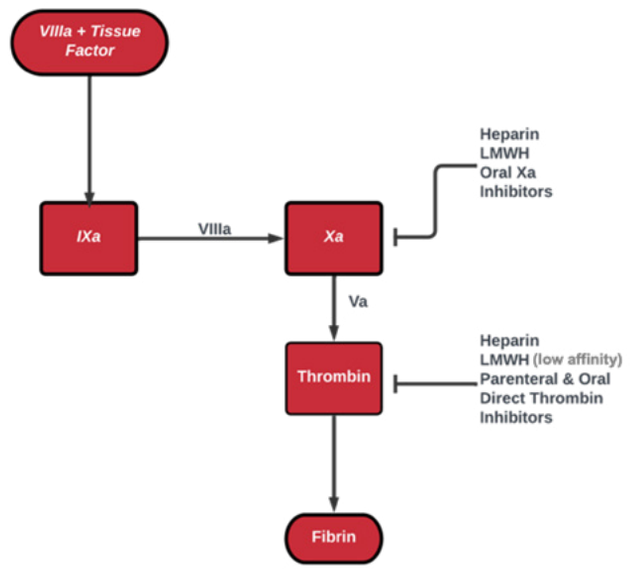
Figure 1. Pharmacology of heparin and low molecular weight heparin[10,16]



The unfractionated heparin/ATIII complex binds to non-fibrin bound thrombin (IIa) at a high affinity and inactivates it. The same complex inactivates factor Xa, but the heparin molecule only binds to ATIII in this situation. In contrast, the ATIII/LMWH complex inactivates factor Xa in a similar fashion, but at a much greater affinity compared to UFH. There is clinically insignificant binding of LMWH/ATIII to thrombin.

The pharmacokinetics of heparin are complex. It is extensively bound to plasma proteins, and it also binds to endothelial cells, macrophages, and von Willebrand factor which inhibits von Willebrand factor-dependent platelet function.[10] Heparin is degraded by heparinases and cells in the reticuloendothelial system. Initial clearance of heparin at lower doses is rapid and linear but at higher doses the clearance becomes non-linear. The apparent biological half-life of heparin is thus dependent on the dose given (Table 1 and Figure 3)[10,17] and this should be taken into consideration when determining protamine dosage required for reversal (if quantitative testing for heparin concentration is not in use).

Figure 2. Anticoagulant effects on the coagulation cascade (simplified)

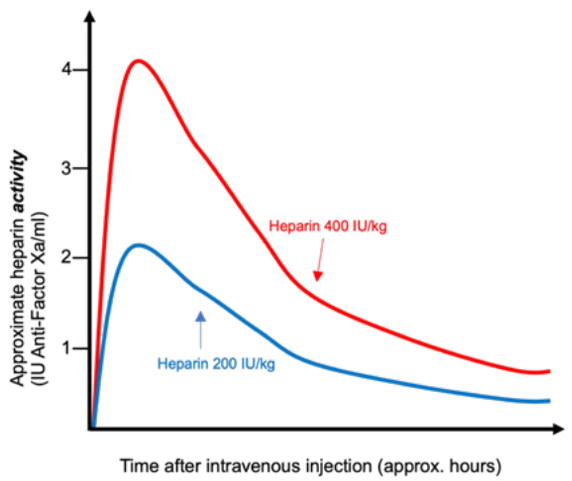


Anticoagulant activity of commonly used clinical agents occurs at two primary locations in the coagulation cascade.

Table 1. Heparin dose and variability in duration of action

Heparin dose (IU/kg)	Approximate apparent biological half-life (mins)
25	30
100	60
400	150

Figure 3. Schematic representation of heparin dose and impact on anti-Xa pharmacology



The pharmacology of heparin's anticoagulant activity varies based on the amount (and subsequent concentration) administered.[18,19] Reproduced with permission from Dr Bruce Cartwright.

The dose of heparin utilised varies markedly with different clinical indications. Very low doses of heparinised saline (10U/ml) are used to keep intravascular devices patent. For arterial vascular surgery, 100U/kg is often recommended, aiming for an ACT approximately 200-250 seconds as a standardised dose of 5000 units is often inadequate.[20] Targeting higher ACT levels, up to 350 seconds, may increase bleeding complications without reducing thrombotic complications.[21] When heparin is used for cardiopulmonary bypass a higher dose of 300-400U/kg is used whilst aiming for an ACT of >480 secs. Heparin is excreted in the urine, but in contrast to LMWH, there is no renal dose adjustment required. There is insufficient evidence to make recommendations for dose adjustment in obesity, although it has been suggested that adjusted body weight (ideal body weight + 40% of excess) could be used.[22]

Heparin does not cross the placenta and isn't excreted in breast milk. Bleeding time is usually unaffected and clotting time is not measurably affected by low dose heparin but is prolonged by therapeutic doses. Patients older than 60 may have a longer APTT prolongation for a given dose of heparin. Half-life may be slightly prolonged in renal impairment and either increased or decreased in hepatic impairment. Heparin does not have fibrinolytic activity and as such, should not be used to lyse existing clots.

Clinical monitoring of heparin effect

The anticoagulant effect of therapeutic parenteral heparin is traditionally, and most accurately, monitored using clot based or chromogenic laboratory tests such as Activated Partial Thromboplastin Time (APTT) or anti-Xa assays respectively (see Table 2). Additionally, in cardiac surgery, whole-blood heparin levels may be determined using an automated protamine titration device (Hepcon).[23]

Heparin infusions are commonly titrated to achieve a "therapeutic" APTT of 1.5-2.5x the normal range, corresponding to a heparin level of 0.2-0.4 IU per ml by protamine titration.[6] The processing time required for protamine titration (typically thirty minutes or more) usually make these tests impractical for intraoperative use. Although there are instruments available to measure point of care APTT, these have shown poor precision and comparability to the laboratory standard.[24] Activated clotting time (ACT) is widely available and familiar in the theatre environment and gives rapid results.

Table 2. Functional (clot-based) and chromogenic assays

	Clot-based assays	Chromogenic assays
Point of care examples	ACT, TEG, ROTEM	-
Laboratory examples	PT, APTT, TT	Anti-Xa
Advantages	Simple, fast, some are point of care	Quantitative
Limitations	Semi-quantitative, result less specific – e.g., High Factor VIII levels could underestimate heparin effect. Presence of lupus anticoagulant will overestimate it.	Lab based. Need specific assays for different anti-coagulants. Longer processing times.

ACT tubes use clot-promoting reagents such as celite or kaolin to standardise and quicken fibrin formation induced by contact activation of the coagulation protein factor XII. The ACT test results reflect the ability of a blood sample to clot in this fashion and the ACT is thus prolonged in the presence of heparin. The more prolonged the ACT result is from baseline or normal values the greater the degree of anticoagulation. The ACT result is not entirely specific and can be affected by haemodilution, hypothermia, pharmacologic compounds, and various coagulopathies. There are numerous different machines available in Australia such as Actalyke (HELENA laboratories), Haemochron (Werfen), and ACT Plus (Medtronic) (Table 3). Different cartridges/tubes should be used depending on the clinical application – for example 'low range' (LR) during haemodialysis/ECMO or 'high range' (HR) during vascular surgery or cardiopulmonary bypass. Using the incorrect cartridge can be misleading, as the ratio of activators to heparin concentration determines the response curve of ACT vs plasma heparin concentration. For example, at a heparin concentration of approximately 1.2IU/ml a HR cartridge may show an ACT of approximately 180 seconds whereas a LR cartridge may produce an ACT of 350 seconds. The use of a heparinase/control cartridge after protamine administration can help the clinician decide if there is ongoing heparin effect or other factors causing the ACT to be prolonged.

Point of care viscoelastic testing such as TEG or ROTEM also allows for additional assays to be run with heparinase added. This can be used alongside the ACT to guide protamine administration, although it should be noted that viscoelastic assays are relatively insensitive to low range heparin concentrations, below 0.3 IU/ml.

Table 3. Examples of point of care testing

Instrument	Manufacturer	Sample	ACT activator	ACT clot detection method	Alternative analyses available
Haemochron Signature Elite	Accriva Diagnostics	Capillary or whole blood (WB) (native or citrated)	ACT+ test uses a mixture of silica, kaolin, and phospholipids; ACT-LR test uses Celite activator.	Optical/ mechanical	ACT HR or LR, POC INR & APTT
iSTAT	Abbott	WB	Kaolin, celite	Electrogenic, amperometry	ACT, POC INR
Actalyke Mini II	Helena Laboratories	WB	Celite, kaolin, glass beads	Magnet rotation	
ACT Plus	Medtronic	WB (native or citrated)		Plunger motion	ACT HR or LR, heparinase

Adapted from[24]. Whole blood (WB), Point of care (POC).

Heparin resistance

Heparin resistance is usually defined as the need for greater than 35,000 units of heparin in 24 hours to reach a therapeutic APTT[25] (in non-cardiopulmonary bypass). It is more common in patients undergoing cardiopulmonary bypass (up to 20%) where it is defined as the need for more than 500 units per kilogram of body weight to achieve an activated clotting time of 400 to 480 seconds.[26] Measuring a baseline ACT does not appear to help predict heparin resistance preoperatively.[26]

Causes of heparin resistance

- Antithrombin (AT) deficiency
  - Congenital
    - ~1:5000 incidence
    - AT levels of 40-60% of normal
  - Acquired
    - Heparin therapy - the thrombin-antithrombin complex is cleared by the reticuloendothelial system - AT levels decline by ~5-7% per day.
    - Liver disease
- Upregulated coagulation system
  - Disseminated Intravascular Coagulation (DIC)
  - SARS-CoV-2
- Non-specific binding
  - Anionic heparin molecules bind many different proteins including platelet factor 4, glycoproteins, von Willebrand factor, fibrinogen, and factor VIII.
- Platelet interactions
- Andexanet alpha
  - Xa decoy - apixaban/rivaroxaban reversal agent
- Pseudo (apparent) heparin resistance

Although most heparin resistance is due to antithrombin deficiency, supplemental antithrombin doesn't always raise ACT, suggesting there is also an anti-thrombin-independent mechanism.

Management of heparin resistance

When heparin resistance is discovered, the first step is to determine whether there is true heparin resistance (*in vivo* blunting of heparin's anticoagulant effect) or pseudo (apparent) heparin resistance, where there are subtherapeutic APTT/ACT values despite therapeutic *in vivo* anticoagulation. To help differentiate true from pseudo heparin resistance, the APTT and anti-Xa assay levels should be measured on the same blood sample. The anti-Xa assay relies on free factor Xa (i.e., not bound by the antithrombin-heparin complex) and, unlike the APTT and ACT, it is not affected by other clotting factors (e.g., high factor VIII levels as seen in SARS-CoV-2 patients[27]) or acute-phase reactants.[28] True heparin resistance, where both APTT/ACT and anti-Xa levels are concordantly lower than expected, is most commonly due to decreased antithrombin activity. Antithrombin chromogenic functional assays are the best first test for antithrombin deficiency with a normal range being approximately 80-130%. Additional specialised tests to differentiate type 1 (quantitative deficiency) vs type 2 (dysfunction) are not standard but are available in some laboratories. Unfortunately, it is often not practical to wait for formal anti-Xa or antithrombin III assays during surgery and empirical treatment is often used. As antithrombin III deficiency is the most common cause of heparin resistance, empirical treatment with 1000 units of purified human antithrombin III concentrate is expensive but usually effective in achieving a therapeutic ACT.[29] If antithrombin concentrate is not available, fresh frozen plasma (FFP) can be used with 1ml of FFP containing approximately 1 IU of antithrombin.

Andexanet alpha (a factor Xa decoy) is a new reversal agent for rivaroxaban and apixaban, but it also binds to antithrombin III reducing the thrombin III-heparin complexes which could preclude adequate anticoagulation with heparin. Administration of antithrombin III or bivalirudin could be considered in this settting.[30]

Protamine

Protamine sulfate is a positively charged basic protein, originally isolated from salmon fish sperm but increasingly manufactured with recombinant technology.[31] Protamine neutralises the effect of anionic heparin through electrostatic binding in a 1:1 ratio to form a protamine-heparin aggregate. As neutralisation is dependent on molecular weight, protamine will only partially neutralise low molecular weight heparin.[32] Protamine has a rapid onset of action, within 5 minutes, and a short half-life of approximately 10 minutes. 1mg of protamine will neutralise 100 units of heparin but as heparin is being continuously excreted, the dose of protamine should be reduced if more than 15 minutes has elapsed since the heparin administration. If excessive protamine is given it will have anticoagulant effects via interference with platelet function, clotting factors, and enhanced fibrinolysis.[31] Adverse effects to protamine (Table 4) can be non-immunologic or immunologic and are highest in patients with previous protamine exposure (including in some insulin formulations) and patients with vasectomy or fish allergies. The haemodynamic effects of protamine administration are greatly reduced if it is given by slow infusion.

Table 4. Adverse effects of protamine administration

Adverse effect	Clinical sequelae
Vasodilation	Hypotension
Pulmonary vasoconstriction	Pulmonary hypertension or right ventricular dysfunction
Anaphylaxis or Anaphylactoid reactions	Hypotension, bronchospasm

Heparin induced thrombocytopaenia

Heparin induced thrombocytopaenia (HIT) has two main types. Type 1 (sometimes simply referred to as "heparin associated thrombocytopaenia" to avoid confusion) affects up to 10% of patients exposed to heparin and usually causes a mild thrombocytopaenia within 1-4 days of heparin administration. It is due to a direct and non-immune mediated activation of platelets causing clumping or sequestration but carries no increased risk of thrombosis.[33] In contrast, Type 2 HIT, which occurs in approximately 0.3% of vascular surgical patients,[34] causes a delayed (typically 5-11 days post heparin exposure) and more severe reduction in the platelet count as it is immune mediated. IgG develops in response to formation of a heparin-platelet factor 4 (PF4) antigen. This can cause irreversible aggregation of platelets and progress to the development of arterial and venous thromboses and mortality in up to 30% of patients. If a diagnosis of HIT is suspected, a pre-test probability can be estimated using the 4T scoring system (Table 5) prior to performing heparin-PF4 antibody testing, as it not necessary (or usually recommended) for patients with low pre-test probability.[33] If a patient has intermediate or high-risk probability, heparin should immediately be discontinued, and haematological advice sought as further testing with immunoassays and/or functional assays should be strongly considered. Low molecular weight heparin (LMWH) cannot be used in patients with HIT due to the strong cross reactivity of the HIT antibody with LMWH-PF4 complex. Alternative anticoagulants, such as bivalirudin (a direct thrombin inhibitor), should be used for all patients with suspected, acute, or subacute HIT. Patients are said to have "Remote HIT" if enough time has elapsed such that both functional and immunoassays are unable to detect anti-PF4 or anti-heparin antibodies. In these patients it is reasonable to use heparin in emergency settings if non-heparin anticoagulants are not available or clinical experience is lacking.[35]

Table 5. 4T Scoring System

	2 points	1 point	Not significant
Platelet fall	>50% Drop by 20-100	>30-50% Drop by 10-19	<30% fall Drop <10
Timing	Onset 5–10 days	Outside 5–10 days by 1 day	<4 days
Thrombosis	Skin necrosis, new DVT/PE	Progressive or recurrent (e.g., new defect with existing PE)	None
Other cause of thrombocytopenia	None	Possible – e.g., haemodilution	Definite

Low risk <3 points; Intermediate risk 3-5 points; High risk >5 points

Bivalirudin is a synthetic direct thrombin inhibitor first introduced for percutaneous coronary intervention (PCI) in the early 1990s. It has the theoretical advantages of inhibiting fibrin-bound thrombin, a predictable effect of anticoagulation and a short half-life of approximately 30 minutes if renal function is normal.[36] Unlike heparin, it lacks a specific reversal agent, and its half-life is significantly prolonged in renal impairment. Argatroban can be used as an alternative in patients with severe renal impairment (Table 6).

Table 6. Heparin alternatives – pharmacology and suggested dosing

Heparin alternative	Mechanism	Half-life (mins)	Indication	Dose	Dose adjustments
Bivalirudin	Direct thrombin inhibitor	25	HIT/Acute coronary syndrome (ACS)	0.1-0.15mg/kg then 0.25mg/kg/hr	Reduce dose in renal impairment.
			Percutaneous coronary intervention (PCI)	0.75mg/kg then 1.75mg/kg/hr	
Argatroban[37]		50	HIT/ACS	2mcg/kg/min	Reduce dose in hepatic impairment.
			PCI	250mcg/kg then 15-25mcg/kg/min	Consider 100mcg/kg bolus titration to effect.

In a meta-analysis comparing bivalirudin (0.75mg/kg loading + 1.75mg/kg/hr) versus unfractionated heparin (50-100 U/kg) for peripheral endovascular procedures (PEP) there were no significant differences in rates of procedural success, major and minor bleeding, transfusion requirements, perioperative TIAs, or haemorrhagic strokes.[36] Another meta-analysis of retrospective studies showed that bivalirudin used for PEP may be associated with lower all-cause mortality and bleeding complications but further large RCTs were considered necessary to confirm these results.[38]

Heparin allergy

The most common adverse effect of heparin is haemorrhage. Late side effects can include alopecia, osteoporosis, lipodystrophy, and raised liver enzymes. Although true allergy to heparin is rare, all types of allergic reactions have been described. The most common allergic mechanisms are cell mediated type IV (e.g., erythematous cutaneous plaques) and antibody mediated Type II reactions (e.g., HIT type 2, as previously discussed).[39] Immediate Type I reactions are very rare. Heparin necrosis, a differential diagnosis of Type IV mediated rashes, can also occur and is the cutaneous manifestation of the severe form of HIT Type 2.

Perioperative management of heparin infusions

For patients on therapeutic heparin infusions, if the APTT is in the therapeutic range (typically 55-90 seconds) it is usually recommended to cease the infusion six hours prior to surgery. This may vary depending on the clinical assessment of the patient's relative risk of bleeding compared to their risk of TEC.

The American Society of Regional Anesthesia (ASRA) recommend cessation of intravenous heparin six hours prior to neuraxial blockade or epidural catheter removal.[40] It should be noted that if the APTT is above the therapeutic range, a longer cessation time is required, and normal coagulation status should be verified prior to neuraxial blockade or surgery with critical bleeding risk (e.g., neurosurgery).

ASRA recommend waiting at least one hour after neuraxial anaesthetic procedures before restarting a heparin infusion. Recommencing heparin infusions post-surgery is largely based on surgical preference and again must consider the patient's bleeding versus TEC risk profile.

CONCLUSION

Intravenous heparin is a familiar drug that is widely available, low cost, and rapidly reversible. It has numerous applications in anaesthesia and perioperative medicine, and understanding its advantages, shortcomings, and nuances is valuable for all anaesthetists and perioperative staff.

REFERENCES

1. Mclean J. The discovery of heparin. Circulation. 1959;19:75-78.
2. Weitz JI. Low-molecular-weight heparins. N Engl J Med. 1997;337:688-698.
3. Cartwright B, Mundell N. Anticoagulation for cardiopulmonary bypass: part one. BJA Educ. 2023;23:110-116.
4. Johnson EA, Kirkwood TB, Stirling Y et al. Four heparin preparations: anti-Xa potentiating effect of heparin after subcutaneous injection. Thromb Haemost. 1976;35:586-591.
5. Andersson LO, Barrowcliffe TW, Holmer E, Johnson EA, Sims GE. Anticoagulant properties of heparin fractionated by affinity chromatography on matrix-bound antithrombin iii and by gel filtration. Thromb Res. 1976;9:575-583.
6. Hirsh J. Heparin. N Engl J Med. 1991;324:1565-1574.
7. Oduah EI, Linhardt RJ, Sharfstein ST. Heparin: Past, Present, and Future. Pharmaceuticals (Basel). 2016;9:38.
8. Royston D. Pharmacology and Physiology for Anesthesia Anticoagulant and Antiplatelet Therapy. In: Hemmings HC, MD, PhD, FRCA, Egan TD, MD2019. p. 870-894.
9. Datz H. Religious-related concerns and animal-derived medications during anesthetic care. Anaesthesia, Pain & Intensive Care. 2018
10. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e24S-e43S.
11. Levy JH, Connors JM. Heparin Resistance - Clinical Perspectives and Management Strategies. N Engl J Med. 2021;385:826-832.
12. Tollefsen DM, Majerus DW, Blank MK. Heparin cofactor II. Purification and properties of a heparin-dependent inhibitor of thrombin in human plasma. J Biol Chem. 1982;257:2162-2169.
13. Hirsh J, Weitz JI. New antithrombotic agents. Lancet. 1999;353:1431-1436.
14. Béguin S, Lindhout T, Hemker HC. The mode of action of heparin in plasma. Thromb Haemost. 1988;60:457-462.
15. Ofosu FA, Sie P, Modi GJ et al. The inhibition of thrombin-dependent positive-feedback reactions is critical to the expression of the anticoagulant effect of heparin. Biochem J. 1987;243:579-588.
16. Hirsh J, Warkentin TE, Shaughnessy SG et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest. 2001;119:64S-94S.
17. Weitz JI. Blood Coagulation and Anticoagulant, Fibrinolytic, and Antiplatelet Drugs. In: Brunton LL, Knollmann BCNew York, NY: McGraw-Hill Education; 2023.
18. Despotis GJ, Summerfield AL, Joist JH et al. Comparison of activated coagulation time and whole blood heparin measurements with laboratory plasma anti-Xa heparin concentration in patients having cardiac operations. J Thorac Cardiovasc Surg. 1994;108:1076-1082.
19. Qi Y, Zhao G, Liu D et al. Delivery of therapeutic levels of heparin and low-molecular-weight heparin through a pulmonary route. Proc Natl Acad Sci U S A. 2004;101:9867-9872.

20. Doganer O, Jongkind V, Blankensteijn JD, Yeung KK, Wiersema AM. A Standardized Bolus of 5 000 IU of Heparin Does not Lead to Adequate Heparinization during Non-cardiac Arterial Procedures. Ann Vasc Surg. 2021;71:280-287.
21. Kasapis C, Gurm HS, Chetcuti SJ et al. Defining the optimal degree of heparin anticoagulation for peripheral vascular interventions: insight from a large, regional, multicenter registry. Circ Cardiovasc Interv. 2010;3:593-601.
22. Myzienski AE, Lutz MF, Smythe MA. Unfractionated heparin dosing for venous thromboembolism in morbidly obese patients: case report and review of the literature. Pharmacotherapy. 2010;30:324.
23. Raymond PD, Ray MJ, Callen SN, Marsh NA. Heparin monitoring during cardiac surgery. Part 1: Validation of whole-blood heparin concentration and activated clotting time. Perfusion. 2003;18:269-276.
24. Wool GD. Benefits and Pitfalls of Point-of-Care Coagulation Testing for Anticoagulation Management: An ACLPS Critical Review. Am J Clin Pathol. 2019;151:1-17.
25. Heparin resistance. [editorial]. Br J Anaesth 2002;88(4):467.
26. Staples MH, Dunton RF, Karlson KJ, Leonardi HK, Berger RL. Heparin resistance after preoperative heparin therapy or intraaortic balloon pumping. Ann Thorac Surg. 1994;57:1211-1216.
27. Beun R, Kusadasi N, Sikma M, Westerink J, Huisman A. Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2.[letter]. Int J Lab Hematol 2020;42 Suppl 1(Suppl 1):19-20.
28. Downie I, Liederman Z, Thiyagarajah K, Selby R, Lin Y. Pseudo heparin resistance caused by elevated factor VIII in a critically ill patient. Can J Anaesth. 2019;66:995-996.
29. Williams MR, D'Ambra AB, Beck JR et al. A randomized trial of antithrombin concentrate for treatment of heparin resistance. Ann Thorac Surg. 2000;70:873-877.
30. Pauls LA, Rathor R, Pennington BT. Andexanet Alfa-Induced Heparin Resistance Missing From SCA Blood Management in Cardiac Surgery Guidelines.[letter]. J Cardiothorac Vasc Anesth 2022;36(12):4557-4558.
31. Boer C, Meesters MI, Veerhoek D, Vonk ABA. Anticoagulant and side-effects of protamine in cardiac surgery: a narrative review. Br J Anaesth. 2018;120:914-927.
32. Schroeder M, Hogwood J, Gray E, Mulloy B, Hackett A-M, Johansen KB. Protamine neutralisation of low molecular weight heparins and their oligosaccharide components. Analytical and Bioanalytical Chemistry. 2011;399:763-771.
33. Ahmed I, Majeed A, Powell R. Heparin induced thrombocytopenia: diagnosis and management update. Postgrad Med J. 2007;83:575-582.
34. Chaudhry R, Wegner R, Zaki JF et al. Incidence and Outcomes of Heparin-Induced Thrombocytopenia in Patients Undergoing Vascular Surgery. J Cardiothorac Vasc Anesth. 2017;31:1751-1757.
35. Cuker A, Arepally GM, Chong BH et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv. 2018;2:3360-3392.
36. Hu Y, Liu AY, Zhang L et al. A systematic review and meta-analysis of bivalirudin application in peripheral endovascular procedures. J Vasc Surg. 2019;70:274-284.e5.
37. Lewis BE, Wallis DE, Berkowitz SD et al. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation. 2001;103:1838-1843.- Cruz-Gonzalez I, Sanchez-Ledesma M, Osakabe M et al. What is the optimal anticoagulation level with argatroban during percutaneous coronary intervention. Blood Coagul Fibrinolysis. 2008;19:401-404.
38. Olmedo W, Villablanca PA, Sanina C et al. Bivalirudin versus heparin in patients undergoing percutaneous peripheral interventions: A systematic review and meta-analysis. Vascular. 2019;27:78-89.
39. Bircher AJ, Harr T, Hohenstein L, Tsakiris DA. Hypersensitivity reactions to anticoagulant drugs: diagnosis and management options. Allergy. 2006;61:1432-1440.
40. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). Reg Anesth Pain Med. 2018;43:263-309.

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Perioperative considerations for the patient with portal hypertension: Anaesthesia management of common interventions

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BACKGROUND

In Australia and New Zealand, rates of chronic liver disease and its associated complications are on the rise. This increasing burden of liver disease highlights the importance for anaesthetists to understand the risks and complexities that make perioperative management challenging for this unique group. In general, patients with liver disease have a significant risk of morbidity and mortality after anaesthesia and surgery, with potential for deterioration into life-threatening hepatic failure. Overall, patients with liver disease have higher transfusion requirements, higher infection rates, increased rates of cardiac compromise and longer hospital stays compared to those without liver disease.[1]

Advances in screening and management of liver disease and its complications, namely portal hypertension, presents a challenge for the anaesthesia community. Historically, treatment of portal hypertension and its sequelae was limited to medical management or liver transplantation. There have been a number of recent expansions in screening and treatment options that require anaesthetic involvement, and a subsequent need for familiarity by the anaesthetists who are likely to encounter them. These interventions include screening endoscopy, variceal banding and transjugular intrahepatic portosystemic shunts (TIPS). Anaesthesia expertise is required for an increasing number of these procedures in both the acute and elective setting, and frequently in remote anaesthesia locations.

The intention of this article is to discuss the anaesthetic considerations related to these interventions. Of note, smaller procedures, such as drainage of ascites, are typically performed under local anaesthetic with no specialist anaesthetist involvement required. While trans-arterial chemoembolization (TACE) and microwave ablation of liver lesions often do require the involvement of an anaesthetist, these procedures are not specifically due to the presence of portal hypertension and are therefore not discussed.

PORTAL HYPERTENSION

Portal hypertension is a major consequence of liver cirrhosis and the cause of end stage liver disease complications such as ascites, variceal bleeding, and thrombocytopenia. While liver cirrhosis is the leading cause of portal hypertension, several other non-cirrhotic causes exist, with schistosomiasis (a parasitic infection) being the second most common cause.[2] Non-cirrhotic aetiologies of portal hypertension can be categorised into pre, intra and post hepatic causes. These categories are demonstrated below, in Table 1.

Table 1. Non-cirrhotic causes of portal hypertension based on perihepatic pathology[3,4]

Pre-hepatic - Portal or splenic vein thrombosis - Splanchnic arterio-venous fistulas
Intra-hepatic - Pre-sinusoidal ▪ Polycystic liver disease ▪ Congenital hepatic fibrosis ▪ Arterio-venous fistulas ▪ Biliary disease (biliary cholangitis, autoimmune cholangiopathy, primary sclerosing cholangitis, other biliary injury) ▪ Neoplastic occlusion of portal vein ▪ Granulomatous liver disease (schistosomiasis, sarcoidosis) ▪ Idiopathic noncirrhotic portal hypertension - Sinusoidal ▪ Amyloid ▪ Fibrosis of the space of Disse ▪ Sinusoid destruction in acute liver injury ▪ Infiltrative diseases (mastocytosis, Gaucher disease, idiopathic myeloid metaplasia) - Post-sinusoidal ▪ Sinusoidal obstruction syndrome ▪ Budd-Chiari syndrome ▪ Phlebosclerosis of hepatic veins (alcohol-associated liver disease, chronic radiation injury) ▪ Primary vascular malignancies ▪ Granulomatous phlebitis ▪ Lipogranulomas
Post-hepatic - Hepatic vein or IVC obstruction (Budd-Chiari syndrome) - Constrictive pericarditis, restrictive cardiomyopathy

The portal vein receives blood drained from the gastrointestinal tract, stomach, pancreas, gallbladder, and spleen. The blood flows into the liver via these pathways and back to the inferior vena cava via the hepatic vein. Under normal conditions, the portal vein supplies the liver with approximately 75% of its blood supply (the other 25% being from the hepatic artery). Portal hypertension develops when there is an increase in portal venous pressure. This leads to the development of collateral portosystemic vessels which shunt blood back to the systemic circulation, bypassing the liver.

Portal hypertension is typically a diagnosis made in patients with known risk factors (e.g. cirrhosis) who present with clinical manifestations of elevated portal pressures. The gold standard for quantification of portal hypertension is performed by measuring the hepatic venous pressure gradient (HVPG). This procedure is conducted by placing a pressure transducing catheter into a hepatic vein, and the difference between balloon wedged hepatic venous pressure and free hepatic venous pressure is measured. A normal HVPG is up to 5mmHg; portal hypertension is defined as an HVPG ≥ 6mmHg. Clinically significant manifestations of portal hypertension typically occur at a HVPG of > 10mmHg.[5] Measurement of a HVPG does offer prognostic value (particularly when ≥ 20mmHg), however it is not routinely performed.[6,7] Ultrasonography and transient elastography can also be used to assess portal hypertension, but neither are used to confirm diagnosis.

Table 2. Common complications of portal hypertension

- Gastroesophageal varices
- Portal hypertensive gastropathy
- Ascites
- Spontaneous bacterial peritonitis
- Splenomegaly
- Thrombocytopenia
- Hepatorenal syndrome
- Hepatic hydrothorax
- Hepatopulmonary syndrome
- Portopulmonary hypertension
- Cirrhotic cardiomyopathy
- Portal cholangiopathy

Cirrhotic liver disease can be broadly classified into two main stages: compensated and decompensated cirrhosis. The distinction depends on the presence of decompensating events such as variceal haemorrhage, ascites, and encephalopathy. This classification has significant implications for expected lifespan. With compensated cirrhosis, median survival exceeds 12 years, whereas patients with decompensated cirrhosis have a median survival of 1.8 years.[8] A list of common and important complications secondary to portal hypertension is presented in Table 2.

GASTROESOPHAGEAL VARICES

One of the earliest consequences of portal hypertension is the development of portosystemic collaterals and the subsequent formation of gastroesophageal varices. By definition, patients who have developed gastroesophageal varices have clinically significant portal hypertension (HPVG ≥ 10mmHg) and are more likely to progress to decompensated cirrhosis.

Incidence

Gastroesophageal varices are present in 25-40% of patients with compensated cirrhosis, and in up to 85% of those with decompensated cirrhosis.[9]

Surveillance

Patients with advanced chronic liver disease will commonly present to the endoscopy suite for elective screening or surveillance endoscopy. Since the introduction of the Baveno criteria, a validated tool used to rule out high risk varices based on non-invasive tests, screening endoscopy can now be avoided in a significant number of patients.[10-12] Depending on the result of previous endoscopy, surveillance can generally be performed every 2 years. Repeat endoscopy should be performed in the event of any decompensation.[11,12] Consequently, the indication for endoscopy (for example, decompensation) may inform the anaesthetist of the likelihood of varices being present and any intervention required.

Prevention of variceal haemorrhage

Advanced chronic liver disease patients with clinically significant portal hypertension commonly receive non-selective beta blockers (e.g. carvedilol or propranolol) as first line treatment to prevent variceal bleeding.[10,11] Patients with high-risk varices who have a contraindication to non-selective beta blockers will receive prophylactic endoscopic ligation, repeated until eradication is achieved.[11] Any contraindication to non-selective beta blockade therapy may be of interest to the anaesthetist, and may include second- or third-degree heart block, asthma, or persistent hypotension.

In the broader surgical population, a history of chronic liver disease and treatment with a non-selective beta blocker should trigger an awareness that there is probable significant portal hypertension and sequelae may be present. Care should be taken with any procedures in the oesophagus (for example, nasogastric/orogastric tube insertion or insertion of a transoesophageal echocardiogram probe).

Anaesthesia considerations for endoscopy and band ligation

Routine patient assessment should be performed and an assessment of the severity of liver disease made (compensated versus decompensated). The decision to use sedation or general anaesthesia with an endotracheal tube will be influenced by usual factors, including aspiration risk and the patient's ability to maintain their airway. Additionally, the risk of peri-procedural bleeding and a reduced respiratory reserve (from massive ascites, for example) will also impact this decision. Considerations for tailoring of anaesthetic agents and dose adjustments will be discussed later in this article.

ACUTE VARICEAL BLEEDING

Gastrointestinal bleeding is a common decompensating event in patients with end-stage liver disease. The most common cause of bleeding in these patients is gastroesophageal varices, followed by gastroduodenal ulceration.[13] Concomitant bacterial infection, HVPG >20mmHg and Child Pugh C score are risk factors for mortality after variceal haemorrhage.[10] Rebleeding is common after an index bleed but is significantly reduced by effective treatment of portal hypertension.[13]

Pharmacological treatments

Typically, patients will receive a bundle of care aimed to reduce the risk of rebleeding and the overall risk of mortality. This may include:

- Early antibiotic prophylaxis[13,14]
- Intravenous proton pump inhibitor therapy, continued until varices are confirmed[13,15]
- Intravenous splanchnic vasoconstrictor (e.g. octreotide, terlipressin)[16,17]
- Prokinetic agents (e.g. erythromycin, metoclopramide) to promote gastric emptying and to improve procedural visualisation[11]

Interventional procedures

All patients with suspected variceal haemorrhage should be referred for endoscopy within 12 hours of presentation, or sooner if haemodynamic instability is present.[11] Endoscopic band ligation is the intervention of choice when oesophageal varices are present. While band ligation is preferred for oesophageal varices, patients with gastric varices are generally treated with cyanoacrylate injections, as band ligation is typically less successful.[10,15]

If haemostasis of variceal bleeding varices cannot be achieved endoscopically, balloon tamponade can be used as a temporising intervention. Commonly used devices are the Sengstaken-Blakemore and Minnesota tubes. These methods should only be used as a bridge (<24 hours) to definitive therapy (that is, a transjugular intrahepatic portosystemic shunt). Patients must be intubated, ventilated and admitted to an intensive care unit. Balloon techniques are associated with a high risk of complications, including oesophageal ulceration, perforation and pneumonia.[18] Oesophageal stenting with self-expanding metal stents can also be considered as a bridging therapy. These stents can be left in place for 7 days or more. Potential complications of stenting include migration and ulceration, though complications of stenting may be less common compared to balloon tamponade techniques.[11,18]

ANAESTHESIA CONSIDERATIONS FOR PATIENTS WITH ACUTE VARICEAL HAEMORRHAGE

General measures

Large bore peripheral IV access should be established and resuscitation with a balanced crystalloid solution initiated. Consideration should be given to placement of an arterial line for haemodynamic monitoring and serial blood sampling. Activation of the massive transfusion protocol or discussion with blood bank may be prudent. Hypothermia should be avoided, given the pre-existing propensity to coagulopathy in this population and the possibility of large volume transfusion.

Transfusion strategy

It has been suggested that aggressive restitution of the intravascular volume increases portal pressure and, therefore, may worsen variceal bleeding or cause rebleeding.[11] A restrictive transfusion strategy (haemoglobin threshold of ≤ 70g/dL prior to packed red blood cell administration) has been associated with lower mortality and rebleeding rates.[19] This strategy is recommended for patients with acute gastrointestinal haemorrhage who are haemodynamically stable and do not have a history of significant cardiovascular disease. Patients with significant cardiovascular disease should have a more liberal transfusion threshold (e.g. ≤ 80g/dL).

It is critical, however, to recognise the distinction between patients who are haemodynamically stable and those who are exhibiting signs of shock and instability. Bleeding can be rapid and the clinical picture dynamic. Consequently, a haemoglobin value ≥ 70g/dL may be falsely reassuring in the face of active bleeding. Withholding resuscitative efforts and transfusion for an unstable patient is not appropriate and may lead to catastrophic outcomes.

Correction of coagulopathy

Anticoagulation agents should be ceased and reversed where possible. Thought should be given to general measures which support the coagulation system. This includes ensuring a core temperature of greater than 35 degrees Celsius, avoiding acidosis, and maintaining an ionised calcium level > 1.1 mmol/L, with particular vigilance required in the setting of a massive transfusion.

Despite thrombocytopaenia, prolonged prothrombin time and a raised INR being common features of advanced chronic liver disease, they may not necessarily correlate with bleeding risk in these patients.[20] Routine transfusion with platelets and fresh frozen plasma (FFP) is not recommended, nor can a threshold value for transfusion be definitively suggested.[10] Rather, correction of coagulopathy should be guided by viscoelastic testing where possible.[21] Unnecessary transfusion is not only a waste of a valuable resource, but it may cause harm.[22] Prothrombin complex concentrate may be a more effective option than FFP in correcting the INR, while avoiding additional intravascular volume expansion.[22] Recombinant factor VIIa has not been demonstrated to be of benefit.[11]

Haemodynamic goals

Early introduction of vasopressors to avoid haemodynamic compromise at induction is recommended in addition to any ongoing transfusion requirement. While vasopressin may provide theoretical benefit of splanchnic vasoconstriction, administration should be via a central venous line. Practically, metaraminol or phenylephrine are suitable. A mean arterial pressure target of 65mmHg is reasonable, acknowledging there may be patient factors which alter this target. Overzealous administration of vasopressors and subsequent hypertension prior to gaining control of the bleeding source is potentially harmful.

Airway protection

Generally, airway protection with rapid sequence induction and endotracheal tube placement will be required for patients having interventional procedures for variceal haemorrhage. Early extubation is encouraged but will be dictated by the haemostasis achieved and the patient condition at the end of the procedure.

TIPS PROCEDURE

Transjugular intrahepatic portosystemic shunts (TIPS) are used to reduce portal hypertension. A radiologically placed TIPS creates a low-pressure route between the intrahepatic portion of the portal and hepatic veins. This effectively shunts blood from the congested portal system, directly back to the hepatic vein for return to the systemic circulation. Offloading the portal system helps reduce complications of portal hypertension, such as ascites and variceal bleeding. Prior to the modern TIPS procedure, open surgical porto-caval shunts were performed, but these were associated with high rates of morbidity and mortality.[23]

TIPS may be used electively or as a rescue intervention where medical management has failed. TIPS have shown both survival and symptomatic benefit in patients requiring serial large-volume paracentesis.[3,24] While endoscopic treatment of variceal disease is the gold standard treatment, TIPS have shown a survival benefit when used for management of varices and variceal bleeding.[24] Less common indications for TIPS include portal hypertensive gastropathy, gastric antral vascular ectasia, refractory hypertensive hydrothorax, hepatorenal syndrome, Budd-Chiari syndrome, hepatic veno-occlusive disease and hepatopulmonary syndrome. Evidence for these indications, however, is more limited. Other indications for TIPS include elective placement prior to surgery in cirrhotic patients (as an attempt to reduce the risk of hepatic decompensation perioperatively), and as a bridge to liver transplantation.[25,26] Despite these indications, there are several conditions that are considered both absolute and relative contraindications for TIPS placement. These are presented below, in Table 3.

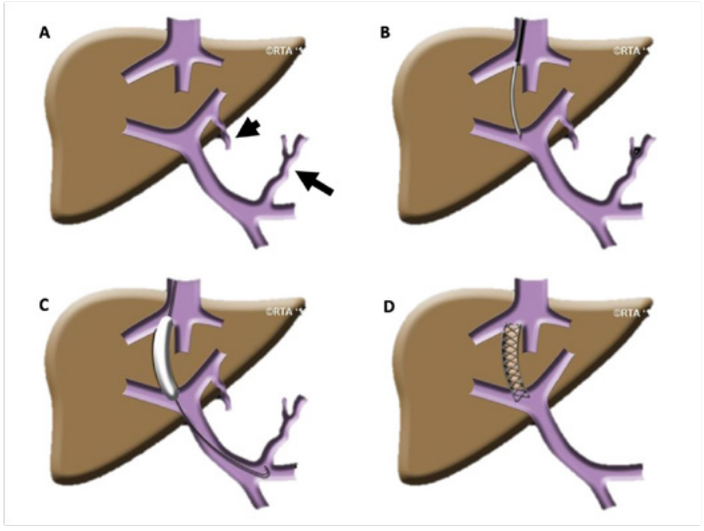
Table 3. Contraindications to insertion of a TIPS[23,27,28]

Absolute contraindications ▪ Congestive heart failure ▪ Severe tricuspid regurgitation ▪ Severe pulmonary hypertension ▪ Polycystic liver disease ▪ Active systemic sepsis ▪ Unrelieved biliary obstruction
Relative contraindications ▪ Hepatic encephalopathy ▪ Hepatocellular carcinoma, particularly if centrally located ▪ Obstruction of all hepatic veins ▪ Portal vein thrombosis ▪ Thrombocytopenia (platelet count <20) ▪ Severe coagulopathy (INR >5) ▪ Moderate pulmonary hypertension

THE PROCEDURE

TIPS is an interventional radiology procedure commonly performed under general anaesthesia. The internal jugular vein (usually right) is cannulated, and a catheter passed into the hepatic vein. A wedge pressure is measured and the HVPG is calculated. Contrast is used to identify the relevant hepatic vascular anatomy and a tract is made between a branch of the hepatic venous and the portal venous system. The newly formed tract is then dilated using a balloon, and a stent is deployed to maintain patency. Typically, a TIPS procedure is deemed successful if the HVPG returns to normal, with a minimum goal of <12mmHg.[24,28] The procedure is summarised in Figure 1. The patients selected for a TIPS often present with numerous comorbidities. These comorbidities, the invasive nature of the procedure and the physiological changes during and after TIPS placement present several periprocedural complications that should be familiar to those providing care to these patients. These complications are summarised in Table 4.

Figure 1. Steps in a TIPS procedure



A) portal hypertension has caused the coronary vein (arrow) and the umbilical vein (arrowhead) to dilate and flow in reverse; B) a needle has been introduced (via the jugular vein) and is passing from the hepatic vein into the portal vein; C) the tract is dilated with a balloon; D) stent is deployed and portal pressure is normalised, with the coronary and umbilical veins no longer dilated. ("Tips schematic," R. Torrance Andrews, MD, Wikipedia, CC BY 1.0)

Table 4. Potential complications from TIPS insertion[29-31]

Procedural related complications - Internal jugular vein access complications ▪ Carotid, right atrial or tracheal puncture ▪ Pneumothorax ▪ Haemothorax ▪ Thoracic duct injury ▪ Brachial plexus injury - Arrythmias due to catheter passage into right atria/right ventricle - Complications associated with portal vein puncture ▪ Catastrophic haemorrhage/haemoperitoneum ▪ Liver capsule puncture - Injury to surrounding structures ▪ Inferior vena cava ▪ Hepatic artery ▪ Biliary structures ▪ Right kidney - Stent complications ▪ Misplacement ▪ Stent recoil/migration - Radiation injuries
Other complications - Issues relating to porto-systemic shunting ▪ Hepatic encephalopathy ▪ Cardiac decompensation/failure - Liver failure - Infection/sepsis - TIPS dysfunction ▪ Stent occlusion/thrombosis/dislodgement - Rare complications ▪ Haemolytic anaemia ▪ Cardiac perforation due to stent embolization ▪ Mechanical haemolysis

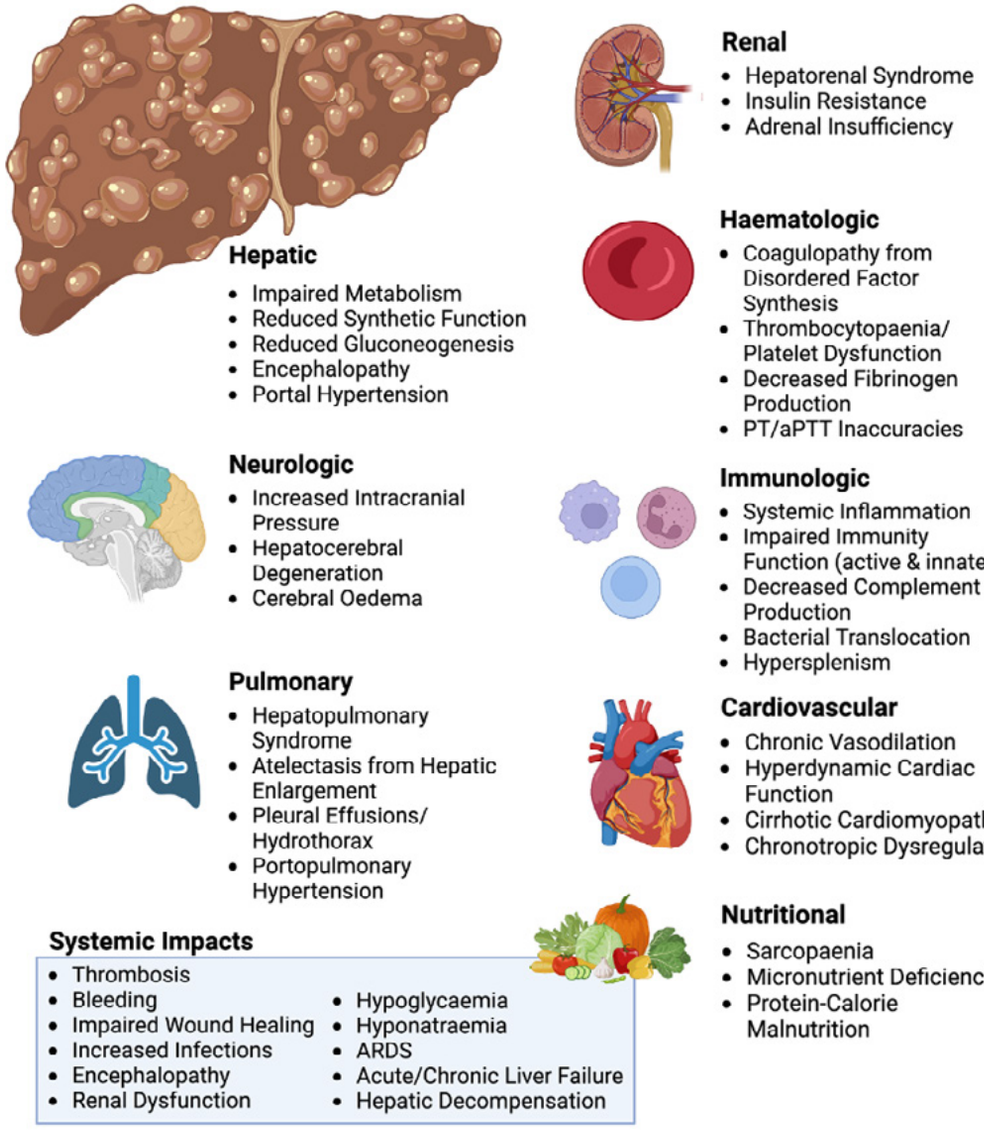
ANAESTHESIA MANAGEMENT

Pre-optimisation will involve the local hepatology team. The patient's eligibility for liver transplant is important to note. Although uncommon, TIPS can result in acute decompensation and deterioration into fulminant liver failure, potentially necessitating rapid assessment for liver transplantation.

In addition to a standard pre-operative assessment, consideration should be given to the physiological and pharmacological complications of advanced liver disease. A broad, by no means complete, list of systemic derangements that may need to be considered in the patient presenting with hepatic dysfunction is presented in Figure 2. Specific focus should be given to the cardiovascular system, identifying any history or clinical evidence of heart failure or pulmonary hypertension. Up to 50% of patients with advanced cirrhosis may have some form of cardiac dysfunction and often present with a hyperdynamic circulation. While these patients have an increased cardiac output at rest, there is reduced ability to respond to physiological stress.[30] Post TIPS, there is an increase in venous return as the portal system is offloaded and circulating volume returns to the systemic circulation. This fluid challenge results in an increase in cardiac output and exposure to inflammatory

mediators, which can lead to cardiac decompensation in the acute (post-procedural) setting. Patients with a chronically hyperdynamic circulation and low SVR are believed to be more predisposed to acute cardiovascular collapse immediately after a TIPS procedure. Up to one year after the procedure, patients are still at risk of cardiac decompensation, but via a different mechanism, which develops more slowly. It is estimated that up to 20% of patients will demonstrate cardiac decompensation post TIPS.[32] As well as a cardiovascular examination, a recent chest X-Ray, ECG and echocardiogram should be reviewed.

Figure 2. Common systemic pathophysiology in the patient with hepatic dysfunction



Ascites and hepatic hydrothorax impact on aspiration risk, respiratory function, and the likelihood of desaturation during induction. Patients who require regular ascitic drainage should ideally have this done prior to proceeding to TIPS. Any large volume paracentesis in the immediate pre-operative period should be paired with albumin replacement to reduce the risk of post-paracentesis circulatory dysfunction and renal impairment. Symptomatic or large volume hepatic hydrothorax may also require drainage pre-operatively.

Encephalopathy should be graded and documented. In an elective setting, moderate to severe encephalopathy may be a contraindication to TIPS due to the risk of worsening symptoms following placement.

There is no widely accepted consensus regarding pre-operative investigations prior to a TIPS procedure. Patient risk factors for bleeding and transfusion requirement, as well as the risk for hepatic or renal decompensation should be noted. A valid group and screen is required. This group of patients may have had repeated blood transfusions, leading to the possibility of red cell antibodies and cross match delays.

When a TIPS is performed in an acute setting, such as massive variceal haemorrhage, complications and mortality rates are significantly increased.[31]

INTRAOPERATIVE

TIPS procedures are performed in the interventional radiology suite. The usual challenges and safety concerns of both remote location anaesthesia and radiation exposure apply.

Limited literature exists around the use of local and sedation versus general anaesthesia for TIPS. Individual patient factors, as well as proceduralist preference will guide decision making regarding the optimal type of anaesthesia for each individual patient. The risk of intraoperative complications after shunt deployment (e.g. cardiac decompensation or pulmonary oedema) are arguably better managed in an anaesthetised, intubated patient.[31] TIPS procedures can be technically challenging and lengthy, with most centres in Australasia performing TIPS under general anaesthesia. Drug choices, venous access and monitoring should be guided by the severity of liver disease, concurrent patient comorbidities and local protocols.

In carefully selected patients, conscious sedation using a combination of propofol and/or remifentanil may be used. The patient must be able to lay flat for a prolonged period and have a low risk of aspiration. Balloon dilatation of the intrahepatic tract is painful and often poorly tolerated by conscious patients. The anaesthetist must be prepared for conversion to general anaesthesia at any point, acknowledging this can be difficult with limited access to the patient in the interventional suite once the procedure has begun.

Premedications, particularly benzodiazepines, should be used with caution due to the possibility of impaired hepatic metabolism and prolonged duration of action. Rapid sequence induction should be considered to mitigate the risk of aspiration in patients with severe ascites or hepatic hydrothorax. Tracheal intubation with paralysis also confers the benefit of controlled ventilation and the ability to perform breath holds.

Large bore intravenous access is recommended, and arterial cannulation should be considered. Although central venous access is not routine, if it is required, it will usually be via the left internal jugular or the femoral veins, depending on the radiologist's planned approach. In actively bleeding patients, rapid infusion devices and point of care coagulation testing should be available.

Suxamethonium is safe in advanced liver disease although it may have a prolonged duration of action. Atracurium and cisatracurium offer more dependable pharmacokinetic profiles due to their organ independent metabolism, but rocuronium and vecuronium can also be used safely. Maintenance of anaesthesia with either volatile or propofol TIVA is appropriate.[31] Dose reduction of propofol may be necessary secondary to an increased sensitivity. Fentanyl and remifentanil are the opioids of choice for this group as their metabolism remains largely unchanged in severe liver disease. Opioid use should be minimised where possible, and long-acting agents should be avoided.[33] Ketamine, clonidine, dexmedetomidine and gabapentinoids should be used with care due to their impaired metabolism and side effect profiles. Residual sedation will cloud the assessment of encephalopathy and should be a factor for consideration in anaesthetic planning. Broad spectrum antibiotics should be given in accordance with local guidelines.

The anaesthetist must be prepared to manage several potential intra-operative complications including massive haemorrhage, cardiac decompensation, and pulmonary oedema. Venous air embolism is a risk, particularly at the time of jugular sheath removal and in the spontaneously breathing patient. In the absence of complications, most patients are appropriate for extubation at the end of the procedure. Attention should be paid to the avoidance of coughing and straining on emergence, given the recent removal of a large jugular access sheath and the risk of bleeding and neck haematoma. If there is persisting haemodynamic instability, respiratory concerns, or evidence of acute cardiac or neurological deterioration, admission to the intensive care unit for haemodynamic and ventilatory support may be required.

POSTOPERATIVE

Postoperatively, there is potential for multisystem dysfunction. TIPS patients should be cared for in a monitored setting with ongoing specialist hepatology input. Patients with cardiac decompensation may require diuresis. In extubated patients, postoperative CPAP may be beneficial if there is evidence of pulmonary oedema. Encephalopathy occurs in up to 20% of patients following TIPS. Acute post TIPS hepatic encephalopathy occurs due to a rapid increase in ammonia levels with associated cerebral oedema. Conversely, chronic/late post TIPS encephalopathy does not present with cerebral oedema. Encephalopathy is generally managed medically; with a low protein diet and lactulose or rifaximin to reduce intestinal neurotoxin production and absorption. In refractory encephalopathy, the TIPS may need to be revised, reduced in size or re-occluded.[34]

Monitoring for worsening hepatorenal syndrome, contrast induced nephropathy and haemolytic anaemia is necessary. Shunt patency is checked using ultrasound, usually within one week post TIPS, and then for ongoing surveillance thereafter.

Post TIPS, close attention should be given to signs of developing sepsis and a low threshold exists for initiation of antibiotics. Responsible pathogens are typically *Escherichia coli, Klebsiella, enterococcus and Streptococcus.* Early identification and initiation of antibiotics to reduce deterioration in organ function is important.

CONCLUSION

Patients with advanced chronic liver disease are increasingly encountered by the general anaesthetist for interventions relating to their disease complications. Understanding the pathophysiology of portal hypertension, the perioperative interventions these patients often present for, the steps to consider for optimisation, and the potential pitfalls of each procedure are key in improving perioperative outcomes and effectively managing acute events for this high-risk group of patients.

REFERENCES

1. D. Kiamanesh, J. Rumley and V. K. Moitra. Monitoring and managing hepatic disease in anaesthesia. British Journal of Anaesthesia. 2013; 111(S1): i50–i61
2. Berzigotti A, Seijo S, Reverter E, Bosch J. Assessing portal hypertension in liver diseases. Expert Review of Gastroenterology and Hepatology. 2013;7(2):141-155.
3. Fanelli, F. The evolution of Transjugular Intrahepatic Portosystemic Shunt: TIPS. Review article, ISRN Hepatology. 2014, Article ID 762096. http://dx.doi.org/10.1155/2014/762096.
4. Schouten J, Garcia-Pagan J, Valla D, Janssen H. Idiopathic noncirrhotic portal hypertension. Hepatology. 2011; Sep 2;54(3):1071-1081. doi: 10.1002/hep.24422
5. Simonetto A, Liu M, Kamath P. Portal Hypertension and Related Complications: Diagnosis and Management. Thematic review series on gastroenterological diseases. 2019; 94(4):714-726.
6. Pinzani M, Rosselli M, Zuckermann M. Liver Cirrhosis. Best Practice & Research Clinical Gastroenterology. 2011; 25(2):281-290.
7. Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. Hepatology. 2004; 39(2):280-2.
8. Diaz-Soto MP, Garcia-Tsao G. Management of varices and variceal hemorrhage in liver cirrhosis: a recent update. Therapeutic Advances in Gastroenterology. 2022; 15:1-12. doi:10.1177/17562848221101712.
9. Kovalak M, Lake J, Mattek N, Eisen G, Lieberman D, Zaman A. Endoscopic screening for varices in cirrhotic patients: data from a national endoscopic database. Gastrointestinal Endoscopy. 2007; 65(1): 82-88. doi:10.1016/j.gie.2006.08.023
10. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal Hypertensive Bleeding in Cirrhosis: Risk Stratification, Diagnosis, and Management: 2016 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2017; 65(1): 310-335.
11. Gralnek IM, Duboc M C, Garcia-Pagan JC, et al. Endoscopic diagnosis and management of esophagogastric variceal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2022; 54(11):1094-1120. doi:10.1055/a-1939-4887
12. De Franchis R. Expanding consensus in portal hypertension. Report of the Baveno VI Consensus Workshop: Stratifying risk and invidualizing care for portal hypertension. Journal of Hepatology. 2015; 63:743-752.
13. Zanetto A, Shalaby S, Feltracco P, et al. Recent Advances in the Management of Acute Variceal Hemorrhage. Journal of Clinical Medicine. 2021; 10(17):3818. doi:10.3390/jcm10173818
14. Martínez J, Hernández-Gea V, Rodríguez-de-Santiago E, et al. Bacterial infections in patients with acute variceal bleeding in the era of antibiotic prophylaxis. Journal of Hepatology. 2021; 75(2): 342-350. doi:10.1016/j.jhep.2021.03.026
15. Krystallis C, Masterton GS, Hayes PC, Plevris JN. Update of endoscopy in liver diseases: More than just treating varices. World Journal of Gastroenterology. 2012; 18(5):401-411.
16. Baiges A, Hernández-Gea V, Bosch J. Pharmacologic prevention of variceal bleeding and rebleeding. Hepatology International. 2018; 12(Suppl 1):68-80. doi:10.1007/s12072-017-9833-y
17. Huaringa-Marcelo J, Huaman MR, Brañez-Condorena A, et al. Vasoactive Agents for the Management of Acute Variceal Bleeding: A Systematic Review and Meta-analysis. Journal of Gastrointestinal and Liver Diseases. 2021; 30(1):110-121. doi:10.15403/jgld-3191

18. Edelson J, Basso JE, Rockey DC. Updated strategies in the management of acute variceal haemorrhage. Current Opinion in Gastroenterology. 2021; 37(3):167-172. doi:10.1097/MOG.0000000000000723
19. Odutayo A, Desborough MJR, Trivella M, et al. Restrictive versus liberal blood transfusion for gastrointestinal bleeding: a systematic review and meta-analysis of randomised controlled trials. Lancet Gastroenterology and Hepatology. 2017; 2(5):354-360.
20. Northup PG, Lisman T, Roberts LN. Treatment of bleeding in patients with liver disease. Journal of Thrombosis and Haemostasis. 2021; 19(7):1644-1652. doi:10.1111/jth.15364
21. Rout G, Shalimar, Gunjun D et al. Thromboelastography-guided blood product transfusion in cirrhosis patients with variceal bleeding: a randomised controlled trial. Journal of Clinical Gastroenterology. 2020; 54(3):255-262.
22. O'Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA Clinical Practice Update: Coagulation in Cirrhosis. Gastroenterology. 2019; 157(1):34-43.e1. doi:10.1053/j.gastro.2019.03.070
23. Agarwalla K. Anesthesia for Transjugular Intrahepatic Portosystemic Shunt (TIPS) procedures. Anesthesia for Uncommon and Emerging Procedures. 2021; 173-180. https://doi.org/10.1007/978-3-030-64739-1_19#DOI
24. Chana A, James M, Veale P. Anaesthesia for transjugular intrahepatic portosystemic shunt insertion. BJA Education. 2016; 16(12): 405–409.
25. Jain D, Mahmood E, V-Bandres, M, Feyssa Y. Preoperative elective transjugular intrahepatic portosystemic shunt for cirrhotic patients undergoing abdominal surgery. Annals of Gastroenterology. 2017; 31, 330-337.
26. Sellers M, Nezami N, Schilsky M, Kim, H. Transjugular intrahepatic portosystemic shunt as a bridge to liver transplant: Current state and future directions. Transplantation Reviews. 2019; 33(2):64-71.
27. Dariushnia S, Haskal Z, Midia M, Martin L, Walker T, Kalva S, Clark T, Ganguli S, Krishnamurthy V, Saiter C, Nikolic B. Society of Interventional Radiology Standards of Practice Committee. Quality Improvement Guidelines for Transjugular Intrahepatic Portosystemic Shunts. Journal of Vascular and Interventional Radiology. 2016; 27(1):1. Epub 2015 Nov 21.
28. Boyer TD, Haskal ZJ, American Association for the Study of Liver Diseases. The role of Transjugular Intrahepatic Portosystemic Shunt (TIPS) in the management of portal hypertension. Hepatology. 2010; 51(1):306. https://doi.org/10.1002/ hep.23383.
29. Ripamonti R, Ferral H, Alonzo M, Patel NH. Transjugular intrahepatic portosystemic shunt-related complications and practical solutions. Seminars in Interventional Radiology. 2006; 23:165–76.
30. Zardi E, Zardi D, Dobrina A, Margiotta D, Van Tassell B, Afeltra A, Sanyal AJ. Cirrhotic Cardiomyopathy. Journal of the American College of Cardiology. 2010; 56(7):539. Department of Clinical Medicine, University Campus Bio-Medico, Via Alvaro del Portillo, Rome, Italy.
31. DeGasperi A, Corti A, Corso R, Rampoldi A, Roselli E, Mazza E, Fantini G, Prosperi, M. Transjugular intrahepatic portosystemic shunt (TIPS): the anesthesiological point of view after 150 procedures managed under total intravenous anesthesia. J Clinical Monitoring and Computing. 2009; 23:341–6.
32. Billey C, Billet S, Robic MA, Cognet T, Guillaume M, Vinel JP, Péron JM, Lairez O, Bureau C. A Prospective Study Identifying Predictive Factors of Cardiac Decompensation After Transjugular Intrahepatic Portosystemic Shunt: The Toulouse Algorithm. Hepatology. 2019 Dec;70(6):1928-1941. doi: 10.1002/hep.30934. PMID: 31512743.
33. Soleimanpour H, Saeid S, Shahsavari Nia K, Sanaie S, Alavian SM. Opioid drugs in patients with liver disease: a systematic review. Hepatol Mon. 2016; 16(4):e32636.
34. Schindler P, Heinzow H, Trebicka J. and Wildgruber, M. Shunt induced hepatic encephalopathy in TIPS: Current approaches and clinical challenges. Journal of Clinical Medicine. 2020; 23;9(11):3784.

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Perioperative management of patients on naltrexone

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INTRODUCTION

Naltrexone is a long-acting opioid receptor antagonist increasingly prescribed in the community for a wide variety of conditions. Patients taking naltrexone present particular challenges in pain management in the perioperative period. Depending on the dose, formulation, and recency of taking naltrexone, patients may be very resistant to opioid analgesics or may also show increased sensitivity to the analgesic and respiratory effects of opioids. This complexity means that patients are at risk of both poorly controlled pain and respiratory depression, potentially within the same presentation. Patients should therefore be managed by multidisciplinary teams with experience in complex acute pain with the availability of respiratory monitoring and support.

This review will examine the current clinical uses of naltrexone including different dosages and administration. We will discuss the implications of naltrexone therapy for elective and emergency procedures and suggest approaches to analgesic and anaesthetic management in these complex patients.

PHARMACOLOGY

Naltrexone is a long-acting competitive antagonist of opioid receptors, with the highest affinity for μ-receptors. It has a half-life of 5 hours. It also has an active metabolite, 6β-naltrexone, which has a much longer half-life of 15 hours.[1] Oral doses are subject to extensive first pass metabolism in the liver, with only 2% excreted unchanged in the urine.[2] Naltrexone has an excellent safety profile, and is generally well tolerated by patients.[3] It has been associated with hepatotoxicity when given in very high doses[4] but has been shown to be safe even in patients with compensated cirrhosis at clinically relevant doses.[5] Common currently prescribed formulations of naltrexone are presented in Table 1.

CLINICAL INDICATIONS

Alcohol or opioid abstinence

Naltrexone is indicated as part of a comprehensive treatment plan for alcohol dependence with a goal of abstinence.[1] Naltrexone has also been show to decrease rates of relapse after abstinence from alcohol.[6,7] The mechanism of action is thought to be via reduction in reward and intoxication associated with drinking alcohol,[8] with the greatest clinical effect being in reducing heavy or excessive drinking.[9] Naltrexone is less commonly used for opioid abstinence as opioid substitution with buprenorphine or methadone is generally preferred in Australia.[10] The oral formulation is also used to treat opioid related side effects such as severe constipation in the palliative care setting as an off-label use.[11] Methylnaltrexone has a methyl group added to reduce its lipid solubility and to limit blood brain barrier crossing, and therefore is more selective for peripheral opioid receptors. It can be given as a subcutaneous injection to relieve severe constipation without counteracting analgesic effects on central nervous system.

In this high dose, naltrexone is available in several formulations. Oral naltrexone is taken in a dose of 50mg per day and this formulation is TGA approved in Australia and Medsafe approved in New Zealand. A subcutaneous implant is available through the Special Access Scheme only. Implants have a variable duration. The formulation accessible in Australia has a stated duration of action of approximately 180 days. A depot formulation, not currently available in Australia or New Zealand, has a duration of action of approximately 28 days.

Table 1. Naltrexone formulations in clinical use in Australia and New Zealand

Formulation (brand name)	Dose (route)	TGA/ Medsafe NZ Approved	Indications
Naltrexone Hydrochloride (Generic health, Naltraccord)	50mg daily (orally)	Yes	For use within a comprehensive treatment program for alcohol dependence. OR as adjunctive therapy in the maintenance of formerly opioid-dependent patients who have ceased the use of opioids such as diamorphine (heroin) and morphine.
O'Neil Long acting naltrexone implant (Go Pharmaceuticals)	1.8g surgical implant, every 6 to 12 months	Special Access Scheme approval only (TGA)	As above
Naltrexone depot for intramuscular injection (Vivitrol)	380mg every 4 weeks (intramuscular)	No	Alcohol dependence or for the prevention of relapse to opioid dependence, following opioid detoxification.
Naltrexone HCl / Bupropion (Contrave)	8-32mg / 90-360mg daily (orally)	Yes	Contrave is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial Body Mass Index (BMI) of ≥ 30 kg/m^2 (obese), or ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension)
Naltrexone Hydrochloride (pharmacy compounded medicine)	1-7mg daily (orally)	Off-label use of oral formulation	Used for a wide range of disorders, including chronic pain conditions and inflammatory conditions

Management of weight loss

A combination weight loss pill (Contrave – naltrexone/bupropion) was approved in 2019 by the TGA for patients with morbid obesity and at least one associated condition (for example, diabetes).[12] Patients on this therapy receive between 8 and 32 mg of naltrexone per day, in combination with sustained release bupropion. Naltrexone and bupropion work synergistically on central neural pathways in the hypothalamus to both reduce appetite and cravings for food[13] resulting in effective weight loss.[14]

Chronic pain and inflammatory conditions

Low dose naltrexone (1-6 mg per day) may be prescribed for the management of chronic pain conditions, and has been described for the treatment of a wide range of conditions such as fibromyalgia, Crohn's disease, multiple sclerosis, complex-regional pain syndrome, Hailey-Hailey disease, and cancer.[15] Low dose naltrexone is currently being explored as a treatment for chronic fatigue syndrome[16] and Post-COVID-19 Syndrome.[17] Anaesthetists may see patients presenting for fertility treatments on low dose naltrexone as it is increasingly utilised in this setting.[18] At low doses it is thought to display differential pharmacodynamics, and in this dose range may act as a glial modulator through actions at toll-like protein receptors in neural cells, as well as enhancing endogenous endorphin release.[19] Although there are promising in vitro studies,[20] high quality clinical evidence for low dose naltrexone in these conditions is lacking.[21] Evidence of clinical efficacy is largely anecdotal, with limited numbers of small randomised controlled trials.

All of these indications are currently off-label uses of naltrexone, and the prescription must be made up by a compounding pharmacy for patients in Australia and New Zealand. Given the wide range of conditions for which low dose naltrexone is prescribed, it is likely that anaesthetists will encounter increasing numbers of patients on this medication in their practice. Familiarisation with these off-label uses of naltrexone is important as it may not be expected or readily detected in the broader patient population.

Ultra-low dose naltrexone (in the range of picograms to nanograms per kilogram) is sometimes used in patients with chronic non-malignant pain who require high doses of opioids. In ultra-low doses, naltrexone appears to enhance analgesic efficacy and decrease certain side effects of opioid analgesics, and potentially reduce tolerance.[22] This is a relatively uncommon off-label use of naltrexone and is beyond the scope of this review.

PERIOPERATIVE CONSIDERATIONS

As a competitive antagonist of all opioid drugs, naltrexone has serious implications for the pain management of all patients presenting to hospital.[23] Patients utilising formulations of naltrexone may experience inadequately controlled pain and exceedingly high opioid requirements, as well as difficult to manage hypertension under general anaesthetic.[24] Without careful titration of opioid analgesia and monitoring of these patients, there is a risk of respiratory depression with the offset of naltrexone.[25]

Patients can be considered opioid naive after the cessation of naltrexone.[26] After discontinuation, enhanced opioid sensitivity may occur due to selective upregulation of μ-receptors. This means that response to opioids may be unpredictable, resulting in potentially higher risk of respiratory depression requiring close monitoring throughout the perioperative period.[27] These patients therefore may not be suitable for day case surgery and a need for post-operative admission to hospital should be assessed in each case.

Management of patients on naltrexone formulations is complex, and the best approach will vary depending on the needs of the patient, the procedure required, the dose of naltrexone and the need for opioid analgesia.

MANAGEMENT OF PATIENTS PRESENTING FOR ELECTIVE PROCEDURES

The approach to patients presenting for elective procedures is summarised in Figure 1. In essence, management of these patients requires identification of those taking naltrexone and then ensuring that this is ceased appropriately prior to surgery. If the patient is taking a combined naltrexone/bupropion preparation, replacement therapy may be required.

It may be appropriate to continue naltrexone therapy throughout the perioperative period. These decisions should be made on a case-by-case basis by surgical and anaesthesia teams in consultation with the naltrexone prescriber. Procedures that are expected to cause mild or no pain, or that can be managed entirely with non-opioid analgesia may be appropriate for this, such as cataract surgery, minor plastic procedures or colonoscopy.[27] This may be of particular benefit in patients at high risk of relapse of opioid or alcohol abuse if naltrexone therapy is ceased.

Management of patients on naltrexone for opioid or alcohol abstinence

Patients who are on naltrexone for opioid or alcohol abstinence will require cessation of therapy prior to most surgeries. Management of naltrexone in the perioperative period should be done in co-ordination with the patient's general practitioner and their naltrexone prescriber.[26] Preoperative patient and family education is important, to set expectations and ensure appropriate supports are in place.[28] Oral naltrexone should be stopped at least 24 hours, and ideally 72 hours, prior to elective surgery due to prolonged opioid receptor antagonism.[26] After 24 hours, a 100mg dose of naltrexone will effectively block 96% of μ-opioid receptors. This

falls to 86.5% at 48 hours and 46.6% at 72 hours.[28] In our institution, we recommend cessation of naltrexone 72 hours preoperatively to ensure best achievable opioid responsiveness for patients during the perioperative period. The period of cessation may need to be further prolonged in patients with renal or hepatic impairment.[1]

Naltrexone implants may need surgical removal in cases of severe acute pain, where opioid responsiveness is required.[26] Duration of action after removal of an implant is unknown, and it may be advisable to plan non-opioid analgesia rather than attempt removal.[29] If patients are on intramuscular injections of extended release naltrexone, this will need to be stopped at least 25 days prior to surgery in order to ensure naltrexone has been cleared.[30] Patients may need to be transitioned to oral naltrexone for this period, which can then be stopped 72 hours prior to surgery. This must be done in co-ordination with the patient's naltrexone prescriber.

Patients may be at high risk of relapse of alcohol or opioid abuse while off naltrexone and may benefit from extra supports during this period.[31] This may include early admission to hospital for observation and support if appropriate. Patients should be educated that the highest mortality risk is from patients taking pre-naltrexone doses of opioids, which may result in overdose and respiratory arrest.[32]

Management of patients on combined Naltrexone/Bupropion (Contrave)

There is no clear guidance from the manufacturer or in the literature about when Contrave should be stopped in the lead up to surgery. Given the dosages, it is prudent to cease 72 hours prior to surgery as for high dose naltrexone as similar issues are encountered intraoperatively.[33] This should be done in consultation with the patient's naltrexone prescriber as consideration needs to be given as to whether to continue bupropion as a single agent. The manufacturers do not recommend a taper for discontinuation of Contrave as no withdrawal syndromes were seen in initial randomised controlled trials.[12] However there have been case reports of withdrawal symptoms associated with bupropion discontinuation[34] and tapering regimens are recommended.[35] If the patient wishes to avoid antidepressant discontinuation syndrome, bupropion can be continued as a single agent. In Australia, bupropion is only available as an extended-release preparation, which should not be split.[36] A suggested dosing regimen is shown in Table 2, which facilitates minimal change in dose of bupropion.

It should be noted in these patients some opioid alternative medications must be used with caution. Bupropion is an inhibitor of CYP2D6, which may prevent tramadol being converted to its active metabolite and decrease its effectiveness.[37] Bupropion also lowers the seizure threshold.[38]

Table 2. Suggested replacement dosing of bupropion as a single agent for patients on Naltrexone/Bupropion (Contrave)

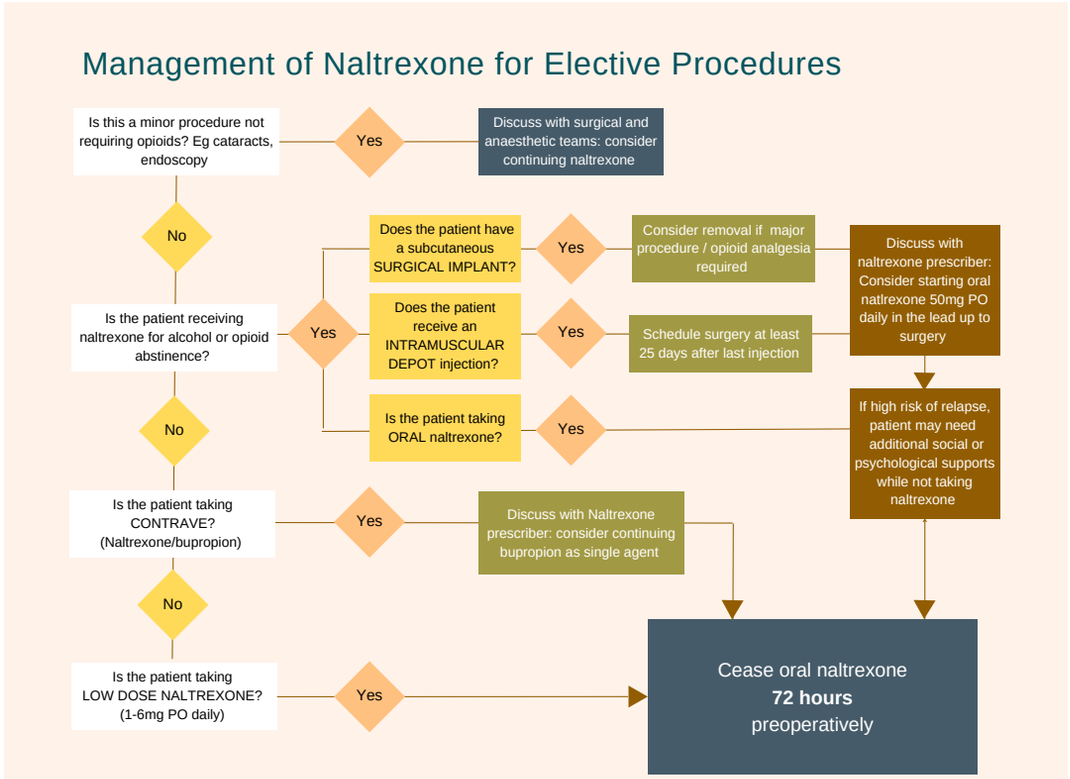
Daily dose of Contrave (Naltrexone/Bupropion)	Replacement dose of Zyban (Bupropion Extended Release)
One tablet per day (Total dose 8mg/90mg)	No replacement bupropion required
One tablet twice per day (Total dose 16mg/180mg)	150mg PO once daily
Three to four tablets per day (Total dose range 24mg/270mg to 32mg/360mg)	150mg PO twice daily

Management of patients on low dose naltrexone for chronic pain or inflammatory conditions

There is little data available regarding the impact of low dose naltrexone on analgesia and anaesthesia. Research into combined preparations of morphine and naltrexone have shown that low dose naltrexone (1.2mg) co-administered with oral and intravenous morphine significantly reduces both the subjective opioid effects as well as objective measures such as pupillometry.[39] In one study, low dose naltrexone co-administered with morphine resulted in significantly reduced end tidal CO_2, equivalent to placebo levels, when compared to morphine alone.[40] Patients taking these low doses of naltrexone will likely require higher than expected doses of opioid medication to achieve adequate pain control. It is not clear if cessation of naltrexone at this low dose results in similar opioid sensitivity as seen with cessation of high dose naltrexone.

Evidence is lacking as to the optimal timing for cessation of low dose naltrexone. General patient advice recommends cessation anywhere from 24 hours to 7 days before a procedure.[41,42] There are descriptions in the literature of uneventful anaesthesia 24 hours after low dose naltrexone,[43] however no detailed case reports are available. In our clinical experience, low dose naltrexone (1-6mg per day) continued throughout the perioperative period results in significantly increased opioid requirements, even when maximising non-opioid analgesia. Pain may also be more difficult to manage post operatively as a result. On the basis of this, we suggest low dose naltrexone to be withheld for 24 to 72 hours preoperatively. Our institutional guideline recommends a 72-hour period, for consistency across all naltrexone formulations.

Figure 1. Preoperative management of naltrexone for elective procedures



MANAGEMENT OF PATIENTS PRESENTING FOR EMERGENCY SURGERY OR WITH TRAUMA

All patients on naltrexone presenting for emergency surgery or with trauma should be managed by an experienced team with input from an acute pain service.

It is important to determine the timing of the last dose of naltrexone.[25] If this was within the last 72 hours, patients may require higher than usual doses of opioids to manage their pain. As a competitive antagonist, the effects of naltrexone can be overcome with sufficiently high dose opioid. In rats, the dose of opioids needed to accomplish this may be 10–20 times the standard clinical doses.[44] These doses may be associated with severe respiratory depression and non-opioid receptor related side-effects including erythema and bronchoconstriction.[45] The offset of the naltrexone may be abrupt and cause respiratory depression secondary to the un-antagonised action of now excessive opioids.[46] After cessation of naltrexone, patients are at risk of respiratory depression due to transient increased opioid receptor sensitivity as well as direct decrease in effect of naltrexone resulting in lower analgesic opioid dose requirements.[26] Patients should therefore be monitored in a high dependency environment with the capacity for ventilatory management.[47]

Cessation of naltrexone will allow the most analgesic options for patients with major surgery or multi-trauma during their recovery. If a patient is taking a naltrexone/bupropion preparation (Contrave), consider continuing bupropion as a single drug to avoid anti-depressant withdrawal symptoms. It may be appropriate for patients having only minor surgery with minimal postoperative pain to continue naltrexone uninterrupted. Patients on low dose naltrexone may be able to continue their naltrexone, compensating for this by utilising higher doses of opioids, but this remains an individual risk:benefit decision. An approach to patients presenting for emergency procedures is summarised in Figure 2.

Opioid medications

Intraoperative management can be particularly challenging in patients who are still on naltrexone. Profound hypertension may be seen with laryngoscopy and surgical stimulation.[48,49] Short acting opioids are preferred to manage these effects, given the high doses required and high risk of respiratory depression post-operatively. High dose remifentanil is a pharmacologically favourable opioid which can be titrated to effectively overcome naltrexone blockade with rapid and predictable offset.[49] Use of remifentanil can be associated with opioid induced hyperalgesia and there are concerns that this may contribute to difficult postoperative pain management.[50] Opioid antagonists are protective against the development of hyperalgesia[51] meaning this effect may be less relevant in this population.

Short acting opioids are most suitable for analgesia to facilitate titration to patient response given inter-individual variation.[52] Because naltrexone competitively binds to μ-receptors, utilising opioids with higher affinity for μ-receptors such as fentanyl and hydromorphone may result in greater effect.[53] The high doses required of histamine releasing opioids such as morphine may result in unacceptable non-opioid mediated side effects such as erythema, bronchospasm, and hypotension. Hydromorphone and fentanyl do not stimulate histamine release,[54] further reinforcing their utility in this setting. Although tramadol exerts some of its analgesic effects through action at μ-receptors, it may still have analgesic efficiency in the presence of naltrexone. This is however associated with increased nausea and vomiting.[55]

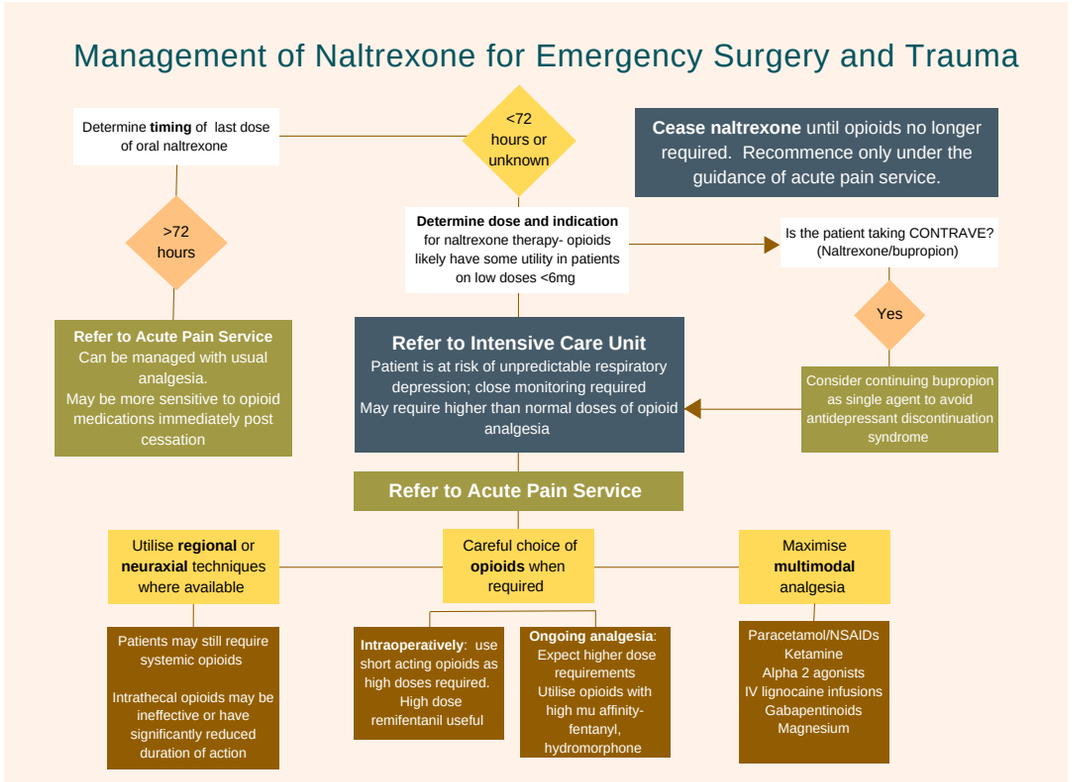
In patients on low dose naltrexone, opioids are likely to still have some clinical utility; albeit requiring higher than normal doses. Low dose naltrexone has been used to prevent adverse effects associated with intrathecal and high dose oral morphine. A 250 microgram dose of intrathecal morphine was shown to provide analgesia for Caesarean section in the presence of low dose naltrexone (6mg) although with significantly shorter duration of action.[56] There is some suggestion that a 1mg dose of naltrexone does not significantly impact analgesia in patients on high dose oral morphine or continuous intrathecal morphine for chronic pain.[57] Patients should be monitored carefully for adequate analgesic effect and adverse side effects of opioid medications.

Opioid sparing anaesthesia and analgesia

Due to the prolonged opioid antagonist action of naltrexone, patients will require maximisation of non-opioid analgesia, including regional or neuraxial analgesia, as appropriate.[58] Regional anaesthesia can provide superior analgesia to parenteral opioids.[59] Where neuraxial or peripheral nerve blocks are used, placement of catheters should be considered to facilitate extended postoperative opioid-sparing analgesia. Neuraxial or regional analgesia may not be completely effective in controlling pain and this may require the addition of short acting opioids in a monitored environment.[47]

Ketamine has been used effectively as an adjunct for both anaesthesia and analgesia in patients receiving naltrexone.[48,49] Multimodal analgesia is recommended, including paracetamol, non-steroidal anti-inflammatory medications, gabapentinoids, magnesium, lignocaine infusions and alpha-2 agonists such as clonidine and dexmedetomidine.[26] Doses that can be utilised for analgesia are limited by side effects[54] and opioid medications may still be required in the presence of severe pain.

Figure 2. Management of naltrexone for emergency surgery and trauma



TRANSITIONAL PAIN MANAGEMENT

The decision of when to recommence naltrexone is complex and requires multidisciplinary collaboration. All patients on naltrexone formulations should be referred to a specialist acute pain management service postoperatively. Manufacturers recommend recommencement of naltrexone 5 to 7 days after last dose of opioid.[1,12] Naltrexone has a higher affinity for μ-receptors than most opioid agonists and so can preferentially displace circulating opioids and precipitate acute withdrawal.[60] Abrupt precipitated opioid withdrawal is dangerous and potentially lethal.[61] Clear communication with the multidisciplinary team is important to ensure thorough understanding of the pain management plan[29] and to ensure that naltrexone is not inadvertently given too soon. We have found adding an alert to the patient's medication chart helps to communicate the importance of avoiding naltrexone while the patient is receiving opioids.

Careful planning of transition back to naltrexone should start early in the admission. As patients may be recommencing naltrexone after discharge from hospital, it is important that hospital teams work closely with community providers to ensure patients are well informed and well supported. Patients may benefit from the involvement of alcohol and other drug services as they may require extra support during this high-risk time for relapse.[30]

Timing of recommencement is a case-by-case decision, requiring specialist input especially where shorter time frames may be desired. Shorter intervals should only be considered where very limited doses of short acting opioids have been used. Australian guidelines for the introduction of high dose naltrexone for opioid abstinence recommend an interval of 5 days between last buprenorphine and first naltrexone and up to 10-14 days if methadone was the last opioid used.[10] There is an absence of guidance as to when it is safe to recommence low dose naltrexone, and this should be a risk:benefit decision made on a case-by-case basis.

If there are any concerns about recommencement of naltrexone, a naloxone challenge test should be performed, as outlined in Table 3.[1]

Table 3. Naloxone Challenge Test[1]

- Gain intravenous (IV) access.
- Monitor vital signs – Heart rate, blood pressure, oxygen saturation, temperature.
- Observe patient for signs and symptoms of withdrawal:
- E.g. Nausea and vomiting, abdominal cramps, sweating, rhinorrhoea, bone and joint pain, piloerection, anxiety, irritability, pupillary dilatation.
- Give initial dose of naloxone: 200 micrograms Naloxone IV
- Observe for 30 seconds for signs or symptoms of withdrawal.
- If no evidence of withdrawal, give full test dose of naloxone: 600 micrograms IV
- Observe for an additional 20 minutes.
- If there are any indications of opioid withdrawal, the test is positive. Do not administer further naloxone.
- If the test is **positive**, do not administer naltrexone and repeat the test in 24 hours.
- If the test is **negative**, naltrexone can be administered as long as there are no other contraindications.

CONCLUSION

Naltrexone is increasingly commonly used in the community, particularly in low doses for off label indications. Patients on naltrexone present particular challenges in both their anaesthetic and analgesic management when they present in both elective and emergency settings. Management requires close communication of the multidisciplinary team and should involve an acute pain management service wherever possible. Decisions regarding the use of opioids in these patients requires consideration of dosage, timing and indication for naltrexone and the impact on the patient when naltrexone is recommenced. More research is needed, especially to help guide the management of patients on low dose naltrexone.

REFERENCES

1. Therapeutic Goods Administration. Australian Product Information – Naltrexone (naltrexone hydrochloride), film-coated tablets [Internet]. Weston Creek, Canberra: Therapeutic Goods Administration; 2021 [cited 2023 January 20]. Available from https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2013-PI-01168-1&d=20230118172310101&d=20230119172310101
2. Naltrexone hydrochloride. Aust Prescr 1999;22:43-7.
3. Bolton M, Hodkinson A, Boda S, Mold A, Panagioti M, Rhodes S,et al. Serious adverse events reported in placebo randomised controlled trials of oral naltrexone: a systematic review and meta-analysis. BMC Med 2019; 17:10
4. Croop RS, Faulkner EB, Labriola DF. The safety profile of naltrexone in the treatment of alcoholism. Results from a multicenter usage study. The Naltrexone Usage Study Group. Arch Gen Psychiatry. 1997;54(12):1130-5.
5. Ayvala D, Bottyan T, Tien C, Pimienta M, Yoo J, Stager K et al. Naltrexone for alcohol use disorder: Hepatic safety in patients with and without liver disease. Hepatol Commun 2022;6(12): 3433-3442.
6. Crowley P. Long-term drug treatment of patients with alcohol dependence. Aust Prescr 2015;38:41-3.
7. Srisurapanont M, Jarusuraisin N. Naltrexone for the treatment of alcoholism: a meta-analysis of randomized controlled trials. Int J Neuropsychopharmacol. 2005 Jun;8(2):267-80.
8. Anton RF, Oroszi G, O'Malley S, Couper D, Swift R, Pettinati H, Goldman D. An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. Arch Gen Psychiatry. 2008 Feb;65(2):135-44.
9. Pettinati HM, O'Brien CP, Rabinowitz AR, Wortman SP, Oslin DW, Kampman KM, et al. The status of naltrexone in the treatment of alcohol dependence: specific effects on heavy drinking. J Clin Psychopharmacol. 2006 Dec;26(6):610-25.
10. Gowing L, Ali R, Dunlop A, Farrell M, Lintzeris N. National guidelines for medication-assisted treatment of opioid dependence.[Internet] Canberra: Commonwealth of Australia. 2014. [Cited 2023 January 18] Available from: https://www.health.gov.au/sites/default/files/national-guidelines-for-medication-assisted-treatment- of-opioid-dependence.pdf
11. Choi Y S and Billings JA. Opioid antagonists: A review of their role in palliative care, focusing on use in opioid-related constipation. J Pain Symptom Manage 2002; 24(1): 71-90.
12. Therapeutic Goods Administration. Australian Product Information – Contrave (naltrexone Hydrochloride and bupropion hydrochloride), extended-release tablets [Internet]. Weston Creek, Canberra: Therapeutic Goods Administration; 2019. Available from https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2019-PI-01018-1

13. Hausenloy D. Contrave: novel treatment for obesity, Clin Lipidol 2009; 4:3, 279-285.
14. Qingyang S, Yang W, Quikui H, Vandvik PO, Guyatt G, Jing L, et al. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. Lancet 2022; 399(10321):259-269.
15. Toljan K and Vrooman B. Low-dose naltrexone (LDN)- Review of therapeutic utilization. Med Sci (Basel). 2018 Dec; 6(4): 82.
16. Bolton MJ, Chapman BP, Van Marwijk H. Low-dose naltrexone as a treatment for chronic fatigue syndrome. BMJ Case Rep 2020;13:e232502.
17. O'Kelly B, Vidal L, McHugh T, Woo J, Avramovic G and Lambert JS. Safety and efficacy of low dose naltrexone in a long covid cohort; an interventional pre-post study. Brain Behav Immun Health 2022, 24: 100485.
18. Boyle PC, Stanford JB and Zecevic I. Successful pregnancy with restorative reproductive medicine after 16 years of infertility, three recurrent miscarriages, and eight unsuccessful embryo transfers with in vitro fertilization/intracytoplasmic sperm injection: a case report. J Med Case Reports 2022; 16: 246.
19. Agarwal, D.; Toljan, K.; Qureshi, H.; Vrooman, B. Therapeutic value of naltrexone as a glial modulator. Glia 2017, 65, E103–E578.
20. Cabanas H, Muraki K, Eaton-Fitch N, Staines D R, Marshall-Gradisnik, S. Potential therapeutic benefit of low dose naltrexone in myalgic encephalomyelitis/chronic fatigue syndrome: Role of transient receptor potential melastatin 3 ion channels in pathophysiology and treatment. Front Immunol 2021; 12:68706
21. Kim PS and Fishman MA. Low-dose naltrexone for chronic pain: Update and systemic review. Curr Pain Headache Rep 2020; 24: 64.
22. Burns LH, Wang H-Y. Ultra-low-dose naloxone or naltrexone to improve opioid analgesia: The history, the mystery and a novel approach. Clin Med Insights Ther. 2010;2: 857-868.
23. Vickers AP and Jolly A. Naltrexone and problems in pain management: How to manage acute pain in people taking an opioid antagonist. BMJ 2006; 332(7534): 132–133.
24. Schwab CA, Wright DA. Intraoperative high-dose remifentanil in a patient on naltrexone therapy. Anaesth Intensive Care. 2000;28(6):701-703.
25. Burns SL, Maidak P and Urman RD. Perioperative and periprocedural anesthetic management of opioid tolerant patients and patients with active and medically treated opioid use disorder. Curr Opin Anaesthesiol. 2022; 35(4):514-520(7)
26. Schug SA, Palmer GM, Scott DA, Alcock M, Halliwell R, Mott JF. APM:SE Working Group of The Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (2020), Acute Pain Management: Scientific Evidence (5th edition), ANZCA & FPM, Melbourne.
27. Beauchamp GA, Hanisak JL, Amaducci AM, Koons AL, Laskosky J, Maron BM et al. Perioperative management of patients on maintenance medication for addiction treatment: The development of an institutional guideline. AANA J. 2022; 90(1): 50-7.
28. Ward EN, Quaye AN, Wilens TE. Opioid use disorders: Perioperative management of a special population. Anesth Analg. 2018 Aug;127(2):539-547.
29. Vickers AP, Jolly A. Naltrexone and problems in pain management. BMJ. 2006 Jan 21;332(7534):132-3.
30. Harrison TK, Kornfeld H, Aggarwal AK, Lembke A. Perioperative considerations for the patient with opioid use disorder on buprenorphine, methadone, or naltrexone maintenance therapy. Anesthesiol Clin. 2018; 36(3): 345 – 359.
31. Kiefer F, Jahn H, Tarnaske T. Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: A double-blind, placebo-controlled study. Arch Gen Psychiatry.2003;60(1):92–99.
32. Kjome KL, Moeller FG. Long-acting injectable naltrexone for the management of patients with opioid dependence. Subst Abuse. 2011;5:1-9.
33. Ninh, Allen BS; Kim, Sang MD; Goldberg, Andrew MD. Perioperative pain management of a patient taking Naltrexone HCl/Bupropion HCl (Contrave): A case report. A & A Case Rep. 2017; 9(8): 224-226.
34. Berigan TR, Harazin JS. Bupropion-associated withdrawal symptoms: A case report. Prim Care Companion J Clin Psychiatry. 1999 Apr;1(2):50-51.
35. Warner CH, Bobo W, Warner C, Reid S, Rachal J. Antidepressant discontinuation syndrome. Am Fam Physician. 2006;74(3):449-56.
36. Therapeutic Goods Administration. Australian Product Information – Zyban SR (bupropion hydrochloride) sustained release tablets. Contrave [Internet]. Weston Creek, Canberra: Therapeutic Goods Administration; 2021 [cited 18 January 2023]. Available from: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01138- 1
37. Frost, D.A., Soric, M.M., Kaiser, R. and Neugebauer, R.E. Efficacy of tramadol for pain management in patients receiving strong cytochrome P450 2D6 inhibitors. Pharmacotherapy. 2019; 39: 724-729.
38. Sherman MM, Ungureanu S, Rey JA. Naltrexone/Bupropion ER (Contrave): Newly approved treatment option for chronic weight management in obese adults. P & T. 2016 Mar;41(3):164-72.
39. Stauffer, J., Setnik, B., Sokolowska, M. Subjective effects and safety of whole and tampered morphine sulfate and naltrexone hydrochloride (ALO-01) extended-release capsules versus morphine solution and placebo in experienced non-dependent opioid users. Clin Drug Investig. 2009; 29:777–790.
40. Goli, V., Webster, L.R., Lamson, M.J, Cleveland JM, Somerville KW, Carter E. Effects of concurrent intravenous morphine sulfate and naltrexone hydrochloride on end-tidal carbon dioxide. Harm Reduct J. 2012; 9:13
41. Dickson S. LDN Information before and after surgery [Internet]. Glasgow, Scotland: LDN Research Trust; 2021 [cited 18 January 2023]. Available from https://ldnresearchtrust.org/ldn-information-and-after-surgery
42. Fookes C. Low dose naltrexone [Internet]. New York, USA: Healthline Networks; 2022 [cited 18 January 2023]. Available from https://www.drugs.com/medical-answers/low-dose-naltrexone-ldn-3570335/

43. Chopra P, Cooper MS. Treatment of complex regional pain syndrome (CRPS) using low dose naltrexone (LDN). J Neuroimmune Pharmacol. 2013; 8: 470–476.
44. Dean RL, Todtenkopf MS, Deaver DR, Arastu MF, Dong N, Reitano K, et al. Overriding the blockade of antinociceptive actions of opioids in rats treated with extended-release naltrexone. Pharmacol Biochem Behav 2008;89:515–522.
45. Graham JM, Evans B. Severe uncontrolled pain in buttock in a patient on naltrexone: a diagnostic challenge. Anaesth Intensive Care 2005; 33: 808-811
46. Shehebar, M. and Kehlemsky Y. Considerations for perioperative Contrave (naltrexone HCl/bupropion HCl) administration. J Pain. 2016; 17(4): S83.
47. Angst, MS. Editorial Comment: Challenges in the Perioperative Management of the Patient Receiving Extended-Release Naltrexone. A & A Case Reports. 2014; 3(11):145,.
48. Schwab CA, Wright DA. Intraoperative high-dose remifentanil in a patient on naltrexone therapy. Anaesth Intensive Care. 2000;28(6):701-703.
49. Curatolo, Christopher MD, MEM; Trinh, Muoi MD, MPH. Challenges in the perioperative management of the patient receiving extended-release naltrexone. A & A Case Reports. 2014; 3(11):142-144.
50. Santonocito C,Noto A, Crimi C and Sanfilippo F. Remifentanil-induced postoperative hyperalgesia: current perspectives on mechanisms and therapeutic strategies. Local Reg Anesth. 2018; 11: 15–23.
51. Koo CH, Yoon S, Kim BR, Cho YJ, Kim TK, Jeon Y, et al. Intraoperative naloxone reduces remifentanil-induced postoperative hyperalgesia but not pain: a randomized controlled trial. BJA 2017; 119 (6): 1161-1168.
52. Petri CR and Richards JB. Management of sedation and analgesia in critically ill patients receiving long-acting naltrexone therapy for opioid use disorder. Annals ATS, 2020; 17(11): 1343-1498.
53. Volpe DA, McMahon GA, Daniel Mellon TR, Katki AG, Parker RJ, Colatsky T, et al. Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs.Regul Toxicol Pharmacol 2011; 59(3): 385-390.
54. Baldo BA, Pham NH. Opioid toxicity: histamine, hypersensitivity, and MRGPRX2. Arch Toxicol. 2023 Feb;97(2):359-375.
55. Stoops WW, Lofwall MR, Nuzzo PA, Craig LB, Siegel AJ and Walsh SL. Pharmacodynamic profile of tramadol in humans: Influence of naltrexone pretreatment. Psychopharmacology (Berl). 2012 Oct; 223(4): 427–438.
56. Abboud, TK, Lee K, Zhu, J, Reyes A, Afrasiabi A, Mantilla M et al. Prophylactic oral naltrexone with intrathecal morphine for cesarean section: Effects on adverse reactions and analgesia. Anesth Analg.1990; 71(4):367-370.
57. Raffaeli W, Indovina P. Low-dose naltrexone to prevent intolerable morphine adverse events: A forgotten remedy for a neglected, global clinical need. *Pain Med.* 2015; 16(6): 1239–1242.
58. Simpson GK and Jackson M. Perioperative management of opioid-tolerant patients. BJA Educ. 2017; 17(4): 124–128.
59. Hutton M, Brull R, Macfarlane AJR. Regional anaesthesia and outcomes. BJA Educ. 2018 Feb;18(2):52-56.
60. Sirohi S, Dighe SD, Madia PA and Yoburn BC. The relative potency of inverse opioid agonists and a neutral opioid antagonist in precipitated withdrawal and antagonism of analgesia and toxicity. J Pharmacol Exp Ther. 2009; 330 (2): 513-519.
61. Iovcheva M, Zlateva S, Asparuhova M. Precipitated withdrawal reactions to opiates in cases of improper use of naltrexone. J of IMAB. 2007; 13(1): 79-81.

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"Do you feel hungry?" Using gastric ultrasound to eliminate guesswork in perioperative airway management

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INTRODUCTION

Aspiration is a significant perioperative event. Its incidence varies in different studies, from 1 in 1,100 to 1 in 14,000,[1] with increasing incidence recognised in emergency surgery, pregnancy, and higher ASA category patients.[2] In the fourth UK National Audit Project, aspiration was identified as the second-most frequent major airway complication, after failed intubation, and the most common airway-related cause of death.[3] Debilitating respiratory complications are common among survivors of significant aspiration events.[4] Accurate risk assessment to prevent this significant event is a key component of delivering safe perioperative care.

The current method of aspiration risk assessment is subjective, with clinicians integrating fasting status along with known risk factors for slowed rates of gastric emptying, such as opioid consumption or diabetic gastroparesis. It is not uncommon for clinicians to support their judgement by asking patients, "Do you feel hungry?" This provides false reassurance as 30% of subjects continue to feel hungry after a meal and, in those whose hunger is abolished, 86% feel hungry again before completion of gastric emptying.[5] Clinicians integrate this information to determine a patient's aspiration risk and inform their airway management plan, with anecdotally moderate levels of agreement between individual clinicians. Patients with conditions that delay gastric emptying also present a challenge, as fasting guidelines may not work as intended in certain population groups.

Gastric ultrasound is the only practical tool that provides us with quick, reliable, and objective information on actual gastric volume and content. It is a useful adjunct when uncertainty exists regarding a patient's fasting status and in patients with risk factors for delayed gastric emptying. Gastric ultrasound gives clinicians the ability to make a more informed decision when selecting an airway management strategy.

HOW IT'S DONE

The basic premise of gastric ultrasound is simple. By visualising stomach contents, the risk of pulmonary aspiration can be determined more accurately than relying on fasting time or other factors. Gastric ultrasound works because: (1) a sonographic window exists just below the xiphisternum, allowing visualisation of the gastric antrum adjacent to the left lobe of the liver; (2) the 5-layered gastric wall gives the antrum a distinct appearance, aiding identification; (3) positioning in the right lateral decubitus (RLD) position causes gravitational drainage of gastric contents into the dependent antrum, allowing even the smallest volumes to be visualised.

Figure 1 shows the position of the probe on the patient to obtain accurate imaging. Proper instruction in performing gastric ultrasound is best conveyed in a face-to-face or workshop setting. Experienced operators typically complete routine scans in 2-3 minutes. Table 1 outlines items from a published direct observation of procedural skills (DOPS) checklist for gastric ultrasound, for readers to use as an introductory resource.[6]

Figure 1. Position of probe in gastric ultrasound in the right lateral decubitus position

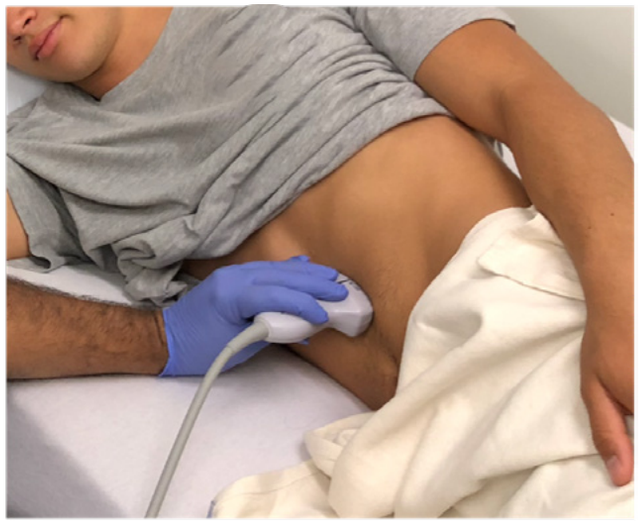


Table 1. Gastric ultrasound DOPS items, from Sidhu et al (2022)[6]

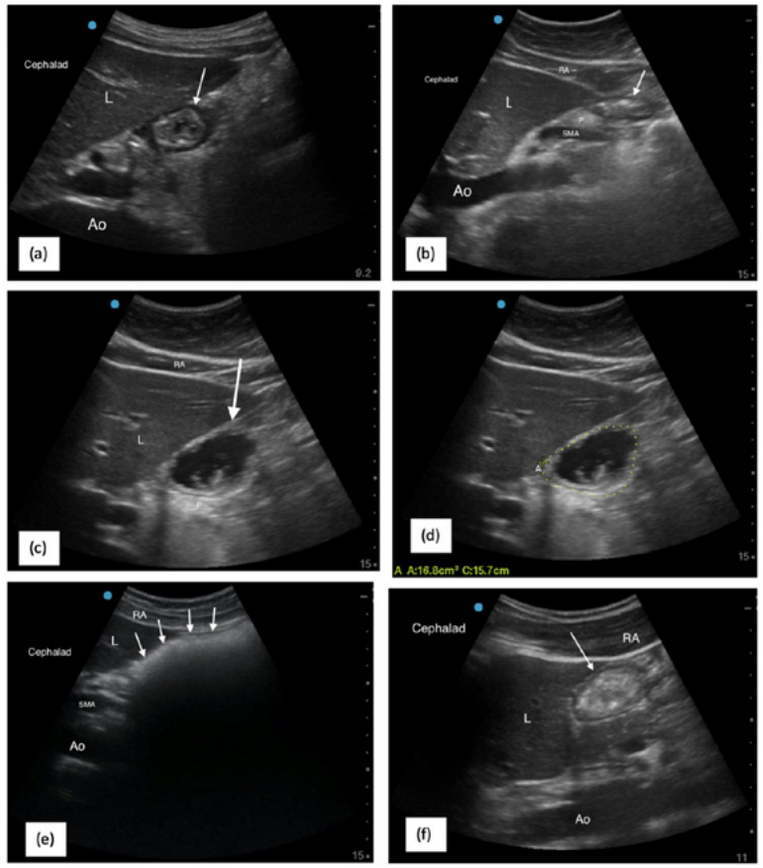
Domain	Item
Indication	Clinical 1. Identifies appropriate indication to perform gastric point-of-care ultrasound Patient 2. Introduces self to patient, describes procedure, explains rationale 3. Obtains verbal consent 4. Maintains patient privacy, modesty, and comfort at all times
Acquisition	Set-up 5. Ergonomic positioning of equipment and operator, in relation to patient 6. Machine: appropriate settings, correct transducer, uses acoustic medium 7. Positions patient appropriately and exposes upper abdomen Scanning technique 8. Identifies surface anatomy through manual palpation 9. Performs survey scan 10. Identifies pertinent structures 11. Optimises image by adjusting probe position, machine settings, or patient factors* 12. Identifies antrum at level of aorta, using Doppler to confirm 13. If clear fluid content, measures antral cross-sectional area in right lateral decubitus position
Interpretation	14. Describes image using pattern recognition 15. If clear fluid present, estimates gastric volume 16. Correctly determines grade of antrum
Medical decision making	17. Determines clinical context 18. Grades image analysis 19. Determines aspiration risk based on findings 20. Formulates plan based on findings

*Modifiable patient factors include taking slow deep breaths to move any overlying structures, or performing a 'water challenge' to aid identification of the antrum or to differentiate small-volume solid content from an empty antrum. A 'water challenge' involves the patient drinking 40–50 ml of water followed by immediate rescanning in the right lateral decubitus (RLD) position.[7]

Gastric ultrasound is traditionally taught to be performed in first the supine and then RLD position.[8] In our unit and in workshops we run, we advocate scanning in the RLD position first, performing supine scanning only if RLD scans are inconclusive. This is because scanning in the supine position cannot confirm an empty stomach, cannot rule out a full stomach, and cannot be used to measure volume of clear fluid.[9] Supine scanning only has diagnostic utility if solid content is viewed, for which RLD scanning will suffice.

Figure 2 shows the common findings in gastric ultrasound. This utility of POC gastric ultrasound has been validated in different patient groups, including obese, pregnant, and paediatric patients.[10] Patient pain/discomfort and patient refusal are contraindications, whilst previous upper gastrointestinal surgery results in scar tissue and altered anatomy, making image interpretation unreliable.

Figure 2. Common findings in gastric ultrasound

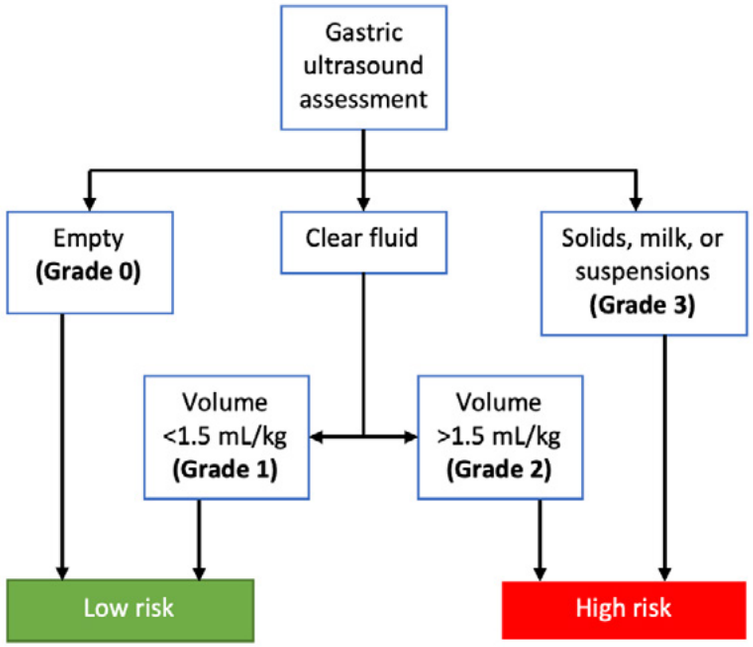


(a) Empty antrum with bullseye or target appearance; (b) Empty antrum with flattened ovoid appearance; (c) Antrum with hypoechoic clear fluid; (d) Manual tracing of antral cross-sectional area to determine fluid volume; (e) Antrum with early-stage solid content showing 'frosted glass' pattern with obscuring of deeper structures; (f) Hyperechoic late-stage solid content. Arrows = antrum; L = liver, Ao = Aorta, RA = rectus abdominis muscle

DECISION-MAKING

Patients can be broadly categorised as low-risk (grades 0 and 1) or high-risk (grades 2 and 3) for aspiration (see Figure 3). Volume assessment of clear fluid is used to differentiate between grades 1 and 2. Two-thirds of appropriately fasted patients have an empty gastric antrum, but a low volume (<1.5mL/kg) of gastric secretions is a normal finding in some fasted patients.[10]

Figure 3. Algorithm for aspiration risk assessment with gastric ultrasound, modified from Perlas et al (2016)



There is clinical utility in adopting an ultrasound-guided grading system rather than our current use of time-defined "full stomach" and "empty stomach" labels. A grading system allows assessment of the perceived risk to guide the appropriate clinical response. For example, while both grades 2 and 3 indicate an elevated aspiration risk, they are managed differently. A grade 2 antrum (>1.5 mL/kg of clear fluid) caused by recent fluid intake is likely to transition to grade 1 (low risk) within a relatively short period of time. Conversely, a grade 3 antrum may take longer to empty depending on what was consumed and when. In addition, a grade 3 antrum that can be attributed to factors that prolong gastric emptying, such as excessive anxiety or medication effects, requires alternative preoperative planning or airway management approaches. The use of a grading system can help drive practice change in the future as more evidence emerges.

Multiple mathematical models to estimate volume of gastric fluid have been published.[12] The model most commonly used to estimate gastric volume of clear fluids from the antral cross-sectional area (CSA) is validated in non-pregnant adults up to a body mass index (BMI) of 40 kg/m2, accurately predicting gastric volumes up to 500 mL.[13] In patients with higher BMIs (> 40 kg/m2), the model is reasonably accurate but tends to over-estimate at low volume states (mean over-estimation 35mL).[14] The model has "nearly perfect" inter- and intra-rater reliability.[15] Though the threshold of gastric volume that increases aspiration risk is a topic of debate, there is substantial data on normal levels of baseline secretions. The figure of 1.5mL/kg is extrapolated from this data and there is a large body of agreement for this cut-off volume,[9] though a threshold of 1.25 mL/kg is suggested for children.[16] Models for different patient populations are outlined in Table 2.

Table 2. Mathematical models to estimate gastric fluid volume in different populations

Patient Population	Mathematical Model
Non-pregnant adult[13]	Volume (mL) = 27 x (14.6 x CSA) – (1.28 x age)
Third-trimester pregnancy[17]	Volume (mL) = 327.1 + (215.2 x log CSA)*
Paediatric[18]	Volume (mL) = -7.8 + (3.5 x CSA) + (0.127 x age in months)

*Measured in the semi-recumbent right lateral position (others in right lateral decubitus);
CSA = cross-sectional area

Reliance on fasting time alone may not be enough to minimise aspiration risk. A prospective cohort study using gastric ultrasound in 190 elective patients showed that 5% had a 'full stomach' (grade 2 or 3 antrum), with failure to follow fasting instructions a cause in only one-fifth of cases.[19] A larger similar study in 512 patients revealed a 'full stomach' in 6.2% of elective patients[20] while a more recent study of 222 elective patients showed a 'full' stomach prevalence of 2.7%.[21] In patients presenting for elective laparoscopic cholecystectomy for symptomatic gallbladder disease, 13% had a grade 2 or 3 antrum on scanning despite having fasted for the appropriate length of time.[22] This higher rate may be due to underlying active gallbladder disease of varying intensity, despite the planned elective nature of the surgery. In the paediatric population, using a threshold of 1.25 mL/kg for aspiration risk, a 'full' stomach prevalence of 1% was observed in 200 elective patients.[16]

These figures are unsurprisingly higher in acute patients. Bouvet et al (2017) demonstrated a 'full stomach' in 56% of emergency cases, despite a median fasting duration of 18 hours (inter-quartile range = 11-24 hours).[19] When considering all 440 cases in this study, factors associated with a 'full stomach' were emergency surgery, preoperative morphine, diabetes mellitus, and obesity.[19] In paediatric patients who were fasted in anticipation of procedural sedation and using 1.2 mL/kg of clear fluid as a threshold for aspiration risk, 69% were classed as having a 'full stomach' with >90% of these identified as solid content.[23] These studies bring into question the applicability of current fasting guidelines in emergency patients.

Using gastric ultrasound provides additional information to clinicians when deciding on the appropriate anaesthetic or sedation plan for patients. In a study of elective patients who did not follow fasting instructions, the use of gastric ultrasound altered anaesthetic management in 71% of patients from the plan based only on clinical assessment and fasting history.[24] The use of gastric ultrasound in 143 paediatric patients undergoing emergency surgery resulted in 47% having their induction plan changed, from routine induction to rapid sequence or vice versa.[25]

PERFORMANCE AND LEARNING

Gastric ultrasound is a highly sensitive and specific diagnostic tool, regardless of operator background (see Table 3). After brief didactic instruction and a 3-hour hands-on workshop, one study showed that anaesthetists were required to perform 24 and 33 scans with expert feedback to achieve success rates of 90 and 95%, respectively.[26] A more recent study found that regional anaesthetists required 9 scans after a teaching intervention (1-hour lecture, 1-hour workshop, and 10 practice scans) to achieve a 90% success rate.[27]

Table 3. Diagnostic performance of gastric ultrasound

Context	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Experienced operator in gastric ultrasound[28]	100% (92.5-100%)	97.5% (95.0-100%)	97.6% (87.8-100%)	100% (92.0-100%)
Two regional anaesthetists after a workshop[27]	98.7% (93.1-100%)	93.8% (69.8-99.8%)	98.7% (92.0-99.8%)	93.8% (92.5-99.1%)
Emergency physician experienced in ultrasound[29]	92% (73-99%)	85% (62-97%)	88% (72-95%)	90% (69-97%)

PRACTICAL APPLICATION

We are of the opinion that gastric ultrasound should be performed by trained operators on all emergency or semi-acute patients. In elective patients, it is warranted when the following risk factors are present: diabetes mellitus, preoperative opioid use, obesity, severe renal or hepatic impairment, Parkinson's disease, untreated coeliac disease (that is, still consuming gluten), clinically significant stroke, significant preoperative anxiety, or non-adherence to fasting guidelines. Recent Australasian and American recommendations suggest using gastric ultrasound on patients taking glucagon-like peptide-1 (GLP-1) receptor agonists, a relatively new class of drugs used to treat obesity and diabetes mellitus, as they delay gastric emptying.[30, 31]

There are a number of steps clinicians can take to incorporate gastric ultrasound into routine clinical practice. In the absence of a departmental training set-up or local expertise, we recommend attending a dedicated gastric ultrasound workshop to begin the journey to competence. Next, set aside dedicated sessions (typically your own administrative time) to scan all preoperative patients for practice, not necessarily to make clinical decisions, recording images and videos and sharing these with a mentor or an experienced practitioner. In our

unit, workshop facilitators volunteer themselves as distant mentors to review images and videos as practitioners develop competence and gain confidence in their image interpretation. Based on previous studies, competence is achieved after approximately 30 practice scans for novices and 9 practice scans for those experienced in ultrasound-guided regional anaesthesia.[26, 27]

The following are some common or notable clinical scenarios we have encountered in our unit when using gastric ultrasound:

- Does the acute patient require a rapid sequence induction (RSI) or is routine tracheal intubation safe and appropriate? An empty stomach with acute appendicitis does not require a RSI in the absence of risk factors for regurgitation.
- Is a supraglottic airway (SGA) safe and appropriate? Many orthopaedic patients experience pain and receive preoperative opioid analgesia, both of which are risk factors for delayed gastric emptying. A SGA is not always appropriate and patients may require a RSI or have their surgery delayed.
- A patient scheduled for elective surgery confesses to having "a bite of a sandwich 4 hours ago." Gastric ultrasound can determine if the stomach is empty and the case can proceed or if the case needs to be delayed or cancelled. A dogmatic adherence to the 6-hour fasting threshold is not required.
- A large fatty meal may take >6 hours to empty from the stomach. It is important to obtain information on the last meal from all elective patients and to consider if gastric ultrasound is appropriate.
- An extremely anxious patient presents for elective surgery, having been adequately fasted. They are worried about 'waking up' during surgery. Preoperative monitoring notes an elevated heart rate. Gastric ultrasound reveals solid content, presumably due to prolonged sympathetic nervous system activation secondary to anxiety.
- A patient with a nasogastric (NG) tube in situ is scheduled for abdominal surgery. There is minimal aspirate through the NG but gastric ultrasound reveals copious amount of particulate (not clear) fluid. Gastric ultrasound allows confirmation of the effectiveness of NG suction as thick fluid such as faecal matter or coagulated blood may not be able to be adequately aspirated via the NG tube.

CONCLUSION

Gastric ultrasound is a relatively new tool with a constantly expanding evidence base. It is the only practical objective method for assessing gastric content and volume. Based on current available evidence, the group of patients most likely to benefit from gastric ultrasound are those presenting for acute or emergency surgery. Routine scanning of healthy patients presenting for elective surgery is not recommended unless they have risk factors for delayed gastric emptying, provide a suspicious fasting history, or admit to a large fatty meal just prior to their fasting period.

Gastric ultrasound should be included as a core skill in anaesthesia training. It is relatively simple to learn, feasible to use, and has widespread clinical utility in large groups of patients. Consideration should be given to amending fasting guidelines to incorporate gastric ultrasound assessment in specific situations.

REFERENCES

1. Engelhardt T, Webster NR. Pulmonary aspiration of gastric contents in anaesthesia. Br J Anaesth 1999; 83: 453–60
2. Abdulla S. Pulmonary aspiration in perioperative medicine. Acta Anaesthesiol Belg 2013; 64: 1–13
3. Cook TM, Woodall N, Frerk C. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 1: Anaesthesia. Br J Anaesth 2011; 106: 617–31
4. Sakai T, Planinsic RM, Quinlan JJ, Handley LJ, Kim T-Y, Hilmi IA. The Incidence and Outcome of Perioperative Pulmonary Aspiration in a University Hospital: A 4-Year Retrospective Analysis. Anesth Analg 2006; 103: 941
5. Sepple CP, Read NW. Gastrointestinal correlates of the development of hunger in man. Appetite 1989; 13: 183–91
6. Sidhu NS, White C, Pozaroszczyk A. Development of a direct observation of procedural skills tool for gastric ultrasound. Anaesthesia 2022; 77: 712–4
7. Sidhu NS. 'Water challenge' to improve diagnostic accuracy in gastric point-of-care ultrasound. Anaesth Rep [Internet] 2022 [cited 2023 Jan 3]; 10 Available from: https://onlinelibrary.wiley.com/doi/10.1002/anr3.12192
8. Perlas A, Arzola C, Van de Putte P. Point-of-care gastric ultrasound and aspiration risk assessment: a narrative review. Can J Anesth Can Anesth 2018; 65: 437–48
9. Haskins SC, Kruisselbrink R, Boublik J, Wu CL, Perlas A. Gastric Ultrasound for the Regional Anesthesiologist and Pain Specialist: Reg Anesth Pain Med 2018; 1
10. El-Boghdadly K, Wojcikiewicz T, Perlas A. Perioperative point-of-care gastric ultrasound. BJA Educ 2019; 19: 219–26

11. Perlas A, Van de Putte P, Van Houwe P, Chan VWS. I-AIM framework for point-of-care gastric ultrasound. Br J Anaesth 2016; 116: 7–11
12. Van de Putte P, Perlas A. Ultrasound assessment of gastric content and volume. Br J Anaesth 2014; 113: 12–22
13. Perlas A, Mitsakakis N, Liu L, et al. Validation of a Mathematical Model for Ultrasound Assessment of Gastric Volume by Gastroscopic Examination. Anesth Analg 2013; 116: 357–63
14. Kruisselbrink R, Arzola C, Jackson T, Okrainec A, Chan V, Perlas A. Ultrasound assessment of gastric volume in severely obese individuals: a validation study. Br J Anaesth 2017; 118: 77–82
15. Kruisselbrink R, Arzola C, Endersby R, Tse C, Chan V, Perlas A. Intra- and Interrater Reliability of Ultrasound Assessment of Gastric Volume. Anesthesiology 2014; 121: 46–51
16. Bouvet L, Bellier N, Gagey-Riegel A-C, Desgranges F-P, Chassard D, De Queiroz Siqueira M. Ultrasound assessment of the prevalence of increased gastric contents and volume in elective pediatric patients: A prospective cohort study. Pediatr Anesth 2018; 28: 906–13
17. Arzola C, Perlas A, Siddiqui NT, Downey K, Ye XY, Carvalho JCA. Gastric ultrasound in the third trimester of pregnancy: a randomised controlled trial to develop a predictive model of volume assessment. Anaesthesia 2018; 73: 295–303
18. Spencer AO, Walker AM, Yeung AK, et al. Ultrasound assessment of gastric volume in the fasted pediatric patient undergoing upper gastrointestinal endoscopy: development of a predictive model using endoscopically suctioned volumes. Anderson B, editor. Pediatr Anesth 2015; 25: 301–8
19. Bouvet L, Desgranges F-P, Aubergy C, et al. Prevalence and factors predictive of full stomach in elective and emergency surgical patients: a prospective cohort study. Br J Anaesth 2017; 118: 372–9
20. Van de Putte P, Vernieuwe L, Jerjir A, Verschueren L, Tacken M, Perlas A. When fasted is not empty: a retrospective cohort study of gastric content in fasted surgical patients. Br J Anaesth 2017; 118: 363–71
21. Ohashi Y, Walker JC, Zhang F, et al. Preoperative Gastric Residual Volumes in Fasted Patients Measured by Bedside Ultrasound: A Prospective Observational Study. Anaesth Intensive Care 2018; 46: 608–13
22. Chang J-E, Kim H, Won D, et al. Ultrasound assessment of gastric content in fasted patients before elective laparoscopic cholecystectomy: a prospective observational single-cohort study. Can J Anesth Can Anesth 2020; 67: 810–6
23. Leviter J, Steele DW, Constantine E, Linakis JG, Amanullah S. "Full Stomach" Despite the Wait: Point-of-care Gastric Ultrasound at the Time of Procedural Sedation in the Pediatric Emergency Department. Macy ML, editor. Acad Emerg Med 2019; 26: 752–60
24. Alakkad H, Kruisselbrink R, Chin KJ, et al. Point-of-care ultrasound defines gastric content and changes the anesthetic management of elective surgical patients who have not followed fasting instructions: a prospective case series. Can J Anesth Can Anesth 2015; 62: 1188–95
25. Gagey A-C, de Queiroz Siqueira M, Monard C, et al. The effect of pre-operative gastric ultrasound examination on the choice of general anaesthetic induction technique for non-elective paediatric surgery. A prospective cohort study. Anaesthesia 2018; 73: 304–12
26. Arzola C, Carvalho JCA, Cubillos J, Ye XY, Perlas A. Anesthesiologists' learning curves for bedside qualitative ultrasound assessment of gastric content: a cohort study. Can J Anesth Can Anesth 2013; 60: 771–9
27. Tankul R, Halilamien P, Tangwiwat S, Dejarkom S, Pangthipampai P. Qualitative and quantitative gastric ultrasound assessment in highly skilled regional anesthesiologists. BMC Anesthesiol 2022; 22: 5
28. Kruisselbrink R, Gharapetian A, Chaparro LE, et al. Diagnostic Accuracy of Point-of-Care Gastric Ultrasound: Anesth Analg 2019; 128: 89–95
29. Mackenzie DC, Azad AM, Noble VE, Liteplo AS. Test performance of point-of-care ultrasound for gastric content. Am J Emerg Med 2019; 37: 123–6
30. Olesnicky B. GLP-1 agonists and gastric emptying. ANZCA Bull 2023; Winter 2023: 37
31. Joshi GP, Abdelmalak BB, Weigel WA, et al. American Society of Anesthesiologists Consensus-Based Guidance on Preoperative Management of Patients (Adults and Children) on Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists [Internet]. 2023 [cited 2023 Jul 17]. Available from: https://www.asahq.org/about-asa/newsroom/news-releases/2023/06/american-society-of-anesthesiologists-consensus-based-guidance-on-preoperative

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Medicolegal issues associated with multidisciplinary teams – a discussion relevant to anaesthesia and pain medicine specialists

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INTRODUCTION

Over the past 30 years, there has been a large increase in the number of acute and chronic medical conditions that are managed by multidisciplinary teams (MDTs), such that they are now considered the gold standard of care. Along with the development of evidence-based medicine, the MDT has enabled the development of treatment regimens according to best practice, taking into account the individual patient circumstances. Despite being commonplace and considered the gold standard, there are few guidelines as to how MDTs should be conducted. In the absence of guidelines and subsequent lack of standardisation it is difficult to determine whether an MDT is functioning effectively. In the situation of a unanimous decision regarding a treatment regimen, and an optimal treatment decision being made, there is probably little medicolegal risk to any member of an MDT. However, in the not unlikely situation when a variety of treatment options exist, and a suboptimal treatment regimen recommended, then the medicolegal risks to a member of an MDT are less clear. Pain specialists are frequently involved in MDT decision making. Anaesthetists may be of the opinion that their participation in MDTs is limited, but with an ageing population demographic, patients surviving longer with extensive co-morbidities, and the possibilities of alternative less invasive therapies, it is not surprising that the expertise of anaesthetists, particularly as perioperative physicians, will be sought in MDTs.

Increasingly, the theoretical medicolegal risks of MDT participation have been considered but have not been conclusively tested in legal proceedings.[1] In Australia and other jurisdictions, MDTs have come under increasing scrutiny in both public and private health systems. This has occurred as a result of public inquiries into suboptimal care provided without MDT input, employment law relating to participation in MDTs, regulatory body discipline determinations, and two Australian coronial inquest findings. One finding, having determined the absence of MDT decision making, highlighted the necessity for MDT involvement in patient care. While this outcome would seem to paint a clear picture of legal support for the utilisation of MDTs in similar situations, the other finding found fault and culpability in the consequences of poor communication within MDT processes.[2,3,] It is into this environment of heightened awareness and scrutiny of MDT practices that anaesthetists will be asked for their input.

When looking at an MDT process from a patient's point of view, Australian law professor Ian Freckleton AO KC writes "For the person at the centre of such a gathering, several reasonable assumptions can be made – that it is the convenor of the meeting who makes the decisions, or that all who are present, unless they explicitly voice their dissent, contribute to or at least acquiesce in the decision."[4] While MDTs are yet to feature prominently in litigation, there has been a clarification in the legal sense of doctor-patient relationships over recent years, with implications for MDT members.

In this chapter we will discuss the major medicolegal issues for MDT members relating to the existence of a duty of care and dissent from a treatment decision and consider strategies to reduce the risk from MDT participation.

THE DUTY OF CARE OF MDT MEMBERS

The relationship between a treating physician and a patient may range in a spectrum from that of the primary treating physician through to that of the Good Samaritan helping out in an emergency. The duty of care is evidently clear in the situation of an individual doctor treating an individual patient. However, tertiary, and quaternary hospitals increasingly garner input from the myriad of specialties present in an equally diverse spectrum of formality. These nuanced and sometimes complex relationships have created a chasm in quantifying how a duty of care overlays these interactions, and this assessment continues to evolve from a legal point of view, especially with the increasing use of telehealth services. This conundrum is reflected in a recent United States court judgment which stated "[i]n light of the increasing complexity of the health care system, in which patients routinely are diagnosed by pathologists or radiologists or other consulting physicians who might not ever see the patient face-to-face, it is simply unrealistic to apply a narrow definition of the physician-patient relationship in determining whether such a relationship exists..."[5] This begs the question, "what is your duty of care if you participate in an MDT"?

There are two likely scenarios in which an anaesthetist or perioperative physician may be involved in an MDT setting, the first being that of an *informal consultation*, seeking an opinion as to whether a patient may be fit for surgery, the second is that a formal request to participate in the MDT process to determine treatment, which may or may not be in the form of a *second opinion.* These relationships have now been considered and developed within legal proceedings, such that it may be assumed that a duty of care exists within the varying roles of contributors in the MDT process.

THE INFORMAL CONSULTATION

Despite being extremely common, the informal consultation is an enigma. Most medical practitioners would feel comfortable identifying an "informal consult," yet objectively defining the boundaries of what would constitute one is more vexatious. Although the term "informal consultation" is not a legal term, there are certain commonalities that appear when discussing what it is; these being that the doctor does not examine the patient, has no direct communication with the patient, does not review the patient's records, has no obligation for formal consultation, receives no payments for services, gives opinion and advice only to the primary treating physician, and that the treating physician remains in control of the patient's care and treatment.[6] These features are often seen in anaesthesia practice, when a proceduralist may seek an opinion as to whether a patient may be "fit" for anaesthesia, or the optimal type of anaesthesia. They also may describe the way an anaesthetist may be consulted by an MDT as to whether a patient may be fit for a proposed treatment regimen. Both these situations may occur in a less formalised way within private or independent healthcare systems.

Traditionally, courts have tended to view an informal consultation as one colleague providing a service to another, enabling the provision of better healthcare, and that the informal consultations typically did not result in a formal relationship between the consulted doctor and physician. Courts have however noted that doctors consulted "have professional and ethical obligations to act with the skill, knowledge, and diligence commonly expected in their field of specialty."[6]

Given the more litigious environment of the United States, it is not surprising that this is where legal developments and precedents may originate. A recent court decision has looked at the informal consultation from a new perspective. Rather than looking at an expressed physician-patient relationship for a finding of medical negligence, this judgement has considered the foreseeability of harm.[7] This was considered from two perspectives. Firstly, in this type of consultation (informal consultation) a doctor owed patients a duty of care because their advice may expose a patient to danger if their advice was acted on, and the doctor was bound to know that the patient would be likely to follow that advice. Secondly, that when a doctor provides medical advice and it is foreseeable that another party will rely on that advice, a duty of care therefore exists. It would not be unreasonable to speculate that even with the advice that a treating practitioner may receive from an informal consultation, that a patient would be likely to follow this advice when it is presented by a treating practitioner with whom they are already likely to have an express relationship.

As argued above, it would be reasonable to consider that in any legal process for negligence, the nature of the informal consultation could be considered to describe a practitioner's participation in an MDT.

THE SECOND OPINION CONSULTATION

What constitutes a (clinical) second opinion differs according to the expectation of that opinion for both practitioners and their patients, and within jurisdictions. Within an MDT process, the more traditional expectation of a second opinion is applicable. This describes a situation in which "a treating doctor asks a patient to see a colleague so that the two doctors can discuss the case with the aim of allowing the treating doctor to better understand the case and its significant aspects. Therefore, a second opinion is provided to and for the treating doctor, to help their assessment and formulation of a treatment plan."[8]

It could be considered within certain MDT frameworks, especially those that are becoming more streamlined and protocol managed, that the role of the MDT members is to provide a second opinion, from which to confirm a diagnosis and treatment, having considered the information that has been prepared according to protocol. Although this may appear similar to the informal consultation role, the second opinion role occurs in a much more formalised and structured process.

There are relatively few legal cases relating to doctors who have provided a second opinion. This may be because a second opinion is almost always considered a beneficial process, as alternative treatments may be considered. Particularly in the case of an MDT, a clinician may be able to offer a new perspective or rein in potentially bullish treatment options that may be affected by human factors, such as unconscious bias, by the primary treating doctor.

An early case looking at the role of the second opinion was from New South Wales in 1980.[9] In this case, a consultant orthopaedic surgeon requested a second opinion from a consultant neurosurgeon for the management of a spinal condition. As the treatment had already commenced, the neurosurgeon elected to review the patient later in the admission. By the time of this review, the patient had suffered irreversible neurological damage and had become a paraplegic. The court determined that although the neurosurgeon had not seen the patient, they should have been aware of the possibility of spinal cord damage, and that the potential for this damage would depend on their advice.

The judgement stated that:

> "…it could be concluded that he [the neurosurgeon] knew and accepted that the question of the possible danger to the patient's cord would be to some extent dependent on his advice; and this factor alone, in my view, imposed a duty on him. She became, for relevant purposes, his patient…. Even though he had only been consulted for a second opinion, had not initiated the treatment, and had not been primarily responsible for the care of the patient…[the court] held that the neurosurgeon had a duty of care to the patient."

The three key elements in this judgment that may be relevant to MDT members is that: firstly members are consulted because of their expertise, secondly there may be seen to be a failure to intervene to prevent damage, and thirdly that, although the surgeon in this case was only consulted for a second opinion and was not the primary treating practitioner, a duty of care was found to have still existed.

CONSENT AND INFORMATION SHARING IN MDT PROCESSES

Karas et al propose that there are four conditions which need to be met for a person to give informed consent for their disease to be considered by an MDT.

1. That the patient of interest (or carer) understands the purpose of the MDT meeting.
2. That this patient is aware of the disciplines that may participate.
3. The patient is informed about those who in the MDT process will be present in an observational capacity.
4. The patient is informed about what data from their medical history will be shared.

However, for any doctor to make an informed treatment decision, they reasonably require a patient's more complete medical history. For this reason, consideration should be given to adding a fifth condition, that patients should be informed about the breadth of their medical history that will be provided and that needs to be considered by the MDT, and why this information is necessary.

A specialist, in this case an anaesthetist, will be aware of the points in a history that would be considered relevant to their decision making, but it may be that these salient points are not considered within an MDT process prior to an anaesthetist being involved in decision making. Without access to an anaesthetist-patient consultation, it is not feasible for an anaesthetist to have all relevant information and examination findings available for decision making without a formal consultation having taken place prior. This is relevant in the potential for liability, which will be discussed below.

DISSENT AMONG MDT MEMBERS, AND DOCUMENTATION OF DISSENT

Casarett writes that it is "unrealistic to expect that health care professionals will always agree about which plan of care is best. It is essential, though, that they discuss their differences openly."[10] Despite the negative connotations of the word, dissent is common, but it is not necessarily harmful: it has the potential to improve health outcomes. Martin proposes a model for the search for truth in medicine, using the concepts of a unitary or plurality of truths, and whether the search occurs by conflict, as shown (with examples suggest by the writers of this chapter) in the table below.[11]

Table 1: Unitary truth versus plurality of truths in the context of conflict and cooperation.

	Cooperation	Conflict
Unitary truth	Cooperative search for truth and social benefit *e.g., Non-surgical treatment for single vessel coronary disease*	Orthodoxy versus dissent/heresy *e.g., HIV is the virus that causes AIDS versus HIV does not cause AIDS*
Plurality of truths	Cooperative tolerance *e.g., Haemodialysis versus peritoneal dialysis for renal failure*	Competition; market struggle. *e.g., Different varicose vein treatments (as they are not covered by public health)*

One of the reasons MDTs were instituted was that there was a plurality of truths to treat certain disease processes, and that no single practitioner would be able to make an optimal treatment decision. It is extremely unlikely that any dissent in an MDT would be by conflict against a unitary truth; instead, it almost certainly will be based upon considered thought and review of the evidence base of medical science as to the best application of therapies to a patient. In this situation, the purpose of dissent is neither malicious nor resulting from professional jealousy; its purpose is in seeking the best possible patient care. Karas et al note that disagreements or dissents in the workings of MDTs are related to three main areas. Firstly, the uncertainties in the evidence base for more complex cases can lead to multiple potential treatments being reasonably appropriate. Secondly, differing beliefs surrounding the technical/treatment feasibility between practitioners. Thirdly, inadequate awareness and consideration of the patient's wishes.[12] With increasing respect for patient autonomy, this third area should (ideally) diminish as a necessary cause of dissent.

It is possible to classify dissent into major and minor dissents. From an anaesthetic point of view, an example of a major dissent may be over whether a patient is fit enough for renal transplant to justify the risks of anaesthesia and the potential loss of a donor organ should there be an adverse anaesthetic outcome. A theoretical example of a minor dissent could be whether a patient should be delayed for curative surgery for a malignant neoplastic disease in the presence of an asymptomatic infection (for example, COVID-19) that was coincidentally detected on a standard screening examination. Regardless of the type of dissent, both are likely to be in the presence of a plurality of truths, and it is important that differing opinions are documented. One reason for documentation of even minor dissent is that this opinion is (potentially) able to be communicated to a patient/carer. This may appear difficult to implement, given the number of minor dissents. To the healthcare professional, the relevance or significance of minor dissent may be trivial, as the long-term outcomes of the disease process are unlikely to differ significantly, but in the eyes of the patient or their family members, these alternative treatments may be significant, especially to patients from certain religious and cultural backgrounds.[13]

The purposes of documentation of dissent are two-fold. The first is ethical, in respecting patient autonomy for decision making, allowing them to be fully informed as part of an informed consent process. The second reason is to provide a framework for the legal protection of the MDT members in a situation where the proposed treatment plan results in unexpected complications or a sub-optimal patient outcome and the MDT process is called into question.

Health professionals who contribute to treatment recommendations within an MDT meeting share responsibility for the decisions made at such meetings, within their area of expertise, and could be potentially liable if a negligence case is brought by a patient.[1] If an MDT member feels that they are being asked to weigh in on decisions that are outside of their area of expertise, it is appropriate that a member abstain from engagement in these areas, and ensure that this abstention is documented and clarified in meeting summaries. Unless there is documented dissent or abstention, it could be argued that all participants are directly involved in and supportive of a patient's care.

FAILURES OF THE MDT PROCESS, AND REDUCTION OF ASSOCIATED MEDICOLEGAL RISKS

Despite the best efforts of all members involved, there will be occasions when the process will fail, and MDT members should consider these points to minimise their medicolegal risks. The main areas by which an MDT process may fail can be classified as follows:

1. Decisions made, based on incorrect or incomplete presentation of information to the MDT. In the case of any doubt, MDT members should always seek further information or clarification prior to decision making.
2. Decisions made on information that has been withheld from the MDT by a patient or a healthcare professional. Despite adequate informed consent processes, some patients may be unwilling to fully disclose their complete medical histories. Ensuring that all available information is documented in patient and meeting summaries is important to reduce risk.
3. Decisions made on the basis of incorrect opinions from MDT members. The onus is on all team members to ensure that their opinions are based on up-to-date evidence-based practices. Once again, an MDT member should ensure that their dissention is clearly recorded if they disagree with the proposed treatment regimen, or their abstention if they believe a decision requested is outside their area of expertise.
4. Failure to continually assess treatment regimens implemented by MDTs. Medical therapies may evolve rapidly, as may patient co-morbidities, side effects, and complications of treatment. It is important that any clinician treating a patient according to a regimen proposed by an MDT, reports back to the MDT regarding progress or issues relating to treatment. These changes likely require frequent re-assessment by the MDT and may require changes to treatment recommendations.
5. Failure of correct documentation and communication. The Craig inquest[3] highlighted issues relating to documentation standards in MDT processes and made a formal recommendation that MDT notes should be taken by a suitably experienced clinician or health practitioner, or where this is not possible, notes should be checked by a suitably experienced clinician prior to being circulated. Within Australia, there exists a national project to ensure that coronial findings and recommendations from one jurisdiction are made known to other jurisdictions.[14] It is not unreasonable to expect that, having been highlighted in one jurisdiction, the issues and common legal pitfalls will become more readily apparent to both courts and healthcare practitioners. With this increasing scrutiny, MDT members would be advised to review notes and summaries from meetings they participate in, to ensure that they are complete and accurately reflect the conduct and decision making for both patient outcomes and legal proceedings.

CONCLUSION

In an editorial on patient expectations and the legal liability of MDTs, Freckleton chillingly notes that "(l)aw, as delivered by the civil courts and the regulatory authorities, is a blunt instrument for enhancing the quality of health service provision and bringing about behaviour change."[4] The reality, however, is that the civil courts and regulatory authorities only come into play when the behaviour of the practitioner or the functioning of a healthcare system results in patient outcomes that do not meet expectations of society. Since that time, MDT processes have been examined in multiple legal cases and inquiries, and process changes initiated. The development and continued increasing use of MDTs means that the MDT is not likely to be replaced anytime in the near future in health care systems; in all probability it will become more complex as the scientific understanding of disease processes increases. It is only by being proactive in identifying and acting upon the legal risks of the MDT processes that practitioners will be protected from appearances before the civil courts and regulatory authorities, and more importantly, patients will receive the best possible outcomes in the management of their diseases.

REFERENCES

1. Evans AC, Zorbas HM, Keaney MA, Sidhom MA, Goodwin HE, Peterson JC. Medicolegal implications of a multidisciplinary approach to cancer care: Consensus recommendations from a national workshop. Med J Aust. 2008 Apr 7; 188(7):401–4.
2. Inquest into the death of Irene Magriplis [2017] NTLC 008 [206]
3. Inquest into the death of Robert Charles Craig [2021] WACOR 35
4. Freckelton I. Multidisciplinary meetings: Patient Expectations and legal liability. J Med Imaging Radiat Oncol. 2008 Jun; 52(3):199–200.
5. *Kelley v Middle Tennessee Emergency Physicians* PC 133 SW3d 587 (Tenn 2004)
6. Olick RS, Bergus GR. Malpractice liability for informal consultations. Fam Med. 2003 Jul-Aug; 35(7):476-81.
7. *Warren v Dinter* 926 NW2d 370 (Minn 2019)

8. Mackay S, 'Doctor, I'm here for a second opinion' [Internet] Sydney: Avant; 2020 [cited 2022 May 19] Available from: www.avant.org.au/news/here-for-a-second-opinion
9. *Albrighton v Royal Prince Alfred Hospital* [1980] 2 NSWLR 542
10. Casarett D. When doctors disagree. AMA J Ethics. 2006 Sep; 8(9):571–6.
11. Martin B. Dissent and heresy in medicine: Models, methods, and strategies. Social Science & Medicine. 2004;58(4):713–25.
12. Karas PL, Rankin NM, Stone E. Medicolegal considerations in multidisciplinary cancer care. JTO Clinical and Research Reports. 2020 Nov 1;1(4):100073.
13. Swihart D, Yarrarapu SN, Martin R. NCBI Bookshelf [Internet]. Cultural Religious Competence In Clinical Practice' (2022) StatPearls. [cited 2023 Mar 23]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493216/
14. National Free Access Coronial Findings, Recommendations and Responses [Internet] Sydney: Australian Research Data Commons; [cited 2023 May19] Available from: https://ardc.edu.au/project/national-free-access-coronial-findings-recommendations-and-responses/

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How organisational culture can improve the safety of anaesthesia care

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INTRODUCTION

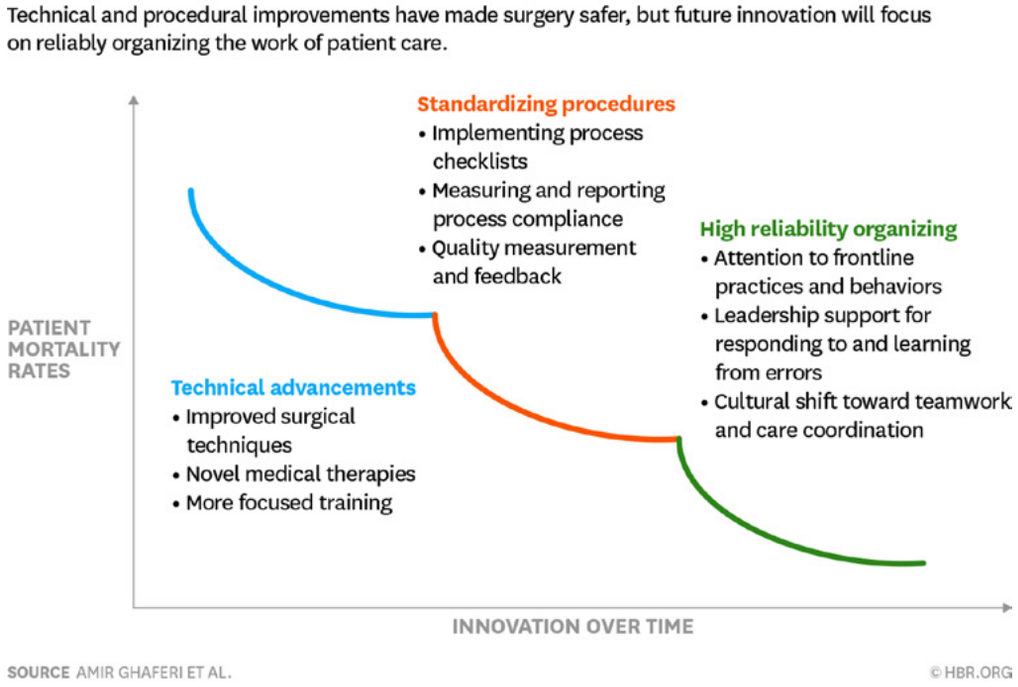
Patients are often harmed by medical care. It has been well recognised and documented for several decades that large numbers of hospitalised patients are harmed by care they receive.[1-3] A recent meta-analysis of 70 studies found that iatrogenic patient harm occurs in 12 per cent of hospital admissions, the prevalence is higher in medical specialties such as intensive care and surgery, and more than half the events of harm are preventable.[4]

The approach to keeping patients safe was transformed in 1999 following the landmark *To Err is Human* report[5] that generated the visceral metaphor of a daily jumbo-jet crash for quantifying iatrogenic mortality in the US. The call for open and transparent recognition of patient harm events to enable learning opportunities and a comprehensive approach to developing systematic care processes was subsequently promulgated in synchrony with awareness of the need for cultural reform. Australia was an early adopter of the new approach. The Australian Council for Safety and Quality in Healthcare was formed in 2000 with one of the priorities of the national action plan being, *redesigning systems and creating a culture of safety within healthcare organisations.*[6]

Frustratingly, despite enormous investment of focus and resources to address patient harm, numerous reviews have found there is little evidence of substantial improvement and the pertinence of a need for safety culture is a recurring theme.[7-10] Where incremental reductions in adverse outcomes are observed[11] the results are a reminder of the scale of the problem, the challenges yet to be met, and the personal impact for patients suffering iatrogenic injury.[12] Research of stagnating safety performance and refractory causes of patient harm continue to draw attention to culture change as an essential priority for future progress.[13,14] However, it is rarely acknowledged that healthcare's understanding of culture is shallow and misguided, demonstrating no real appreciation of its complexity and resistance to change. Referring to the concept of culture as something to be managed, an organisational property that can be measured and adjusted at will, is erroneous.[15]

The significance of organisational culture to anaesthesia care deserves to be prominently acknowledged. It is a central pillar supporting any endeavour to improve the coherence and effectiveness of group problem solving. Culture influences how we assess risk, how we perceive and respond to events, and how we approach the prospect of change. The Anesthesia Patient Safety Foundation list of the top 10 patient safety priorities currently allocates first place to *a culture of safety.*[16] Coherently, future significant advances in reducing perioperative patient harm have been predicted to be attained with a cultural shift toward prioritising teamwork and co-ordination to enable organising for high reliability, rather than with technical innovation or individual developments (see figure 1).[17,18]

Figure 1. Three waves of innovation in patient safety



This review will describe the nature of organisational culture in healthcare, how it can influence the safety of perioperative care, and approaches for developing a culture of patient safety.

WHAT IS ORGANISATIONAL CULTURE?

Culture can be thought of as the foundation of the social order that we live in and the rules we abide by – a shared system of coercive influence that both enables and constrains our behaviour. Culture helps people work together cohesively by creating a sense of identity for a shared understanding and commitment to purpose. It is an essential aspect of collective effort in bringing together large numbers of people and giving them a sufficient similarity of approach, outlook, and priorities to enable them to achieve collaborative responses to problems.[19]

Edgar Schein[20] explains that what we often think of as organisational culture is just the most visible manifestations of underlying shared values, beliefs, and assumptions. Organisational culture can be considered at 3 levels:

Level 1 **Artefacts** – Visible manifestations of culture (also known as "how we do things around here"): the physical layout and style of services, dress codes, staff rostering and reporting arrangements, usual processes of care (for example, ANZCA standards of practice),[21] performance acknowledgement rewards and ceremonies. Artefacts can be explicitly taught and consciously supported with objective knowledge. The most superficial level of culture is easy to observe but very difficult to interpret without understanding deeper levels.

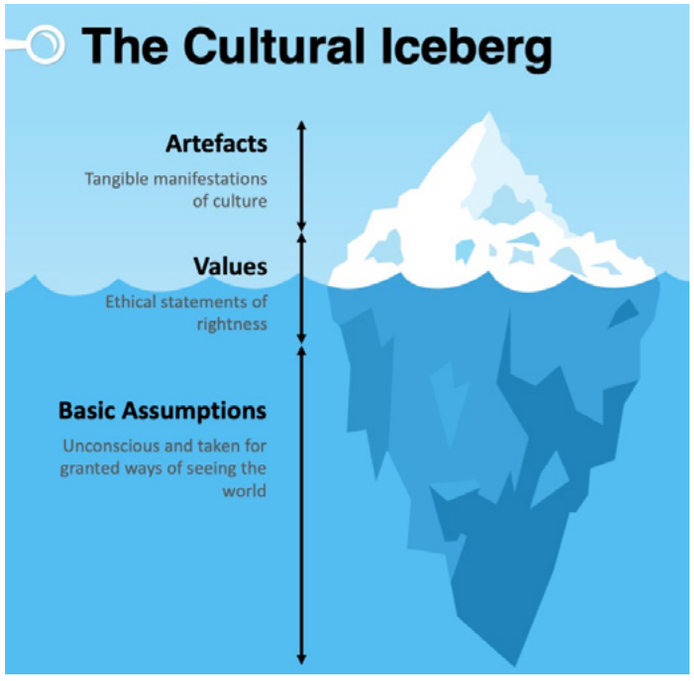
Level 2 **Espoused values** – Overtly stated core principles about the organisation's philosophy, vision, or purpose. Organisational principles can be used to rationalise and justify behaviours, priorities, and choices; distinguishing "right" from "wrong" and judging what behaviours deserve to be rewarded or reprimanded. ANZCA values are expressed by the statement of purpose: *To serve our communities by leading high quality care in anaesthesia, perioperative and pain medicine, optimising health and reducing the burden of pain.*[22]

Level 3 **Underlying basic assumptions** – Deeply held beliefs that are taken for granted and unchallenged. Basic assumptions are "known" but are not discussed or documented. They are implicitly learned and unconsciously held. The core of organisational culture manifests as thoughts, perceptions, and feelings. Individuals are likely to be unaware of the deeper foundations of their immersive culture and deciphering its characterisation requires anthropological techniques of observation and interview.

Culture evolves within an organisation as a group works together to solve problems of external demands and internal tasks. As solutions are developed, the shared experience gradually facilitates synchronisation of individual perceptions and attitudes. If the solutions consistently work well enough to be considered valid, they are taught to new group members as the correct way to act, perceive, think, and feel. As the way continues to work it becomes taken for granted as *the* way and people forget that at one time the successful solutions had to be learnt, and that they evolved in a specific context. The essence of culture is this pattern of shared basic assumptions – automatic, unconscious, and taken for granted.

Culture is an abstract concept and understanding it requires an appreciation that superficial manifestations of behaviour and espoused values are integrated into a coherent whole with deeper basic assumptions. The iceberg analogy illustrates that only a fraction of cultural aspects is observable, while most is hidden and difficult for outsiders or new members to interpret.[23]

Figure 2. The cultural iceberg



The power of culture to enable or constrain behaviour lies in the cognitive stability and comfort of a shared "mental map". Coherent views and aligned social support can be deeply satisfying when considering what deserves our attention, what events mean, and how to react and respond emotionally to various situations. Evolutionary biology describes the survival advantage conveyed by the innate human propensity to conform to the culture of our birth – the human mind is hardwired to fit in.[24] The underlying basic assumptions are deeply held and tend to defy change so the process of challenging or examining cultural attributes can provoke anxiety and defensiveness.[25]

Culture permeates every level of an organisation, but it is not monolithic and can vary widely. Some cultural attributes could be widespread and stable, whereas others might be shared only in subgroups, or held only tentatively. Healthcare organisations are notoriously varied, fractured by specialty, occupational groupings, and professional hierarchies. Cultural divergence can impose significant challenges on opportunities for collaboration due to conflicting assumptions and varying perspectives to approaching problems – doctors may find themselves in disagreement with managers despite sharing a common purpose of aspiring to improve the quality and safety of care.[26] Differences, however, are not necessarily bad and can be a useful resource to provide a diversity of perspectives and interpretations of emerging problems.[27]

A strong culture is often considered a positive attribute for an organisation but correlation of strength with effectiveness is not straightforward. Strength reflects a high level of consensus around agreed core values and can be enhanced by belief in the rightness or moral superiority of an organisation's purpose.[28] Cultural

strength is also a function of group stability, and the duration and intensity of shared experience. Stable teams tend to develop a strong culture over time as repeated shared experience reinforces and normalises behaviour. Team stability is partly explained by the attraction-selection-attrition model.[29] People are drawn to organisations with characteristics similar to their own; organisations are more likely to select individuals who seem to "fit in"; and over time those who don't fit in tend to leave. Culture then becomes a self-reinforcing pattern that grows increasingly resistant to change and external influences. A strong culture can reduce organisational flexibility and adaptability to new problems. Attempts to innovate may be met with resistance or incredulity if they are perceived as being incongruent with present assumptions.[30]

Culture can be used by organisations to guide and influence individual behaviour. Charles Perrow described third-order controls[31] as control over the premise (the underlying basic assumptions) of decision making. First-order controls such as direct orders, supervision, rules, and policies are conventional methods appropriate for low-complexity industries or an unskilled workforce. Second-order controls such as standard operating procedures and specialisation can legitimise individual worker discretion by reducing available options while enabling autonomy. Leaders can establish third-order control over the premise of decision making by moulding the underlying basic assumptions with consistent predictable attention to reinforcing the consequences of particular behaviours. Control through culture, although hard to achieve, is necessary in complex decentralised systems and organisations, and especially when work is nonroutine, less analysable, and uncertain, as it is for many professional disciplines, such as healthcare.[27] Medical specialist training incorporates centralised oversight of culture to establish a shared set of core values and learned assumptions, before autonomous individuals are decentralised into a variety of clinical settings. Culture creates a homogenous set of assumptions and decision premises which maintains compliance without the need for direct oversight or surveillance, and, importantly, preserves individual capacity for interpretation, improvisation, and unique action to manage complexity and uncertainty.[32]

SAFETY CULTURE

The concept of safety culture as a specific entity became prominent in the 1980s and was first given legitimacy by the International Atomic Energy Agency report on the Chernobyl nuclear accident.[33] Nuclear regulatory bodies describe safety culture as the core values and behaviours resulting from a collective commitment by leaders and individuals to emphasise safety over competing goals.[34] Organisations with a positive safety culture are characterised by: communication founded on mutual trust, shared perceptions of the importance of safety, and confidence in the effectiveness of preventative measures.[35]

Safety culture in healthcare is defined as the pattern of individual and organisational behaviour, based on shared beliefs and values, that continuously seeks to minimise patient harm that may result from the process of care delivery.[36] The most frequently cited dimensions of safety culture in healthcare research are: leadership commitment to safety, open communication founded on trust, organisational learning, a non-punitive approach to adverse event reporting and analysis, teamwork, and shared belief in the importance of safety.[37]

CULTURE AND PATIENT SAFETY – ARE PATIENTS AT RISK IN THE OPERATING THEATRE?

Many anaesthetists would reject, and potentially be offended by, the suggestion that patients might be harmed by their care. But culture is a way of seeing, or also not seeing, and can lead to significant blind spots on important issues.[19] Estimated anaesthesia-related mortality in Australia is reassuringly low (1:57,125 anaesthetics)[38] but scarcity of rare events does not necessarily equate to a safe and reliable system of care. Rare events are not a valid method for assessing quality of hospital care[39] as there is no correlation between rare events and other safety indicators.[40] The proportion of hospital deaths that are preventable is small and a focus on causes of mortality may distract from examining the impact of pervasive systematic problems.[41]

Patient safety in anaesthesia can be thought of as the sum total of many small things done well.[42] Even so, most accidents and failures do not result from a single cause or the actions of a single individual, small incidents often link together and expand.[27] Adverse outcomes often arise from a confluence of intersecting factors rather than sequential, linear "domino effects" and the increasing complexity of medical care makes causation more difficult to anticipate and prevent. The challenge of reaching agreement on what incidents or processes should be measured, or even defining what constitutes an anaesthetic complication, should not obscure the reality that the operating theatre represents a hazardous environment for patients.[43]

INCIDENT REPORTING – A COMPLEX SOCIOTECHNICAL PHENOMENON

Quantifying patient harm is difficult as the approach to incident reporting varies widely between healthcare systems. Perioperative mortality, for example, is legislated for mandatory reporting in NSW to the special committee investigating deaths under anaesthesia (SCIDUA),[44] but may be considered for voluntary reporting in other jurisdictions. It has been estimated that adverse events causing serious harm occur 10-20-fold more often than lethal events[45] and non-routine events during anaesthesia (any aspect of clinical care perceived as a deviation from optimal care) have been shown to occur commonly and are often associated with patient harm.[46] Hence, there is a wealth of information from which to potentially derive lessons for improving the safety of patient care, but data collection requires an effective incident reporting system. Despite the mandatory accreditation requirement for all Australian hospitals to utilise incident reporting as a tool for organisational learning, it is recognised that only a small fraction of incidents are reported.[47]

Persistent barriers to voluntary reporting are based on the complex sociocultural approach to adverse events.[48,49] Reporting practices are founded on deep-seated views and beliefs based on individual experience, group interactions, and behavioural norms. A culture of blame, and fear of personal repercussions, may legitimately motivate against reporting. Peer reporting can be inhibited by loyalty, or a sense that a culture of "dobbing" could rebound. There is also systematic bias of reporting as nurses are more likely than doctors to make a notification.[50] Although the limitations of data collection preclude voluntary incident reporting systems being used to measure event incidence or to compare safety performance, the process can provide valuable insights for identifying risk and stimulating in-depth analysis to generate meaningful safety improvements. Large systems such as the web-based anaesthetic incident reporting system (webAIRS),[51] which now has over 10,000 reports, can potentially identify rare or emerging risks by collating data from multiple sites. Furthermore, implementing an effective incident reporting system can, of itself, improve the culture of patient safety by conveying that the organisation prioritises safety and is prepared to change based on frontline feedback. The ultimate benefit of incident reporting systems could be enabling the long-term evolution of cultural change to the organisational approach to risk and patient safety.[52]

NORMALISATION OF DEVIANCE

Clinicians have traditionally placed high value on the measurement of, and response to, events of substantive clinical significance. But, in the same way as soft signs of clinical deterioration may indicate the need for prompt intervention to prevent imminent patient collapse, less clinically significant events of patient harm could be weak signals indicating a need for systematic review to improve the safety and reliability of processes of care. The description of reliability as a *dynamic non-event*[32] reflects the need for constant organisational change to maintain stable outcomes, and the invisibility of successful preventative measures. Safety is defined and measured more by its absence than its presence.[53] When nothing has gone notably wrong it can be difficult to imagine what could have, or to be inspired to implement change. Organising for high reliability is a process, rather than an achievement, and a preoccupation with the prospect of failure is one of the hallmarks of a successful approach.[54] Embedding practices for high reliability in an organisation requires establishing cultural foundations to value the premise of continually monitoring and responding to weak signals, and to believe in the effectiveness of systematic interventions to avoid an event potentially causing significant patient harm.[55]

Anaesthetists have reason to be cautious about complacency with our enviable patient safety record. High standards of care attained with decades of multidisciplinary collaboration could be undone by shifting priorities and increasing tolerance of unsafe actions. Patients are presenting for surgery at increasing age[56] and frailty, with greater associated risk of adverse outcomes and the need for additional resources.[57] Pressure to rationalise resources and efficiently utilise operating theatre time may conflict with anaesthetic concerns, and compromise preferences that can be difficult to justify in the absence of a catastrophic event to reference.

Anaesthetists exhibit a wide range of tolerances for proceeding in situations of suboptimal conditions, even where guidelines are clear that a case should absolutely not go ahead, and the decision is often justified by the belief that their actions reflect a wider professional consensus.[58] The gradual acceptance of incremental erosion of standards – normalisation of deviance – was first described in reference to the NASA space shuttle Challenger disaster.[59] In that instance, the insidious development of a culture that accepted departure from engineering standards was reinforced by a lack of bad outcomes. Inaction did not lead to negative consequences and the collective insensitivity to deviation diminished the value of opposing views to the extent that the warnings of engineers were ignored; refusal to approve the fateful Challenger launch was overruled. Correlations to clinical practice could include examples such as failing to correctly perform time-out procedures, routinely turning off alarms or ignoring safety alerts.[60] A strong culture of patient safety is an important buffer against the pressure of conflicting priorities (such as increased efficiency, reduced staffing, or compromised access to non-clinical or educational opportunities) leading to normalisation of deviation in anaesthesia and potentially catastrophic outcomes.[61]

SAFETY CULTURE ALIGNS WITH CLINICAL OUTCOMES – THE EVIDENCE

Culture affects behaviour, attitudes and cognition and it is logical that a culture of safety would lead to good patient outcomes. Evidence to support a link is evolving but, as yet, benefit is not conclusively shown.[27] A recent meta-analysis found no randomised controlled trials but a consistently positive association in 62 heterogenous articles examining culture and outcomes. The authors concluded that the evidence supports activities that promote positive culture to enhance outcomes.[62]

Understanding the nature of the association between organisational culture and outcomes requires a nuanced appreciation of the research. The study of culture is rooted in the science of anthropology, where research is predominantly qualitative. Surveys such as the Hospital Survey on Patient Safety Culture 2.0[63] that provide quantitative data are limited to measuring safety *climate* – superficial manifestations representing a snapshot in time of individual perceptions of the organisational approach to safety. The challenge of summarising complex cultural phenomena as a numerical score to display a direct association with changing patient outcomes that are similarly complex and difficult to measure may continue to defy attaining level 1 evidence. Furthermore, the nature of system level reform necessary to address cultural issues creates incompatibility with randomisation and controlled study design; research is better suited to observational methodology.[64] It is also recognised that the relationship between organisational culture scores and clinical outcomes is likely to be inherently self-reinforcing; past performance is as likely to shape local culture as culture is to shape healthcare performance. Virtuous circles of high performance leading to high expectations may be seen, as may spirals into decline when poor performance leads to demoralisation and resignation.[65]

Perioperative care is a particularly complex environment with multiple interdependent autonomous individuals contributing to the process. Significant healthcare improvement can be difficult to achieve with isolated interventions and a multitude of independent projects can paradoxically introduce new risks by undermining standardisation and co-ordination. As such, patient safety improvement is more likely to be effective with an integrated approach targeting safety management systems.[66] However, co-ordinating systemic organisational solutions requires multidisciplinary collaboration and a cultural shift to redirect the prevailing narrative from the primacy of individual accountability to a focus on the value of collective activity.[67]

Therefore, while research examining the association between safety culture and patient outcomes evolves, a lack of conclusive evidence should not be a barrier to recognising the effect of culture on processes of care and acting to implement co-ordinated approaches to address systemic issues. Anaesthesia previously became orders of magnitude safer with increased awareness of risk and the introduction of critical incident investigation techniques to examine preventable mishaps.[68] Importing new approaches from other high-risk industries, and the subsequent implementation of human factors engineering, was not impeded by inadequate data, but was applied with consideration to how the solutions made sense in a clinical context.[15]

HOW TO IMPROVE ORGANISATIONAL SAFETY CULTURE

The deep and complex nature of culture defies change with superficial or isolated interventions. Vogus, Sutcliffe, and Weick developed the *enable, enact, elaborate* conceptual framework[69] for understanding an organisational approach to active, purposeful safety culture improvement.

Enable – Leaders enable a safety culture by credibly and consistently communicating their expectations about safety and safe performance, and by recognising and rewarding employees who act in accordance with these expectations. Coherent commitment to safety is reflected by investment in policies, procedures, equipment, and personnel to create a safety infrastructure. Leaders collect and disseminate safety information within a robust safety management information system. They set the tone at the top and make it understood that everybody is responsible for safety. When leaders are credible and communicate and act consistently, individuals begin to develop consistent expectations about what is important, and safe behavioural norms can emerge.

Enact – Shaping safety culture is as much a bottom-up process as it is top-down. People across the organisation collectively enact – put into practice – the commitment to safety. Throughout the organisation, systems and processes that enable people to communicate about potential problems, errors, and risks are in place. This means that people are willing and able to speak up about safety concerns, despite potential costs of doing so. In their day-to-day activities, people are encouraged to be mindful of problems and are preoccupied with risk, particularly when these activities are complex and non-routine. The organisation is collectively vigilant about safety. If there is discrepancy between espoused and enacted priorities (differences in declared organisational policies and informal practice), employees make sense of the overall pattern of signals and discern the underlying organisational values, beliefs, and assumptions.[70]

Enacting recurring organising processes and actively shaping culture are crucial. They work together to overcome inertia and complacency and avoid the practical drift away from safe practice. The common thread in safe cultures is intelligent wariness and the commitment and motivation to enact daily behaviours and activities that increase mindfulness and keep complacency at bay.

Elaborate – The organisation and its units regularly and continuously elaborate its safety culture by reflecting on safety performance and attempting to learn from it. People reflect on causes of incidents, both large and small, in a number of ways, both formal and informal. Employees demonstrate the capability to learn in real time, reflecting on events as they unfold and quickly trying to derive lessons for the future. Moreover, leaders stress organisational learning, taking actions to improve safety infrastructure based on notable past incidents and building into operations opportunities for continuous improvements to policies and procedures.

The sum effect of safety culture in an organisation is a collective mindfulness of the ubiquitous nature of risk and the constant potential for unexpected events. Patient safety is derived from a shared situational awareness that facilitates implementation of systems put in place to minimise the risk and potential impact of harm, and to promptly recognise and effectively manage clinical deterioration.

ORGANISATIONAL CULTURE CAN IMPROVE PERIOPERATIVE PATIENT SAFETY – THE CHECKLIST EXAMPLE

The pervasive nature of cultural influence may manifest throughout an organisation so the potential effect on processes and outcomes is broad. The impact of safety culture on the successful implementation of perioperative checklists is an illustrative example.

The first formal use of checklists was by Boeing in 1935 following the fatal crash of a prototype bomber. The cause was found to be simple human error as the experienced and diligent flight crew launched without releasing a catch that locked all flight controls. It was determined that the technological complexity of advanced aircraft exceeded the reliability of human cognitive performance.[71] While checklists are universal in modern aviation, the introduction was not initially accepted with consensus or enthusiasm. The process was considered particularly useful for inexperienced pilots flying new and complicated aircraft during the Second World War but flying "by the book" was rejected by experienced pilots who preferred their own routines and disliked military discipline.[72] The gradually increasing utilisation of checklists corresponded with decades of cultural evolution to appreciate the value of standardised protocols to the systematic approach to safe flight.

Checklists in healthcare can significantly reduce errors in surgery and using them routinely can result in greater efficiency, consistency, and safety[73] but they have not penetrated medicine to the same degree as other high-risk industries. The difference is partly explained by healthcare's inadequate appreciation of the challenge of checklist implementation and the importance of a supportive safety culture.

The first demonstration in healthcare of effective widespread implementation of a checklist to improve outcomes was the Keystone project initiated at Johns Hopkins University Hospital.[74] The landmark program virtually eliminated central line associated blood stream infections in 103 Michigan intensive care units. The success was widely misunderstood and misrepresented as being due to the introduction of a simple 5-item checklist[75] but the undertaking was better described as a complex cultural and organisational change effort.[76]

The project featured obligatory organisational commitment for each participating unit including: support of executive management, committed medical and nursing team leaders partnered with local infection-control practitioners, an education program teaching the science of safety and the evidence base for each intervention, audit and reporting of infection rates and investigation of any cases, empowerment of nursing staff to speak up if the checklist was not followed, and regular conference calls and meetings for support and mentoring. Local teams were encouraged to customise the checklist to suit their own culture. The checklists themselves were just one component of a comprehensive program to change the culture of the ICUs. The authors caution that "just tell the workers to use checklists" is, quite simply, the wrong conclusion to draw from the study – *when we begin to believe and act on the notion that safety is simple and inexpensive, that all it requires is a checklist, we abandon any serious attempt to achieve safer, higher quality care.*[76]

The surgical safety checklist (SSC) was developed by the World Health Organisation and the Harvard School of Public Health to promote evidence-based practices for reducing preventable surgical complications. The SSC objective is not merely to check that essential processes have been attended to, but to encourage teamwork and facilitate effective communication. It has been shown to impressively reduce perioperative mortality[77,78] and complications[79] but the checklist, as with any clinical intervention, will only be as effective as its implementation.[80] Improvement in surgical outcomes is inconsistent[81] as implementation is varied.[82,83] Successful implementation correlates with team engagement,[84] effective teamwork,[85] and safety culture.[86] Outcomes have been shown to improve in proportion to the degree of checklist implementation, displaying a

positive “dose-response” effect.[87] Disparate outcomes from the standardised checklist introduction reflect the varying underlying organisational cultural factors that determine how the initiative is accepted and integrated into existing organisational workflow.

It has been argued that utilisation of checklists and other safety processes adopted from high-risk industries can only work if unimpeded by barriers of traditional specialist autonomy and discretion.[88] Checklist implementation can be hindered by historical beliefs linking performance and accountability to individual autonomy. A cultural change to reduce hierarchy gradients and encourage constructive dissent could be perceived as a loss of status to specialist doctors unaccustomed to being challenged. Avoiding patient harm requires a degree of humility to accept the premise of collaborative teamwork and willing information exchange. A culture of safety would view acceptance of checklists as cognitive aids, and participation in team processes, as a sign of strength; whereas failing to use them could be regarded as a weakness and perhaps reckless.[89] Effective implementation of checklists is not an individual endeavour, but it does require individuals to adapt to a changing safety culture. That, in turn, requires organisational leadership to understand and demonstrate commitment to the priority of patient safety.[90]

The importance of patient safety culture for successful checklist implementation was demonstrated by the state-wide hospital collaborative in South Carolina. Introduction of a voluntary checklist-based surgical safety program consisted of a comprehensive, multidisciplinary 12-step process. After 3 years, stratified 30-day mortality outcomes showed a reduction from 3.38% to 2.84% for hospitals that completed all 12 steps, compared with an increase from 3.50% to 3.71% for those that did not.[91] Hospitals completing the program had significantly higher levels of executive and physician engagement, and more teamwork training and support.[92] It appears that checklists do not perform well as an isolated intervention but can function effectively as a component of a comprehensive systematic program to improve perioperative care.[93]

Initial enthusiasm and naivety have given way to recognition that benefit to patient outcomes is not inherent to the introduction of a checklist. Improved quality and safety of patient care can be expressed with a checklist-based program when the perioperative team is properly trained and supported by an organisation with a strong safety culture.

CONCLUSION

Since the Anesthesia Patient Safety Foundation introduced the term *patient safety* to describe the modern approach to avoiding iatrogenic harm, anaesthetists have been at the forefront of the field; collaborating with safety experts to implement novel approaches originating from other industries. The challenge of identifying and managing perioperative hazards in an increasingly complex healthcare system is beyond the means of individuals – patient safety is a collective activity with sociocultural implications. To continue as patient safety leaders, anaesthetists must recognise the broad, pervasive influence of organisational culture on the ability of individuals to effectively work together with a common purpose. Understanding the science of patient safety, in the same way as we understand the basic sciences of physiology and pharmacology, is a foundation for enabling collaboration with systematic solutions to safer patient care.[94,95]

REFERENCES

1. Brennan TA, Leape LL, Laird NM, Hebert LD, Localio AR, Lawthers AG, et al. Incidence of adverse events and negligence in hospitalized patients: results of the Harvard medical practice study I. N Engl J Med. 1991 Feb 7;324(6):370-6. doi: 10.1056/NEJM199102073240604
2. Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The Quality in Australian health care study. Med J Aust. 1995 Nov 6;163(9):458-71. doi: 10.5694/j.1326-5377.1995.tb124691.x
3. Thomas EJ, Studdert DM, Burstin HR, Orav EJ, Zeena T, Williams EJ, et al. Incidence and types of adverse events and negligent care in Utah and Colorado. Med Care. 2000 Mar 01;38(3):261-71. doi: 10.1097/00005650-200003000-00003
4. Panagioti M, Khan K, Keers RN, Abuzour A, Phipps D, Kontopantelis E, et al. Prevalence, severity, and nature of preventable patient harm across medical care settings: systematic review and meta-analysis. Br Med J. 2019 Jul 17;366(8208):l4185. doi: 10.1136/bmj.l4185
5. Kohn LT, Corrigan JM, Donaldson MS. To err is human: building a safer health system. Institute of Medicine (US) Committee on Quality of Health Care in America, National Academies Press (US); 2000. doi: 10.17226/9728
6. Barraclough B, Birch J. Health care safety and quality: where have we been and where are we going? Med J Aust 2006 May 15;184(10): S48. II doi: 10.5694/j.1326-5377.2006.tb00362.x
7. Pronovost PJ, Ravitz AD, Stoll RA, Kennedy SB. Transforming patient safety: a sector-wide systems approach. World innovation summit for health (WISH) patient safety forum 2015. Available from: https://www.wish.org.qa/reports/transforming-patient-safety-a-sector-wide-systems-approach/
8. Baker GR. Beyond the quick fix: strategies for improving patient safety. Institute of Health Policy, Management and Evaluation, University of Toronto 2015. Available from: https://ihpme.utoronto.ca/2015/11/beyond-the-quick-fix/

9. Berwick D, Shojania K. Free from harm: accelerating patient safety improvement fifteen years after To err is human. National Patient Safety Foundation, Boston (MA) 2015. Available from: https://www.ihi.org/resources/Pages/Publications/Free-from-Harm-Accelerating-Patient-Safety-Improvement.aspx
10. Illingworth J. Continuous improvement of patient safety: the case for change in the NHS. The Health Foundation, London 2015. Available from: https://www.health.org.uk/publications/continuous-improvement-of-patient-safety
11. Eldridge N, Wang Y, Metersky M, Eckenrode S, Mathew J, Sonnenfeld N, et al. Trends in adverse event rates in hospitalized patients, 2010-2019. JAMA. 2022;328(2):173-83. doi: 10.1001/jama.2022.9600
12. Padula WV, Pronovost PJ. Improvements in hospital adverse event rates: achieving statistically significant and clinically meaningful results. JAMA. 2022;328(2):148-50. doi: 10.1001/jama.2022.10281
13. Jee YK, Matthew RM, Martin DC, Jacqueline AH, Craig SW, Alan FM. Analysis of medication errors during anaesthesia in the first 4000 incidents reported to webAIRS. Anaesth Intensive Care. 2022;50(3):204-19. doi: 10.1177/0310057X211027578
14. Bates DW, Levine DM, Salmasian H, Syrowatka A, Shahian DM, Lipsitz S, et al. The Safety of Inpatient Health Care. N Engl J Med 2023;388(2):142-53. doi: 10.1056/NEJMsa2206117
15. Wears R, Sutcliffe K. Still not safe: patient safety and the middle-managing of American medicine. New York (NY): Oxford University Press; 2020.
16. APSF perioperative patient safety priorities [Internet]. Anesthesia Patient Safety Foundation. Rochester (MN). [cited 2023 Mar 22] Available from: https://www.apsf.org/patient-safety-priorities/
17. Ghaferi AA, Myers CG, Sutcliffe KM, Pronovost PJ. The next wave of hospital innovation to make patients safer. HBR. 2016 Aug 8. Available from: https://hbr.org/2016/08/the-next-wave-of-hospital-innovation-to-make-patients-safer
18. Sevdalis N, Hull L, Birnbach DJ. Improving patient safety in the operating theatre and perioperative care: obstacles, interventions, and priorities for accelerating progress. Br J Anaesth. 2012 Dec;109 Suppl 1:i3-16. doi: 10.1093/bja/aes391
19. Turner BA, Pidgeon NF. Man-made disasters. Boston (MA): Butterworth-Heinemann; 1997.
20. Schein EH. Organizational culture and leadership. 5th ed. Hoboken (NJ): Wiley; 2016.
21. ANZCA - Standards of practice. [Internet] Australian and New Zealand College of Anaesthetists. [Accessed 2023 May 11] Available from: https://www.anzca.edu.au/safety-advocacy/standards-of-practice.
22. ANZCA - Our purpose, vision, and strategic plan. [Internet] Australian and New Zealand College of Anaesthetists. [Accessed 2023 May 11] Available from: https://www.anzca.edu.au/about-us/our-culture/strategic-plan.
23. Hall ET. Beyond Culture. Garden City (NY): Anchor Press; 1976.
24. Pagel M. Wired for Culture: Origins of the Human Social Mind. 1st ed. New York (NY): W.W. Norton and Company; 2012.
25. Schein EH. What you need to know about organizational culture. Train Dev J. 1986 Jan; 40(1):30-4.
26. Mannion R, Davies H. Understanding organisational culture for healthcare quality improvement. Br Med J. 2018 Nov 28;363:k4907. doi: 10.1136/bmj.k4907
27. Sutcliffe K. Organizational and cultural determinants of surgical safety. In: Sanchez JA, Barach P, Johnson JK, Jacobs JP, editors. Surgical patient care: improving safety, quality and value. Basel (Switzerland): Springer International Publishing; 2017. p.145-57. doi: 10.1007/978-3-319-44010-1_11
28. French J, Sutcliffe K. Patient safety: what’s culture got to do with it? MJA Insight. 2022 Feb 28. Available from: https://insightplus.mja.com.au/2022/7/patient-safety-whats-culture-got-to-do-with-it/
29. Schneider B, Smith DB, Goldstein HW. Attraction–selection–attrition: toward a person–environment psychology of organizations. In: Walsh WB, Craik KH, Price RH, editors. Person–environment psychology: new directions and perspectives. Mahwah (NJ): Lawrence Erlbaum Associates publishers; 2000. p.61-85
30. Schein E. Coming to a New Awareness of Organizational Culture. MIT Sloan Manag Rev 1984;25(2):3-15.
31. Perrow C. The bureaucratic paradox: The efficient organization centralizes in order to decentralize. Organ Dyn 1977;5(4):3-14. doi: 10.1016/0090-2616(77)90036-5
32. Weick KE. Organizational Culture as a Source of High Reliability. Calif Manage Rev 1987;29(2):112-127. doi: 10.2307/41165243
33. International Nuclear Safety Advisory Group. Summary report on the post-accident review meeting on the Chernobyl accident. Vienna (Austria): International Atomic Energy Agency; 1986.
34. United Sates Nuclear Regulatory Commission. U.S. NRC - safety culture policy statement. [Internet] Washington DC. United Sates Nuclear Regulatory Commission. (Cited 2023 Mar 22). Available from: https://www.nrc.gov/about-nrc/safety-culture/sc-policy-statement.html#def
35. Advisory Committee on the Safety of Nuclear Installations (ACSNI). ACSNI study group on human factors. London (United Kingdom): Health and Safety Commission Stationery Office; 1993.
36. Australian Commission on Safety and Quality in Healthcare. About patient safety culture. [Internet]. Sydney (NSW): Australian Commission on Safety and Quality in Healthcare; [cited 2023 Mar 22]. Available from: https://www.safetyandquality.gov.au/our-work/indicators-measurement-and-reporting/patient-safety-culture/about-patient-safety-culture.
37. Halligan M, Zecevic A. Safety culture in healthcare: a review of concepts, dimensions, measures and progress. BMJ Qual Saf. 2011;20(4):338-43. doi: 10.1136/bmjqs.2010.040964
38. Australian and New Zealand College of Anaesthetists, Mortality Sub-Committee. Jenkins S. (editor). Safety of anaesthesia: a review of anaesthesia-related mortality reporting in Australia and New Zealand 2015-2017. [Internet]. Melbourne (Vic): Australian and New Zealand College of Anaesthetists; 2021 [cited 2023 Mar 22]. Available from: https://www.anzca.edu.au/resources/incident-reporting-docs/safety-of-anaesthesia-(mortality)-reports/safety-of-anaesthesia-report-2015-2017.pdf
39. Olivarius-McAllister J, Pandit M, Sykes A, Pandit JJ. How can Never Event data be used to reflect or improve hospital safety performance? Anaesthesia. 2021;76(12):1616-24. doi: 10.1111/anae.15476

40. Moppett IK, Moppett SH. Surgical caseload and the risk of surgical Never Events in England. Anaesthesia. 2016;71(1):17-30. doi: 10.1111/anae.13290
41. Shojania KG. Deaths due to medical error: jumbo jets or just small propeller planes? BMJ Qual Saf 2012 Sep;21(9):709-12. doi: 10.1136/bmjqs-2012-001368.
42. Stoelting RK. APSF History [Internet] Rochester (MN) Anesthesia Patient Safety Foundation [cited 2023 Mar 22]. Available from: https://www.apsf.org/about-apsf/mission-and-vision-statements/.
43. Merry AF, Mitchell SJ. Complications of anaesthesia. Anaesthesia. 2018 Jan;73 Suppl 1:7-11. doi: 10.1111/anae.14135.
44. Clinical Excellence Commission. SCIDUA. [Internet] NSW Department of health [Accessed 2023 May 11]. Available from: https://www.cec.health.nsw.gov.au/Review-incidents/mortality-review-authorised-committees/scidua.
45. James JT. A New, Evidence-based Estimate of Patient Harms Associated with Hospital Care. J Patient Saf 2013 Sep 01;9(3):122-8.
46. Liberman J, Slagle J, Whitney G, Shotwell M, Lorinc A, Porterfield E, et al. Incidence and Classification of Nonroutine Events during Anesthesia Care. Anesthesiology 2020 July;133(1):41-52. doi 10.1097/ALN.0000000000003336
47. Blais R, Bruno D, Bartlett G, Tamblyn R. Can We Use Incident Reports to Detect Hospital Adverse Events? J Patient Saf 2008 Mar 01;4(1):9-12. doi :10.1097/PTS.0b013e31816154a4
48. Hewitt T, Chreim S, Forster A. Sociocultural Factors Influencing Incident Reporting Among Physicians and Nurses: Understanding Frames Underlying Self- and Peer-Reporting Practices. J Patient Saf 2017 Sep;13(3):129-37. doi 10.1097/PTS.0000000000000130
49. Braithwaite J, Westbrook MT, Travaglia JF, Hughes C. Cultural and associated enablers of, and barriers to, adverse incident reporting. BMJ Qual Saf 2010 Jun;19(3):229-33. doi: 10.1136/qshc.2010.043679
50. Kingston M, Evans S, Smith B, Berry J. Attitudes of doctors and nurses towards incident reporting: a qualitative analysis. Med J Aust 2004 Jul;181(1):36-9. doi: 10.5694/j.1326-5377.2004.tb06158.x
51. Australian and New Zealand Tripartite Anaesthetic Data Committee. WebAIRS. [Accessed 2022 Dec 12]. Available from: https://www.anztadc.net/Default.aspx?D=.
52. Pham J, Girard T, Pronovost P. What to do with Healthcare Incident Reporting Systems. J Public Health Res 2013;2(3). doi 10.4081/jphr.2013.e27
53. Reason J. Safety paradoxes and safety culture. Inj Contr Saf Promot 2000;7(1):3-14. doi :10.1076/1566-0974%28200003%297%3A1%3B1-V%3BFT003
54. Weick K, Sutcliffe K. Managing the Unexpected: Sustained Performance in a Complex World. 3rd edition. Hoboken (NJ): John Wiley and Sons; 2015. Chapter 3, Principle 1: Preoccupation with Failure p. 45-61.
55. Sutcliffe K, Paine L, Pronovost P. Re-examining high reliability: actively organising for safety. BMJ Qual Saf 2017;26(3):248-51. doi 10.1136/bmjqs-2015-004698
56. Fowler AJ, Abbott TE, Prowle J, Pearse RM. Age of patients undergoing surgery. Br J Surg. 2019 Jul;106(8):1012-18. doi: 10.1002/bjs.11148.
57. McIsaac DI, MacDonald DB, Aucoin SD. Frailty for perioperative clinicians: a narrative review. Anesth Analg. 2020;130(6):1450-60. doi: 10.1213/ANE.0000000000004602.
58. Greig PR, Higham HE, Darbyshire JL, Vincent C. Go/no-go decision in anaesthesia: wide variation in risk tolerance amongst anaesthetists. Br J Anaesth. 2017;118(5):740-6. doi: 10.1093/bja/aew444.
59. Vaughan D. The Challenger Launch Decision: Risky Technology, Culture and Deviance at NASA. Chicago (IL): University of Chicago Press; 1996.
60. Price MR, Williams TC. When doing wrong feels so right: normalization of deviance. J Patient Saf. 2018 Mar;14(1):1-2. doi: 10.1097/PTS.0000000000000157.
61. Prielipp RC, Magro M, Morell RC, Brull SJ. The normalization of deviance: do we (un)knowingly accept doing the wrong thing? Anesth Analg. 2010 May 01;110(5):1499-1502. doi: 10.1213/ANE.0b013e3181d5adc5.
62. Braithwaite J, Herkes J, Ludlow K, Testa L, Lamprell G. Association between organisational and workplace cultures, and patient outcomes: systematic review. BMJ Open. 2017;7(11). doi: 10.1136/bmjopen-2017-017708
63. Australian Commission on Safety and Quality in Healthcare. A-HSOPS 2.0 survey form. [Internet] Sydney (NSW): Australian Commission on Safety and Quality in Healthcare; [cited 2023 Mar 22}. Available from: https://www.safetyandquality.gov.au/publications-and-resources/resource-library/hsops-20-survey-form.
64. Webster CS. Evidence and efficacy: time to think beyond the traditional randomised controlled trial in patient safety studies. Br J Anaesth. 2019 Jun;122(6):723-5. doi: 10.1016/j.bja.2019.02.023.
65. Mannion R, Davies HT, Marshall MN. Cultural characteristics of high and low performing hospitals. J Health Organ Manag. 2005 Dec 1;19(6):431-9. doi: 10.1108/14777260510629689.
66. Dixon-Woods M, Pronovost PJ. Patient safety and the problem of many hands. BMJ Qual Saf. 2016 Feb 24;25(7):485-8. doi: 10.1136/bmjqs-2016-005232.
67. Pronovost PJ, Sutcliffe KM, Basu L, Dixon-Woods M. Changing the narratives for patient safety. Bull World Health Organ. 2017 Jun 1;95(6):478-80. doi: 10.2471/BLT.16.178392
68. Cooper JB, Newbower RS, Long CD, McPeek B. Preventable anesthesia mishaps: a study of human factors. Anesthesiology. 1978 Dec;49(6):399-406. doi: 10.1097/00000542-197812000-00004.
69. Vogus TJ, Sutcliffe KM, Weick KE. Doing no harm: enabling, enacting, and elaborating a culture of safety in healthcare. Acad Manag Perspect. 2010;24(4):60-77. doi: 10.2139/ssrn.1904620
70. Weick K, Sutcliffe K, Obstfeld D. Organizing and the process of sensemaking. In: Shamiyeh M (editor) Driving Desired Futures: Turning Design Thinking into Real Innovation. Boston (MA): Birkhäuser; 2014. p.216-35. doi 10.1515/9783038212843.216
71. Civil Aviation Safety Authority. One thing at a time: a brief history of the checklist. Flight Saf Aust. 2018 Nov 12. Available from: https://www.flightsafetyaustralia.com/2018/11/one-thing-at-a-time-a-brief-history-of-the-checklist/

72. Bohn RE. Not Flying By The Book: slow adoption of checklists and procedures in WW2 aviation. San Diego (CA): University of California; 2013.
73. Gawande A. The Checklist Manifesto: How to Get Things Right. New York (NY): Metropolitan Books; 2009.
74. Pronovost P. An intervention to decrease catheter-related bloodstream infections in the ICU. N Eng J Med. 2006 Dec 28;355(26):2725-32. doi: 10.1056/NEJMoa061115.
75. Gawande A. The Checklist. New York (NY): The New Yorker; 2007 Dec 10. Available from https://www.newyorker.com/magazine/2007/12/10/the-checklist
76. Bosk CL, Dixon-Woods M, Goeschel CA, Pronovost PJ. Reality check for checklists. Lancet. 2009 Aug 8;374(9688):444-5. doi: 10.1016/s0140-6736(09)61440-9
77. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AS, Dellinger EP, et al. A surgical safety checklist to reduce morbidity and mortality in a global population. N Engl J Med. 2009 Jan 29;360(5):491-9. doi: 10.1056/NEJMsa0810119.
78. Abbott TE, Ahmad T, Phull MK, Fowler AJ, Hewson R, Biccard BM, et al. The surgical safety checklist and patient outcomes after surgery: a prospective observational cohort study, systematic review and meta-analysis. Br J Anaesth. 2018 Jan;120(1):146-55. doi: 10.1016/j.bja.2017.08.002.
79. Bergs J, Hellings J, Cleemput I, Zurel Ö, De Troyer V, Van Hiel M, et al. Systematic review and meta-analysis of the effect of the World Health Organization surgical safety checklist on postoperative complications. Br J Surg. 2014 Feb;101(3):150-8. doi: 10.1002/bjs.9381.
80. Haugen AS, Sevdalis N, Søfteland E. Impact of the World Health Organization surgical safety checklist on patient safety. Anesthesiology. 2019 Aug;131(2):420-425. doi: 10.1097/ALN.0000000000002674.
81. Wani MM, Gilbert JH, Mohammed CA, Madaan S. Factors Causing Variation in World Health Organization surgical safety checklist effectiveness—a rapid scoping review. J Pat Saf. 2022 Dec;18(8):e1150-9. doi: 10.1097/PTS.0000000000001035.
82. Delisle M, Pradarelli JC, Panda N, Koritsanszky L, Sonnay Y, Lipsitz S, et al. Variation in global uptake of the surgical safety checklist. Br J Surg. 2020 Jan;107(2):e151-60. doi: 10.1002/bjs.11321.
83. Russ S, Rout S, Caris J, Mansell J, Davies R, Mayer E, et al. Measuring variation in use of the WHO surgical safety checklist in the operating room: a multicenter prospective cross-sectional study. J Am Coll Surg. 2015 Jan;220(1):1-11.e4. doi: 10.1016/j.jamcollsurg.2014.09.021.
84. Borchard A, Schwappach DL, Barbir A, Bezzola P. A systematic review of the effectiveness, compliance, and critical factors for implementation of safety checklists in surgery. Ann Surg. 2012;256(6):925-33. doi: 10.1097/SLA.0b013e3182682f27.
85. Russ S, Rout S, Sevdalis N, Moorthy K, Darzi A, Vincent C. Do safety checklists improve teamwork and communication in the operating room? A systematic review. Ann Surg. 2013 Dec;258(6):856-71. doi: 10.1097/SLA.0000000000000206.
86. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AS, Dellinger EP, et al. Changes in safety attitude and relationship to decreased postoperative morbidity and mortality following implementation of a checklist-based surgical safety intervention. BMJ Qual Saf. 2011 Jan;20(1):102-107. doi: 10.1136/bmjqs.2009.040022.
87. Mayer E, Sevdalis N, Rout S, Caris J, Russ S, Mansell J, et al. Surgical checklist implementation project: the impact of variable WHO checklist compliance on risk-adjusted clinical outcomes after national implementation: a longitudinal study. Ann Surg. 2016 Jan;263(1):58-63. doi: 10.1097/SLA.0000000000001185.
88. Amalberti R, Auroy Y, Berwick D, Barach P. Five system barriers to achieving ultrasafe health care. Ann Int Med. 2005;142(9):756-64. doi: 10.7326/0003-4819-142-9-200505030-00012.
89. Jones CP, Fawker-Corbett J, Groom P, Morton B, Lister C, Mercer SJ. Human factors in preventing complications in anaesthesia: a systematic review. Anaesthesia. 2018 Jan;73 Suppl 1:12-24 doi: 10.1111/anae.14136.
90. Walker IA, Reshamwalla S, Wilson IH. Surgical safety checklists: do they improve outcomes? Br J Anaesth. 2012 Jul;109(1):47-54. doi: 10.1093/bja/aes175
91. Haynes AB, Edmondson L, Lipsitz SR, Molina G, Neville BA, Singer SJ, et al. Mortality trends after a voluntary checklist-based surgical safety collaborative. Ann Surg. 2017 Dec;266(6):923-9 doi: 10.1097/SLA.0000000000002249.
92. Berry WR, Edmondson L, Gibbons LR, Childers AK, Haynes AB, Foster R, et al. Scaling safety: the South Carolina surgical safety checklist experience. Health Aff. 2018 Nov;37(11):1779-86. doi: 10.1377/hlthaff.2018.0717.
93. Urbach D. The checklist paradox. Ann Surg. 2017 Jun 16;266(6):930-1. doi: 10.1097/SLA.0000000000002338.
94. Ritchie-McLean S, Davies M. “In somno securitas?” Is it time for anaesthetists to train in patient safety? Anaesthesia. 2019 Jun 12;75(2):158-61. doi: 10.1111/anae.14735
95. Weller JM, Merry AF. Best practice and patient safety in anaesthesia. Br J Anaesth. 2013 May;110(5):671-3. doi 10.1093/bja/aet011

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The tightrope of haemostatic homeostasis – perioperative methods for coagulation factor manipulation

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A BRIEF HISTORY OF CLOTTING FACTOR DEVELOPMENT

To fully comprehend the advanced and complex options currently available to treat inherited disorders of coagulation, we must first return to a time, just 100 years ago when the prognosis of haemophilia was dire. The only treatment for severe debilitating bleeding and haemarthrosis was splinting, ice, and bedrest. Life expectancy was only 10-15 years, even for patients with mild disease. Those lucky few that did survive were compromised by severe disability.[1]

During the First World War, high numbers of casualties forced medical advancement and the understanding of blood types. This resulted in a low efficacious treatment option for haemophilia; patients were given whole blood, which contained the missing coagulation factors they needed. With only a modest clinical benefit, life expectancy improved to around 20 years of age.[2]

Over time, increasing combat casualties became triggers for the improved preparation of plasma, that contained coagulation factors alone. However, this form of replacement therapy was not widely available and was also of limited clinical efficacy. So, even until the 1960s, the life expectancy of patients with haemophilia was no more than 20-30 years.[2]

In 1964 Judith Pool discovered cryoprecipitation, the process for creating concentrated blood clotting factors including human Factor VIII.[3]

By the 1970s, industrial scale processes were in place for manufacturing factor concentrates, which significantly improved the quality of life for patients with haemophilia, who had access to such treatment. From then on Factor VIII was available to terminate acute bleeding caused by haemophilia, and to preoperatively prepare the patient for surgical procedures previously deemed too high risk.[3]

However, the 1980s saw a dramatic and devastating blight on this progress. Patients treated with clotting factors produced from large plasma pools began contracting blood-borne infections, most notably HIV and hepatitis.[4] Then in the 1990s, advancements in molecular genetics allowed the manufacture of recombinant factors and this, in combination with enhanced screening and virucidal techniques, has halted the transmission of blood-borne viruses, with no reported cases since 1990.[4]

Unfortunately, blood-borne diseases was not the only significant obstacle encountered by patients with inherited clotting disorders, as it emerged that up to one third of patients treated with factor-specific therapies would go on to develop alloantibodies to the factor they received.[5] This made them refractory to replacement therapy because the coagulant activity contained in factor replacement products was neutralised by the patient's own specific antibodies.

Alternative ways of achieving clotting were sought and it was discovered that plasma concentrates of activated factors of the prothrombin complex (aPCC), as well as the recombinant production of activated Factor VII (rFVIIa), offered new ways to bypass the coagulation defect associated with Factor VIII inhibitors. These were termed "bypass agents" and have been extremely successful in improving outcomes for patients with inherited

bleeding disorders, such that their life expectancies now approach those of a person with no clotting disorder.[4] Further advances include the discovery of extended half-life factors, which increase the dosing interval for patients with severe disease who require regular factor therapy. In today's practice, we have access to several purified factor concentrates for use in trauma, cardiac, and obstetric surgery and this is largely thanks to our understanding of the inherited clotting disorders such as the different types of haemophilia, which have been the driving force for progress regarding factor fractionation.

INTRODUCTION

This paper will review the currently available factor concentrates and the evidence and indications for use. Figure 1. summarises the currently available factor preparations available in Australia that will be covered in this article.

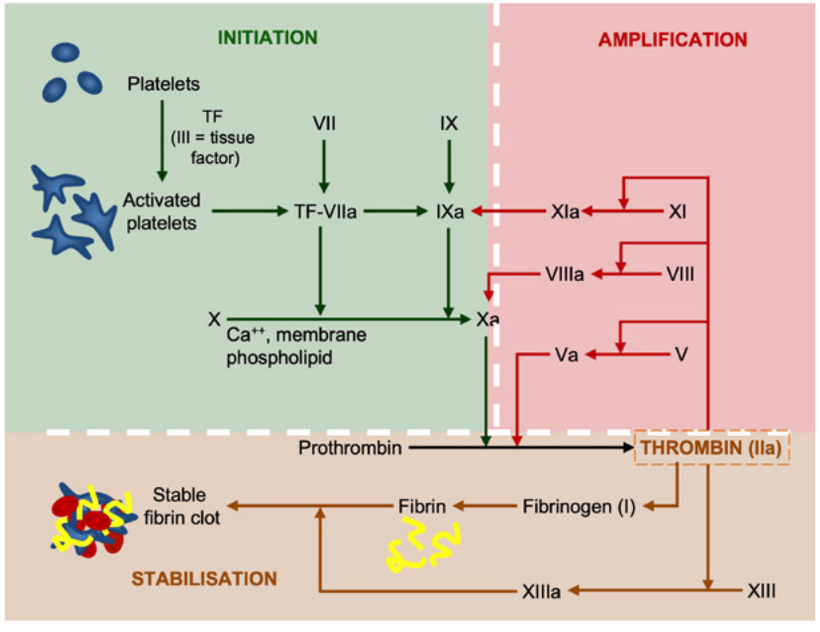
Figure 1. Products available in Australia[6]

	Trade name	Source	Indications	Off label use	Dose*	Cost
I	RiaSTAP	Human plasma	Acute bleeding and prophylaxis in patients with congenital fibrinogen deficiency	Dysfibrinogenemia (acquired deficit)	Trauma/ acquired deficiency 50-70 mg/kg Congenital fibrinogen deficiency – dose calculated according to target levels and current levels	$863/g
VIIa	NovoSeven	Recombinant	Haemophilia A or B with inhibitors Acquired haemophilia Glanzmann thrombasthenia, congenital Factor VII deficiency	Salvage therapy to control microvascular bleeding	Haemophilia 90 mcg/kg Cardiac surgery 30 mcg/kg[7]	$1350/ mg
VIII	Eloctate Adynovate	Human plasma Recombinant	Haemophilia A		Prophylaxis 40-50 IU/kg Max 70 IU/kg	
IX	Alprolix	Human plasma Recombinant	Haemophilia B		Prophylaxis 50 IU/kg Major bleed 133 IU/kg	
XI	Hemoleven	Human plasma	Severe Factor XI deficiency with no inhibitor		15 units/kg	$14/IU
XIII	Fibrogammin	Human plasma	Factor XIII deficiency		25-40 IU/kg	$214/ 250IU
vWF + VIII	Biostate	Human plasma	Willebrand disease,	Haemophilia A	Seek haematology advice	$960/ 1000 IU
Anti-thrombin III	Thrombotrol	Human plasma	Hereditary or acquired AT deficiency	Heparin resistance	Dose required = (desired level – pretreatment level) x weight in kg x 2.2	$1547/ 1000IU
II, IX, X,	Prothrombinex	Human plasma	Rapid normalisation of vitamin K dependent clotting factors		25-50 IU/kg depending on extent of INR derangement.	$305/ 500IU
*Seek haematology advice before prescribing any specialist clotting factors						

FACTOR 1 (FIBRINOGEN)

Fibrinogen (Factor I) is a glycoprotein complex produced by the liver and plays a pivotal role in the stabilisation phase of clot formation in haemostasis (Figure 2). During tissue and vascular injury, it is converted enzymatically by thrombin to fibrin and then to an insoluble fibrin-based clot. It supports thrombin generation and platelet aggregation and facilitates wound healing.[8]

Figure 2. Clotting factors involved in the initiation, amplification, and stabilisation of clot formation



Factor 1 (fibrinogen) is available from fresh frozen plasma (FFP), cryoprecipitate, or as a fibrinogen concentrate (RiaSTAP®). The quantity of Factor I varies significantly depending on the product. Hence the volume of infusion required for a clinically effective dose varies depending on the product used. Fibrinogen concentrate contains 20g/L of Factor I, compared to 15-17g/L for cryoprecipitate and 2g/L for FFP.[9] Additionally, there are several benefits of fibrinogen concentrate including being blood type free, storage at room temperature, and rapid reconstitution and administration. Cost is the main barrier to its widespread use. Cryoprecipitate, on the other hand, has the advantage of containing other important coagulation factors such as von Willebrand Factor (vWF), Factor VIII, and Factor XIII, which may promote more rapid and effective coagulation in bleeding patients.[9]

Congenital fibrinogen deficiency is a rare, autosomal recessive inherited bleeding disorder in which coagulation is impaired by lack of fibrinogen. The lack of fibrinogen expresses itself with excessive and, at times, uncontrollable bleeding most commonly occurring at birth from the umbilical cord.[10]

INDICATIONS FOR USE

In Australia and New Zealand, fibrinogen concentrate is supplied and funded for treatment of acute bleeding and prophylaxis in patients with congenital fibrinogen deficiency (including afibrinogenaemia, hypofibrinogenaemia and dysfibrinogenaemia).[11,12]

The most common off label use for fibrinogen concentrate is in the management of major bleeding as an alternative to cryoprecipitate. Fibrinogen concentrate leads to faster correction of fibrinogen levels compared with cryoprecipitate.[13] However, cryoprecipitate transfusion provides additional factors that restore key fibrinolytic regulators and limit plasmin generation. Consequently, cryoprecipitate led to stronger and more stable clots with a more natural fibrin structure compared with fibrinogen concentrate in an ex vivo study.[14] A large randomised controlled trial comparing fibrinogen concentrate and cryoprecipitate use early in trauma on clinical, patient-centred outcomes is ongoing (FEISTY II).[15]

FACTOR VIIA (NOVOSEVEN™)

Factor VIIa, when bound to tissue factor (Factor III), is important in the initiation phase of clot formation. Factor VII circulates in the blood in the inactive form. Upon vessel injury, Factor VII is exposed to tissue factor (TF) and activated to become Factor VIIa by proteases, among which are thrombin (Factor IIa), Factors Xa, IXa, XIIa, and the Factor VIIa-TF complex itself. The complex of Factor VIIa-TF catalyses the conversion of Factor IX to IXa and Factor X to Xa (Figure 2).[16]

NovoSeven™ is a recombinant Factor VII in an activated form. As Factor VIIa has already been activated, thereby bypassing the body's innate homeostasis, it carries greater risks of thrombosis than other factor products. Clinicians must incorporate clinical judgment to balance the potential benefits of achieving haemostasis against the higher risks of thrombosis when administrating this product.

NovoSeven™ was developed for patients with inhibitors to coagulation Factor VIII or Factor IX, and congenital Factor VII deficiency. It is generated in cultured hamster cells grown in newborn calf serum (purified from culture supernatant) and is converted to Factor VIIa during purification.

INDICATIONS FOR USE

In Australia and New Zealand, NovoSeven™ has been approved for several indications (no age limit) including Haemophilia A and B with inhibitors, acquired haemophilia, Glanzmann thrombasthenia, and congenital Factor VII deficiency.[17] It has an ultra-short half-life of just 2.6 to 6 hours after administration. The initial dose is 90 mcg/kg however there is significant individual variability in the haemostatic response to Factor VIIa, and it can be prothrombotic in non-haemophiliacs.[17]

The off-label use of NovoSeven™ is generally reserved as salvage therapy to control microvascular bleeding when conventional therapy with transfusions and antifibrinolytic therapies have failed. Use under these circumstances has been investigated by multiple RCTs and subsequently a meta-analysis of 993 uses which concluded that rFVIIa did not change mortality (RR, 0.90; 95% CI: 0.50, 1.64; I 2 = 0.0%; P = 0.738).[18]

Individual RCT analyses showed that the use of rFVIIa could reduce the volume of blood loss (including for prostate cancer, severe acute pancreatitis (SAP), and spinal disease) and the transfusion of packed red cells (PRC) and FFP in subsets of perioperative patients. There was also a trend toward reduced surgical re-exploration in cardiac surgery, but this did not meet statistical significance.[18]

Recommendations endorsed by the European Society of Anaesthesiology cited the lack of good evidence for the use of rFVIIa which limits the scope of its use. In summary, there is a rationale for using rFVIIa to treat massive bleeding in certain indications, but only adjunctively to the surgical control of bleeding once conventional therapies have failed.[19] Additionally, it is worth noting the current cost of rFVIIa in Australia is around $6000 for a single adult dose.[6]

FACTOR VIII

Factor VIII is essential for forming a stable blood clot (Figure 2). Factor VIII circulates in a stable noncovalent complex bound with vWF. When tissue is damaged, it is activated by thrombin (Factor IIa) and dissociates from vWF. It then binds to and becomes a cofactor for Factor IXa to activate Factor X, which, in turn, with its cofactor

Factor Va, activates more thrombin. This sets up a positive feedback loop contributing to a 'thrombin burst'. Thrombin cleaves fibrinogen into fibrin which polymerises and crosslinks – using Factor XIII – into an insoluble blood clot.

Factor VIII deficiency results in Haemophilia A. Most commonly, Haemophilia A is a hereditary disorder with an X-linked recessive inheritance pattern and therefore more likely to affect males. It has an incidence of 1 in 5000 male births. Disease can be mild, moderate, or severe depending on the level of activity of Factor VIII. Around 30% of female carriers have Factor VIII activity below 40% and are at risk of increased bleeding in the perioperative period.[20]

Acquired Haemophilia A, an autoimmune disorder, is much rarer (1-6 cases per million inhabitants per year) and is caused by the development of autoantibodies against Factor VIII.[21] About half of acquired Haemophilia A cases are idiopathic. There is, however, an association with the postpartum period, drugs (penicillin, sulfonamides, phenytoin, interferons, fludarabine), other systemic autoimmune diseases – such as rheumatoid arthritis, malignancies, and infections.[21]

Factor VIII therapy is available in three forms, plasma-derived, recombinant, and extended half-life recombinant. Plasma-derived Factor VIII concentrates are prepared by commercial fractionation of carefully screened donor plasma. They are stratified based on purity. Greater purity reflects a higher ratio of Factor VIII to non-Factor VIII proteins. Recombinant Factor VIII products include several genetically engineered proteins produced in either animal or human cell lines. For the most part, these are made using modified versions of the human Factor VIII gene.[22] Longer-lasting recombinant Factor VIII preparations with extended half-lives have the advantage of less-frequent dosing, enhancing the ease of administration for some patients. This is now the gold standard for haemophilia care with Eloctate and Adynovate being the main commercially available products.[23]

The dose for prophylaxis for severe Haemophilia A is 25-40 units/kg, 3 times per week. Levels are monitored via Factor VIII assay with the units reported as a percentage of normal. The dose in emergency bleeding will vary depending on factor levels and is best guided by a haemophilia treatment centre (HTC).[24]

Currently there is no indication for the use of Factor VIII in the perioperative period other than in the management of haemophilia.

FACTOR IX

Factor IX is cleaved by Factor XIa of the contact pathway or Factor VIIa of the tissue factor pathway to form Factor IXa. Then Factor IXa, in the presence of Ca2+, membrane phospholipids, and a Factor VIII cofactor, hydrolyses one arginine-isoleucine bond in Factor X to form Factor Xa which helps begin the initiation of clot formation. Factor Xa is required to convert prothrombin to thrombin. However, if antithrombin is present, Factor IX is inhibited.[25]

Deficiencies in Factor IX manifest as Haemophilia B, also known as Christmas disease, presents with a range of severities depending on the gene defect. Although it is the second most common haemophilia, it is generally less severe than Haemophilia A.[26] It too, is inherited as an X-linked recessive disorder. Female carriers are usually asymptomatic.

Again, like Factor VIII there are three formulations. Plasma-derived Factor IX, recombinant Factor IX, and extended half-life recombinant Factor IX (Alprolix being the most widely used).[4]

In the absence of an inhibitor, the dose required is obtained by multiplying the patient's weight in kilograms by the desired factor level. Each international unit (amount in 1 mL of normal pooled plasma) of Factor IX per kilogram of body weight will raise the plasma Factor IX level by about 1 IU/dl.[27] For example, a 50 kg patient who needs a level of 40 IU/dl would need 2000 units of plasma-derived Factor IX. Vials of Factor IX concentrates are available in doses ranging from 250 to 3000 units each.

FACTOR XI

Factor XI deficiency, Haemophilia C, is an extremely rare condition with prevalence around 1 in 1 million that is usually inherited in an autosomal recessive pattern.[28,29] This condition shows a significant clinical heterogeneity depending on the degree of factor deficiency. It is thought that Factor XI is more important in developing thrombosis, rather than haemostasis, although some case series report higher rates of epistaxis, menorrhagia, and perioperative or post-partum bleeding.[29] The condition is usually much less severe than other forms of haemophilia, usually with minimal impact on patients' daily lives.

Given the rarity of this condition, Haemoleven (Factor XI) is not routinely kept in HTCs and may have to be ordered well in advance if required. It is indicated for prophylaxis in major surgery or for treatment of bleeding in severe Factor XI deficiency with no inhibitor.

If the inhibitor screen is positive, then it is advised to use Factor VIIa as a bypass agent instead. However, most surgical procedures do not require prophylaxis as the coagulation defect tends to be mild. For minor procedures or mild disease, individuals may reasonably choose expectant management or antifibrinolytic therapy. Hemoleven is a high-purity Factor XI concentrate derived from human plasma. The dose should be no more than 10-15 units/kg and there is a 10% thrombosis risk. A reasonable alternative is FFP for emergency situations or when Factor XI is unavailable.[30]

FACTOR XIII

Factor XIII deficiency is an autosomal recessive inherited bleeding disorder, characterised by spontaneous and provoked bleeding from sites such as the umbilical cord, or surgical, joint, and intracranial haemorrhages in patients who are homozygous. Menorrhagia, recurrent miscarriage, and impaired wound healing are also widely reported.[31-33] Heterozygous carriers may show a bleeding tendency upon provocation such as traumatic injury or invasive procedures and in some cases, umbilical cord bleeding, menorrhagia, miscarriages, or postpartum bleeding.[34]

Factor XIII levels of less than 15% of normal have been established as the threshold at which bleeding risk is significantly elevated.[35] However in some patients, effective haemostasis can be achieved with Factor XIII levels as low as 2-5% depending on genes involved in the mutation.[36]

There are several Factor XIII replacement products commercially available including recombinant Factor XIII A-subunit (Tretten) and Factor XIII purified from human plasma (Fibrogammin and Fibrogammin-P).[37] Unlike most other coagulation factors, Factor XIII has a significantly longer half-life of 9-14 days and as such, replacement may be undertaken as infrequently as once per month.

The recommended dose is 25-40 IU/kg administered intravenously. For hospitals that do not have access to purified Factor XIII concentrate, FFP or cryoprecipitate can also be used to supply Factor XIII in an emergency. Factor XIII content in cryoprecipitate is 60IU and in FFP is 288IU.[38]

Perioperative dosing is the same dosing for treatment of spontaneous bleeding (25-40 IU/kg). It is important to note that if a routine prophylaxis dose has been given in the previous seven days, further doses are unlikely to be required. Recent Factor XIII levels and inhibitor screening are suggested preoperatively. Factor XIII replacement products are generally well tolerated. The major disadvantages are limited availability due to low stock kept in most centres and high cost.

VON WILLEBRAND FACTOR AND BIOSTATE

Biostate is a plasma-derived factor product containing both Factor VIII and vWF in a ratio of 1:2 (250 IU FVIII and 500 IU VWF). It is used as prophylaxis and treatment of non-surgical and surgical bleeding and in patients with von Willebrand Disease when desmopressin (DDAVP) treatment is ineffective or contraindicated. It is also effective in Factor VIII deficiency due to Haemophilia A. Dosing is complicated and it is highly recommended that clinicians seek advice from an HTC for guidance.

PROTHROMBIN COMPLEX CONCENTRATE

Prothrombinex, Beriplex, and Octaplex are all commercially available prothrombin complex concentrates (PCC). They all contain human plasma-derived vitamin K-dependent clotting Factors II, IX, X, variable amounts of Factor VII, and proteins C and S. Prothrombinex contains no Factor VII, while Beriplex P/N 250 contains 100-250 IU per vial and Beriplex P/N 500 contains 200-500 IU per vial.[39] Potency of PCC preparations is standardised to Factor IX content (e.g. 500 IU/vial).

The contents and indications of available PCCs are summarised in Figure 3.

Figure 3. Contents, approved indications, and off label uses for PPCs[40]

Concentrate	Coagulation factors functional component(s)	Indications	Off-label use/remark
4F-PCC	Coagulation factors II, VII, IX, X	Treatment and perioperative prophylaxis of bleeding in Acquired deficiency of PCC factors, such as deficiency caused by treatment with vitamin K antagonists Congenital deficiency of the vitamin K-dependent coagulation factors when purified specific coagulation factor products are not available	Treatment of trauma-induced coagulopathy Treatment of bleeds in patients with liver disease Reversal of anticoagulation by direct Factor Xa and thrombin-inhibiting oral anticoagulants (evidence based on several bleeding models in animals and human volunteers; substantial clinical evidence is lacking)
3F-PCC	Coagulation factors II, IX, X	Prevention and control of bleeding in Haemophilia B patients	Anticoagulant reversal agent for for vitamin K antagonists (4F-PCC is superior to 3F-PCC) for direct oral thrombin and factor Xa inhibitors (evidence based on a few bleeding models in animals; substantial clinical evidence is lacking)
Activated-PCC	Coagulation factors II, IX, X, VII-activated form	Treatment and prophylaxis of bleeding in patients (Haemophilia A and B as well as non-haemophiliacs) with inhibitors to Factors VIII or IX	Anticoagulant reversal agent for vitamin K antagonists (evidence based on a limited number of clinical studies) direct oral thrombin and factor Xa inhibitors (evidence based on bleeding models in animals; substantial clinical evidence is lacking)

The main benefits of PCCs are that they are low volume, permit rapid administration, and are readily available and cheap. It is indicated for the rapid normalisation of vitamin K-dependent clotting factors within 30 minutes. The dose is 25-50 IU\kg depending on extent of INR derangement. Generally, 1 IU\kg of Factor IX raises the Factor IX by approximately 1%.

The most common use of PCC in Australia is for the reversal of warfarin, although there is increasing use in off-label use for the management of trauma induced coagulation defects. When used in Haemophilia B, repeated doses result in the accumulation of Factor X due to its much longer half-life compared with that of Factor IX. Venous thromboembolism and disseminated intravascular coagulation have been reported after multiple doses.[41]

ANTITHROMBIN CONCENTRATE (THROMBATE III OR THROMBOTROL®-VF)

Antithrombin functions primarily by deactivating thrombin and activating Factor X and secondarily by deactivating Factors VII, IX and XII. Levels less than 60% result in thrombosis. Thrombate III is a plasma-derived concentrate made from pooled human plasma indicated for hereditary or acquired AT deficiency in the prevention of venous thromboembolism.[42] Antithrombin concentrates are also used in cardiac surgery for the management of heparin resistance as an alternative to FFP.[43]

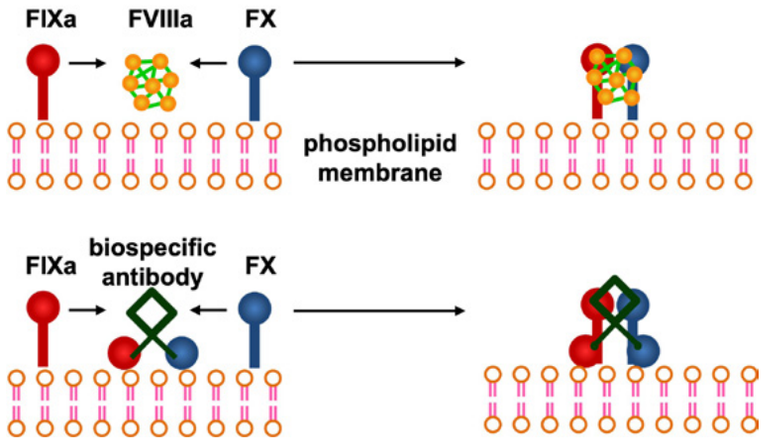
NON-FACTOR THERAPY – EMICIZUMAB

Emicizumab (Hemlibra) is a recombinant humanised monoclonal antibody that binds to Factors IXa and X simultaneously, bringing these two molecules together and substituting for Factor VIIIa as a cofactor for Factor IXa in activating Factor X (Figure 4).[44] This novel monoclonal antibody is an option for prophylaxis in individuals with Haemophilia A with or without inhibitors. However, it is not effective for the management of acute bleeding as it takes up to four weeks to achieve therapeutic effect.

Therapy is started with a loading dose of 3 mg/kg subcutaneously once weekly for four weeks. Subsequent maintenance dosing regimens are 1.5 mg/kg subcutaneously once per week, 3 mg/kg subcutaneously once every two weeks, or 6 mg/kg subcutaneously once every four weeks.

An adequate coagulation response is usually achieved within 4 weeks however there is no routine monitoring of coagulation status with emicizumab as standard aPTT-based coagulation tests and Factor VIII activity assays are affected by emicizumab itself and are therefore inaccurate. If an individual receiving emicizumab prophylaxis requires Factor VIII infusions, the Factor VIII activity and inhibitor titres must be measured using a bovine substrate-based chromogenic assay instead of the standard assay.[45] Haematology input is recommended in this situation.

Figure 4. Mechanism of action of emicizumab in the activation of Factor Xa[44]



ELECTIVE SURGERY

Planning for elective surgery should include the patient, family or caregivers, and all relevant clinicians to ensure that best practices are followed. Patients will often have a good understanding of their condition and know which clinical team to contact for advice. This multidisciplinary approach is outlined in detail in the *Guidelines for Management of Haemophilia in Australia* which is a very useful resource for perioperative clinicians.[46]

These guidelines emphasise the importance of collaborating with experts from an HTC to develop a haemostasis plan to cover the entire perioperative period. Preoperative assessment should include factor assays and inhibitor assays in addition to usual blood tests. It is important to focus on targeted factor replacement in preference to cryoprecipitate or FFP.

Surgery should ideally be undertaken at a centre with access to laboratory monitoring of factor activity levels and immediate availability of replacement factor concentrates. It is useful to care for these patients in hospitals affiliated with an HTC to allow timely and regular communication with the surgical teams and the patient's treating haematologist.

Patients should have their haemoglobin and coagulation optimised preoperatively and meticulous surgical technique should be used, with local haemostatic agents as appropriate. Where possible, procedures should be scheduled for early in the week and early in the day to allow for any management of complications in the following weekday and daylight hours.

In addition, postoperative screening for inhibitors in those that have received factor concentrate for the first time is recommended to detect those patients that have developed inhibitors as this will significantly affect future management.

EMERGENCY SURGERY

Emergency surgery presents additional challenges in what is usually an already challenging situation for patients with an inherited bleeding disorder. Under the guidance of the local HTC, urgent infusion of factor to raise the factor activity to a level appropriate for the procedure is likely to be recommended. Emergency surgical procedures may need to be conducted in non-HTCs. In these cases, surgery should be performed in close consultation with the staff of HTC.[46]

HOSPITALS WITH LIMITED BLOOD PRODUCT RESOURCES

Rural and remote settings may not have access to purified factor concentrates. Options here include the traditional approach of using FFP and cryoprecipitate (or indeed whole blood if available). For patients with Haemophilia A consider cryoprecipitate as an alternative option if available, as each bag will contain approximately 140IU of Factor VIII.[47]

CONCLUSION

In the past decade, there has been tremendous progress in coagulation factor fractionation adding to the available treatment options at our disposal. This is not only of benefit to patients with inherited clotting disorders but also those involved in major trauma, cardiac surgery, and obstetrics. The different types of haemophilia have been the driving force for progress in this area and as such, we have witnessed dramatic improvement in the prognosis for this group of patients.

Coagulation is a complex process and perioperative management of patients with inherited clotting disorders requires specialist haematologist involvement via the local HTC. Anaesthetists need to have a good understanding of coagulation in vivo to understand why patients might be bleeding, and in vitro to accurately interpret the cause of abnormal coagulation test results. An understanding of the perioperative role of the major factor concentrates allows anaesthetists and perioperative physicians to undertake and oversee multidisciplinary decisions and care to assure optimal outcomes for patients.

REFERENCES

1. Franchini M, Mannucci PM. Past, present and future of Hemophilia: A narrative review. Orphanet J Rare Dis. 2012; 7:24.
2. Pier Mannuccio M. Hemophilia therapy: The future has begun. Haematologica. 2020; 105(3):545-53.
3. Kasper CK. Judith Graham Pool and the discovery of cryoprecipitate. Haemophilia. 2012; 18(6):833-5.
4. Peyvandi F, Garagiola I, Young G. The past and future of Haemophilia: Diagnosis, treatments, and its complications. Lancet. 2016; 388(10040):187-97.
5. Ljung R, Auerswald G, Benson G, Dolan G, Duffy A, Hermans C, et al. Inhibitors in Haemophilia A and B: Management of bleeds, inhibitor eradication and strategies for difficult-to-treat patients. Eur J Haematol. 2019; 102(2):111-22.
6. What blood products are supplied - National product price list. [Internet]. Canberra: National Blood Authority; date unknown [cited 2023 apr 16]. Available from: https://www.Blood.Gov.Au/national-product-price-list.
7. Amanda M, Jesse GM, Noelle De L, Candy T. Alternative factor prescribing after low-dose recombinant factor VIIa protocol in cardiac surgery. medRxiv. 2022:2022.04.30.22274528.
8. Mosesson MW. Fibrinogen and fibrin structure and functions. J Thromb Haemost. 2005; 3(8):1894-904.
9. Wong H, Curry N. Do we need cryoprecipitate in the era of fibrinogen concentrate and other specific factor replacement options? ISBT Science Series. 2018; 13(1):23-8.
10. Neerman-Arbez M, de Moerloose P. Mutations in the fibrinogen gene cluster accounting for congenital afibrinogenemia: An update and report of 10 novel mutations. Hum Mutat. 2007; 28(6):540-53.
11. NZ blood. Data sheet Riastap [Internet]. Auckland: New Zealand Government; 2023 [cited 2023 Mar 1]. Available from: https://www.Nzblood.Co.Nz/assets/transfusion-medicine/pdfs/160s016.Pdf.
12. Australian product information Riastap® (human fibrinogen). Canberra: Therapeutic Goods Administration; 2020 May 21 [cited 2023 May 6]. Available from: https://www.Ebs.Tga.Gov.Au/servlet/xmlmillr6?Dbid=ebs/publichtml/pdfstore.Nsf&docid=162828&agid=%28printdetailspublic%29&actionid=1.
13. Winearls J, Wullschleger M, Wake E, McQuilten Z, Reade M, Hurn C, et al. Fibrinogen early in severe trauma study (FEISTY): Results from an Australian multicentre randomised controlled pilot trial. Crit Care Resusc. 2021; 21(1):32-46.
14. Morrow GB, Feller T, McQuilten Z, Wake E, Ariëns RAS, Winearls J, et al. Cryoprecipitate transfusion in trauma patients attenuates hyperfibrinolysis and restores normal clot structure and stability: Results from a laboratory sub-study of the FEISTY trial. Crit Care. 2022; 26(1):290.
15. Clinicaltrials.gov. Fibrinogen Early In Severe Trauma studY II (FEISTY II) [Internet]. Maryland, USA: US National Library of Medicine; 2022 [updated 2023 Mar 02; cited 2023 May 10]. Available from: https://clinicaltrials.Gov/ct2/show/nct05449834.
16. Wajima T, Isbister GK, Duffull SB. A comprehensive model for the humoral coagulation network in humans. Clin Pharmacol Ther. 2009; 86(3):290-8.
17. Hedner U. Recombinant activated factor VII: 30 years of research and innovation. Blood Rev. 2015; 29 Suppl 1:S4-8.

18. Chang Z, Chu X, Liu Y, Liu D, Feng Z. Use of recombinant activated factor VII for the treatment of perioperative bleeding in noncardiac surgery patients without hemophilia: A systematic review and meta-analysis of randomized controlled trials. J Crit Care. 2021; 62:164-71.
19. Vincent JL, Rossaint R, Riou B, Ozier Y, Zideman D, Spahn DR. Recommendations on the use of recombinant activated factor VII as an adjunctive treatment for massive bleeding - a European perspective. Crit Care. 2006; 10(4):R120.
20. Konkle BA, Nakaya Fletcher S. Hemophilia A. 2000 Sep 21 [Updated 2022 Oct 27]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. [cited 2023 Mar 10] Available from: https://www.ncbi.nlm.nih.gov/books/NBK1404/pdf/Bookshelf_NBK1404.pdf
21. Mingot-Castellano ME, Rodríguez-Martorell FJ, Nuñez-Vázquez RJ, Marco P. Acquired Haemophilia A: A review of what we know. J Blood Med. 2022; 13:691-710.
22. Franchini M. Plasma-derived versus recombinant factor VIII concentrates for the treatment of Haemophilia A: Recombinant is better. Blood Transfus. 2010; 8(4):292-6.
23. Chhabra A, Spurden D, Fogarty PF, Tortella BJ, Rubinstein E, Harris S, et al. Real-world outcomes associated with standard half-life and extended half-life factor replacement products for treatment of Haemophilia A and B. Blood Coagul Fibrinolysis. 2020; 31(3):186-92.
24. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH guidelines for the management of Hemophilia, 3rd edition. Haemophilia. 2020; 26 Suppl 6:1-158.
25. Di Scipio RG, Kurachi K, Davie EW. Activation of human factor IX (Christmas factor). J Clin Invest. 1978; 61(6):1528-38.
26. Philip J, Sarkar RS, Kumar S, Prathip BR, Pathak A. Factor IX deficiency (Christmas disease). Med J Armed Forces India. 2012; 68(4):379-80.
27. Björkman S, Berntorp E. Pharmacokinetics of coagulation factors: Clinical relevance for patients with Haemophilia. Clin Pharmacokinet. 2001; 40(11):815-32.
28. Mumford AD, Ackroyd S, Alikhan R, Bowles L, Chowdary P, Grainger J, et al. Guideline for the diagnosis and management of the rare coagulation disorders: A United Kingdom Haemophilia centre doctors' organization guideline on behalf of the British Committee for Standards in Haematology. Br J Haematol. 2014; 167(3):304-26.
29. Dhaha Y, El Borgi W, Elmahmoudi H, Achour M, Fekih Salem S, Ben Lakhal F, et al. Factor XI deficiency: About 20 cases and literature review. Tunis Med. 2022; 100(1):60-5.
30. Duga S, Salomon O. Congenital factor XI deficiency: An update. Semin Thromb Hemost. 2013; 39(6):621-31.
31. Lak M, Peyvandi F, Ali Sharifian A, Karimi K, Mannucci PM. Pattern of symptoms in 93 Iranian patients with severe Factor XIII deficiency. J Thromb Haemost. 2003; 1(8):1852-3.
32. Eshghi P, Abolghasemi H, Sanei-Moghaddam E, Anwar R, Jazebi M, Amid A, et al. Factor XIII deficiency in south-east Iran. Haemophilia. 2004; 10(5):470-2.
33. Anwar R, Minford A, Gallivan L, Trinh CH, Markham AF. Delayed umbilical bleeding - a presenting feature for factor XIII deficiency: Clinical features, genetics, and management. Pediatrics. 2002; 109(2):e32-e.
34. Mahmoodi M, Peyvandi F, Afrasiabi A, Ghaffarpasand F, Karimi M. Bleeding symptoms in heterozygous carriers of inherited coagulation disorders in southern Iran. Blood Coagul Fibrinolysis. 2011; 22(5):396-401.
35. Menegatti M, Palla R, Boscarino M, Bucciarelli P, Muszbek L, Katona E, et al. Minimal factor XIII activity level to prevent major spontaneous bleeds. J Thromb Haemost. 2017; 15(9):1728-36.
36. Inbal A, Oldenburg J, Carcao M, Rosholm A, Tehranchi R, Nugent D. Recombinant factor XIII: A safe and novel treatment for congenital factor XIII deficiency. Blood. 2012; 119(22):5111-7.
37. Gootenberg JE. Factor concentrates for the treatment of factor XIII deficiency. Curr Opin Hematol. 1998; 5(6):372-5.
38. Caudill JS, Nichols WL, Plumhoff EA, Schulte SL, Winters JL, Gastineau DA, et al. Comparison of coagulation factor XIII content and concentration in cryoprecipitate and fresh-frozen plasma. Transfusion. 2009; 49(4):765-70.
39. Australian public assessment report for human prothrombin complex. Proprietary product name: Beriplex p/n. Canberra: Therapeutic Goods Administration; 2010 [cited 2023 May 6]. 51 p. Available from: https://www.Tga.Gov.Au/sites/default/files/auspar-beriplex.pdf.
40. Herm Jan MB. Anticoagulation therapy. Rijeka: IntechOpen; 2016. Prothrombin complex concentrate, a general antidote for oral anticoagulation; p. Ch. 5.
41. Prothrombinx-VF [package insert]. Vic, Australia. CLS Limited; 2020. Available from: https://labeling.Cslbehring.Com/pi/au/prothrombinex-vf/en/prothrombinex-vf-product-information.pdf.
42. Thrombotrol-VF [package insert]. VIC, Australia: CSL Limited; 2020. Available from: https://labeling.Cslbehring.Com/pi/au/thrombotrol-vf/en/thrombotrol-vf-product-information.pdf.
43. Spiess BD. Treating heparin resistance with antithrombin or fresh frozen plasma. Ann Thorac Surg. 2008; 85(6):2153-60.
44. Sampei Z, Igawa T, Soeda T, Okuyama-Nishida Y, Moriyama C, Wakabayashi T, et al. Identification and multidimensional optimization of an asymmetric bispecific IgG antibody mimicking the function of factor VIII cofactor activity. PLoS ONE. 2013; 8(2):e57479.
45. Adcock DM, Strandberg K, Shima M, Marlar RA. Advantages, disadvantages and optimization of one-stage and chromogenic factor activity assays in Haemophilia A and B. Int J Lab Hematol. 2018; 40(6):621-9.
46. Guidelines for the management of haemophilia in Australia. A joint project between Australian Haemophilia Centre Directors' Organisation, and the National Blood Authority, Australia 2016 [coted 2023 apr 16]. Available from: https://www.Blood.Gov.Au/system/files/haemophiliaguidelines-interactive-updated-260317v2.pdf.
47. Bejrachandra S, Chandanayingyong D, Visudhiphan S, Tumliang S, Kaewkamol K, Siribunrit U. Factor viii, factor IX and fibrinogen content in cryoprecipitate, fresh plasma and cryoprecipitate-removed plasma. Southeast Asian J Trop Med Public Health.1993; 24 Suppl 1:162-4.

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REBOA and EDRT in trauma related haemorrhage – is it all in vein?

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INTRODUCTION

Trauma is a leading cause of morbidity and mortality worldwide, with haemorrhage being the predominant causative factor in 40 per cent of cases and the commonest cause of preventable trauma deaths.[1,2] Management of haemorrhage in civilian trauma borrows heavily from the military experience. Resuscitative endovascular balloon occlusion of the aorta (REBOA) is one such intervention that has its roots in the military domain. It was in 1954 in the Korean War that Lieutenant Colonel Carl Hughes first described the use of aortic balloon occlusion in three soldiers with intra-abdominal haemorrhage.[3] REBOA involves the placement of an endovascular catheter via the common femoral artery into the descending aorta and inflation of the balloon at the desired level, thus achieving aortic occlusion proximal to the injury and halting of ongoing bleeding. Limited device availability at that time resulted in it not being readily adopted, with REBOA only experiencing a resurgence in clinical use from 2011 onwards.[4] However, REBOA's role and the evidence behind its use in the civilian population still needs further clarification.[5]

Apart from REBOA, another method of achieving haemorrhage control is a resuscitative thoracotomy. In the civilian domain this is usually performed in the emergency department and is termed an emergency department resuscitative thoracotomy (EDRT, otherwise known as clamshell thoracotomy). In an EDRT, haemorrhage control occurs via open supradiaphragmatic clamping of the descending thoracic aorta.[6] The reported survival rates for EDRT are much poorer than those of REBOA, further adding to the debate and controversy regarding the optimal use of EDRT.[7,8]

The purpose of this article is to review the principles, indications, evidence, and limitations around the use of REBOA and EDRT in civilian major trauma. A brief overview of the critical issues surrounding the management of haemorrhage in trauma will also be provided along with data from the local experience in Western Australia (WA) and its unique geographical challenges.

CRITICAL ISSUES SURROUNDING THE MANAGEMENT OF HAEMORRHAGE IN TRAUMA

Pre-hospital stage

Preparation for the arrival of a trauma patient to hospital begins before the accident has even occurred. Emergency services and hospitals must have pre-existing guidelines in place to allow for the expeditious transfer of severely injured trauma patients to an appropriate trauma centre. Once a severely injured trauma patient has been identified at the scene, on-site emergency services will liaise closely with the receiving hospital which allows for the activation of a trauma call at the hospital. Trauma calls are institution specific and usually encompass a multi-disciplinary group of acute care physicians (for example, trauma surgeons, duty anaesthetists, radiologists, theatre staff, intensive care physicians) who are all involved in planning for the patient's arrival and subsequent care.[9] In the case of a severely injured trauma patient, the receiving hospital will likely be a level one trauma centre.[10] A level one trauma centre is defined by the American Trauma Society as a tertiary hospital which offers a comprehensive approach to the trauma patient, from injury through to rehabilitation.[10] These hospitals have 24-hour, in-house coverage by multiple surgical subspecialties and provide leadership, research and continuing education to the greater community, with the aim of preventing injuries from occurring. Level two to five trauma centres offer progressively more limited services.[10]

In the event of a multi-trauma casualty event, first responders will triage casualties at the scene and liaise with receiving hospitals. This may result in the activation of a Code Brown emergency at the receiving hospital(s).[11] A Code Brown emergency is called by a health service or facility when additional capability and capacity needs to be mobilised within that facility to accommodate an influx of patients due to an external emergency.[11]

Emergency department

Haemorrhage is a major cause of mortality and morbidity in trauma patients, as previously mentioned.[1,2] External and junctional haemorrhage is usually detected at the scene of the accident or during the primary survey.[9] In contrast, the precise site of internal haemorrhage may be difficult to both identify and quantify. It has been noted that mortality increases by up to 0.35 per cent for every minute definitive surgical control is delayed in hypotensive patients bleeding from abdominal injuries.[12] This is why rapidly accessible, quick, point of care tools such as extended focused assessment with sonography in trauma (eFAST) and portable X-rays are preferred over slower and less accessible investigations such as computerized tomography scans in unstable patients.[12] The expertise of the trauma team is critical to determine the likeliest source of haemorrhage and the most appropriate immediate management.

Obtaining haemorrhage source control

The commonest culprits for internal haemorrhage are the chest, abdomen, retroperitoneum, pelvis and long bones.[13] Source control is often challenging due to the nature of the injury.[13] Externally applied devices such as a pelvic external fixation device can be used for haemorrhage originating in the pelvis, or splinting can be used in the case of long bone haemorrhage.[9,13] EDRT can be used to gain proximal control of major haemorrhage from most sources whereas REBOA is only suitable for sub-diaphragmatic haemorrhage.[14] Angio-embolisation is another option for source control in hemodynamically stable patients.[15]

Damage control resuscitation (DCR)

DCR is the modern paradigm of haemostatic resuscitation and entails a multi-pronged approach to the resuscitation of a critically ill patient.[16,17] This approach aims to prevent the lethal triad of hypothermia, acidosis, and coagulopathy from developing and expedites definitive control of the bleeding source.[16,17] The components of this approach can be summarised as follows:

- Maintaining an adequate circulating volume through limiting crystalloid usage to less than 20mL/kg, transfusing warmed blood products in a one packed red blood cells (PRBC): one fresh frozen plasma (FFP): one platelet ratio (haemostatic resuscitation); early (within three hours from injury) administration of tranexamic acid and further blood component therapy as guided by thromboelastography (TEG)/ rotational thromboelastometry (ROTEM).[16,17] This requires large bore intravenous access such as a central sheath, rapid infusion catheter, or multiple large bore peripheral cannula attached to a rapid infuser (for example, Belmont device). The location of vascular access should also consider any anatomical disruptions as a result of the trauma.
- Allowance of permissive hypotension, balancing the risks of end organ ischaemia against the risk of uncontrolled haemorrhage.[16-18] Different trauma societies advocate for a systolic blood pressure (SBP) target of between 80-90mmHg for penetrating or blunt injury.[17,18] In the presence of brain trauma the current guidelines support a SBP of more than or equal to 100mmHg for patients 50-69 years old and a SBP of more than or equal to 110mmHg for patients 15-49 years, or 70 years and older.[19]
- Damage control surgery in the form of limited urgent surgical intervention(s) to address life-threatening injuries only.[16,17] All other surgical care is delayed until metabolic and physiological derangements have been treated (generally at least 24 hours post injury).[16,17]

DCR has been associated with improved mortality, reduction in blood product usage and reduced hospital length of stay.[16] Techniques such as EDRT and REBOA can play an additional role in haemorrhage control and resuscitation in instances wherein exsanguination is occurring faster than blood product replacement, or when all other means of control have failed.[17,20] DCR principles still apply when these two techniques are implemented, and as EDRT and REBOA are only temporising measures, damage control surgery is still required as the definitive method of controlling haemorrhage.

Goals of resuscitation

Achievement of an adequate circulating volume and/or organ perfusion may be reflected by an appropriate level of cognition in the awake patient, an acceptable measured blood pressure (permissive hypotension) or a palpable radial arterial pulse.[16,23] Surrogates used to guide resuscitation include lactate, base excess, stroke volume variation (in the ventilated patient), response to fluid boluses and/or cardiac output monitoring.[24] Table 1 is an example of resuscitation and transfusion targets in major trauma. Physiological endpoints and haemodynamic targets may need to be individualised, based on the nature of the injury and pre-existing medical co-morbidities of the patient.

Table 1. Resuscitation and transfusion targets in major trauma

Temperature	> 35°C
pH	> 7.2
Base excess	< -6mmol/L
Lactate	< 4mmol/L
Ionised Ca	> 1.12mmol/L
Hb	> 80g/L
Platelet count	> 80 x 109/L
INR	< 1.5
APTT	< 50 seconds
Fibrinogen	> 2g/L

Ca = Calcium, Hb = Haemoglobin, INR = international normalised ratio, APTT = activated partial thromboplastin time, °C = degrees Celsius, L = litre, g = gram.

ROLE OF AORTO-OCCLUSIVE TECHNIQUES

Aortic occlusion, whether by REBOA or EDRT, will stop haemorrhage from a source distal to the site of aortic occlusion. A reduction, or halt in ongoing blood loss, will allow time for resuscitation and definitive surgical control. Aortic occlusion also aids in preserving cerebral perfusion and coronary filling via an increased central volume and aortic pressure which results in increased carotid, cerebral and coronary blood flow, perfusion pressure and oxygenation.[25] However, the physiological cost of non-perfused, distal areas will contribute to the metabolic acidosis and general ischaemic burden over time.[25]

REBOA

Principle and indications

The principle behind REBOA is simple; inflation of a balloon in the aorta proximal to an injury will stop the blood flow and resulting bleeding.[26] This enables definitive surgical repair of the injury and achievement of haemostasis, after which the balloon can be deflated.[26] Each of these steps is however practically complex and requires careful decision making. The first question is who would benefit from a REBOA? A REBOA can be placed in situations where there is massive haemorrhage from any amenable subdiaphragmatic cause – examples include a ruptured splenic artery, bleeding placenta accreta, or massive haemorrhage from pelvic trauma. It can also be placed pre-emptively in situations of anticipated potential major haemorrhage in patients who are rapidly deteriorating or becoming unstable.[26,27] In some institutions, a SBP of less than 90mmHg in a partial or non-responder to fluid resuscitation is a trigger for femoral access.[27] In the case of pre-emptive insertion only the femoral sheath required to place the REBOA device needs to be inserted.[27] The sheath furthermore allows for arterial pressure monitoring and avoids unnecessary placement of the catheter and the associated potential complications following balloon insufflation.[27]

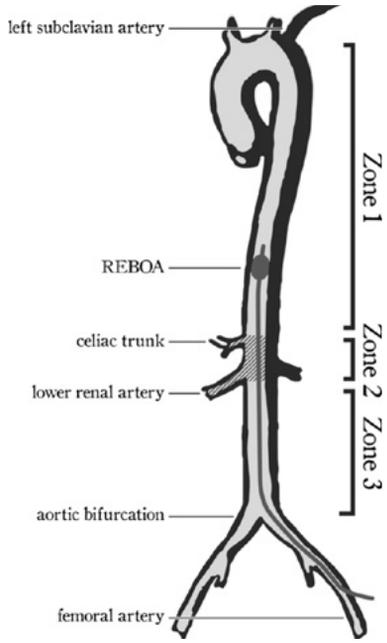
Optimum site for balloon positioning and inflation

Once the decision has been made to place a REBOA, the next question is where the balloon should be positioned in the aorta. To determine the optimum site of balloon position and inflation, the aorta is divided into three zones (Figure 1).[26]

- Zone I: Descending thoracic aorta between the origin of the left subclavian and coeliac artery.[26] Balloon inflation at zone I would physiologically resemble the application of a thoracic aortic cross-clamp. This zone is utilised for patients with intra-abdominal haemorrhage.
- Zone II: Para-visceral aorta between the origin of the celiac artery to the most distal renal artery.[26] This is a no occlusion zone due to the presence of the celiac, superior mesenteric and renal arteries. Occlusion of zone II exposes the patient to the risks of a zone I occlusion (visceral ischaemia) without providing significant benefits compared with a zone III occlusion.[26,27]
- Zone III: Infrarenal abdominal aorta between the lowest renal artery and aortic bifurcation.[26] Inflation here is used for patients with haemorrhage arising from severe pelvic fractures or other injuries at or below this level.

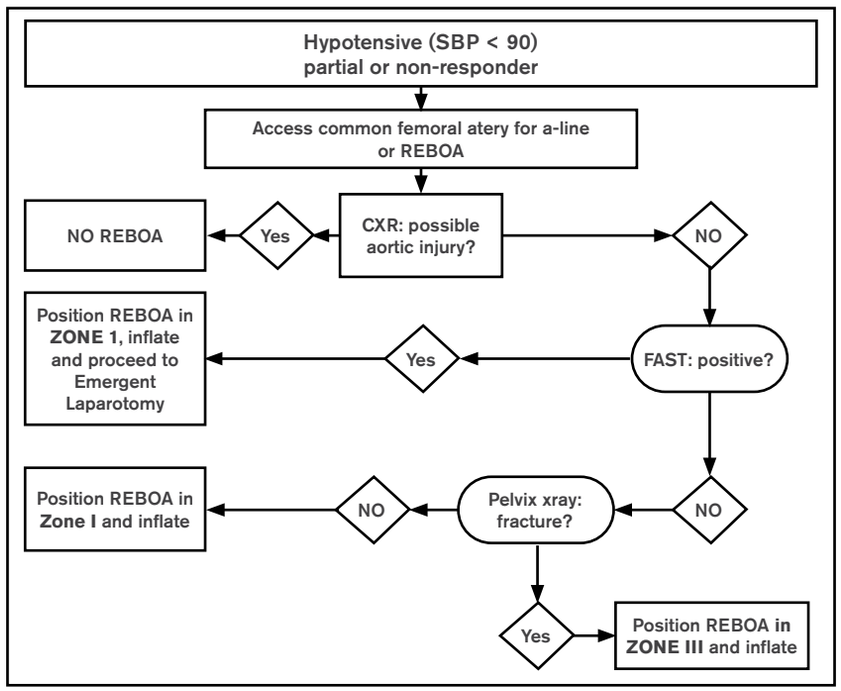
Figure 1. Anatomical aortic zones related to REBOA placement[28]

Zone I extends from the origin of the left subclavian artery to the celiac artery and is a potential zone of occlusion. Zone II extends from the celiac artery to the lowest renal artery and is a no-occlusion zone. Zone III exists from the lowest renal artery to the aortic bifurcation. Reproduced from Olsen et al.[28]



The decision-making process regarding REBOA insertion is summarised in Figure 2.

Figure 2. REBOA decision making algorithm. Reproduced from Moore et al.[29]



Procedural steps to place a REBOA device

The steps to insert a REBOA device are as follows:

1. Arterial access – usually the common femoral artery is accessed via a sheath which can be inserted either percutaneously using a landmark technique, with ultrasound guidance, or via surgical cut down.[27,28] Over time the sheath sizes have reduced, with modern REBOA devices requiring a 7 French (Fr) sheath as opposed to the 12Fr sheaths first used.[28]
2. Balloon insertion and positioning – the endovascular balloon is inserted through the sheath into the aorta.[27] The balloon is then floated into position with radiographic, fluoroscopic, ultrasound or epidemiologically based landmark guidance.[27,28] Direct comparison of the methods of balloon guidance is lacking in the literature; whilst fluoroscopy is the gold standard, it is often not available in emergency department bays or in the pre-hospital setting.[30] In contrast, epidemiological based landmark guidance is quicker but more prone to error.[30] One study reported a REBOA placement accuracy of 71.1 per cent using epidemiological based landmark guidance.[30] Of note, in this study the accuracy of placement of a REBOA device in zone I was greater than that of one placed in zone III (86.7 per cent vs 12.5 per cent respectively) due to the smaller target area in zone III.[30] As previously detailed, the intended zone of balloon placement will depend upon the suspected site of bleeding.
3. Balloon inflation – once the balloon has been sited, it is inflated to approximate against the walls of the aorta.[27,28] Balloon inflation should result in an increase in proximal SBP, with the magnitude of this differing depending on the zone of inflation.[28] Distal pulses should also be diminished. Wasicek found inflation in zone I yields a mean increase of 60mmHg whereas inflation in zone III results in a mean increase of 23mmHg.[31] Balloon inflation should be for the shortest duration possible to minimise the ischaemic time, ideally less than 30 minutes for Zone I and less than 60 minutes for Zone III.[32] Studies have shown an expected increase in mortality associated with an increased duration of balloon inflation.[25,33] The use of partial REBOA (sub-total occlusion of the aorta) or intermittent REBOA (periodic balloon deflation) may extend this ischaemic time limit however its role is still being studied.[34]
4. Balloon deflation – once haemostasis has been achieved or maximum REBOA inflation time reached, the balloon is slowly deflated.[27] Similar to the removal of a vascular cross-clamp elsewhere in the body, if there is haemodynamic instability or severe biochemical abnormalities the balloon may need to be partially or completely re-inflated for a short duration of time.[27,28] Several cycles of this may be needed before complete deflation is possible. This process requires close communication between all members of the operating theatre team. Haemodynamic instability following deflation of zone I balloons are more significant than those of zone III balloons as a result of the pronounced decrease in cardiac afterload and increased ischaemic-reperfusion injury.[35] Once haemodynamic stability has been achieved, the REBOA catheter can be removed. The sheath can remain in-situ and be used for arterial blood pressure monitoring.
5. Sheath removal – the procedure for sheath removal depends on the size of the sheath. Larger 12Fr sheaths require a femoral artery cut down with direct repair of the arteriotomy.[28] In contrast, 7Fr sheaths can be removed without surgical repair but require manual compression for at least 30 minutes.[28] Confirmation of distal perfusion should be carried out immediately post sheath removal and can be done via clinical and/or doppler and/or angiographic means.[28]

***Contra-indications* to REBOA placement include[36]:**

- Severe atherosclerosis.
- Blunt and penetrating aortic injury – recognised by symptoms such as dyspnoea, hoarseness and cough (as a result of aortic expansion and dilation) on the background of hypotension, altered mental state and chest pain.
- Cardiac tamponade.
- Penetrating neck (or any other supradiaphragmatic) trauma (resuscitative thoracotomy is potentially indicated).
- Blunt and penetrating cardiac injury (resuscitative thoracotomy is potentially indicated).

Reported *complications* include: acute kidney injury, iliac artery intimal rupture, REBOA balloon rupture and the need for subsequent lower extremity fasciotomy, thrombectomy, or amputation.[28,37] Complications of REBOA have become less common with the smaller calibre devices now used.[28] A systematic review by Morrison et al found an overall rate of morbidity of 3.7 per cent related to REBOA use, although this review was limited by the quality and quantity of evidence available.[37]

Outcomes following REBOA placement

Studies examining outcomes following REBOA placement have been mainly lower-quality observational studies, with several systematic reviews and meta-analyses based on these studies. The majority of the observational studies do report a positive mortality or survival benefit from REBOA placement, however there are some conflicting studies.[38-41] Harfouche et al carried out a single centre, retrospective matched cohort study examining in hospital mortality in patients who had a REBOA, or not, for trauma related haemorrhagic shock. They found significantly lower in-hospital mortality in the REBOA group compared to their matched contemporary group (19.3% vs 35.1% respectively, p = 0.024).[38] Yamamoto et al did a retrospective propensity score matched study using the nationwide Japanese trauma database of 82,371 patients.[39] Of these 82,371 patients 385 had a REBOA inserted and of these 117 were selected for propensity score matching.[39] Yamamoto et al found a higher survival to discharge in patients treated with REBOA versus those treated without REBOA (45.3% vs 32.5%; odds ratio = 1.72, 95% CI = 1.01 – 2.93; p = 0.04).[39]

In contrast, there are some studies that found harm following REBOA placement. Norii et al used the same Japanese trauma database as Yamamoto et al over a slightly different time period and found an odds ratio of survival after REBOA treatment of 0.30 (95% CI = 0.23-0.4).[40] The contrast in findings between these two studies was attributed to the stricter propensity score matching algorithm and increased number of covariates used in the propensity score matching of Yamamoto et al.[39,40] This example highlights how drastically different statistical analyses can alter the findings of a study. Joseph et al carried out a large multi-centre retrospective analysis of the 2015-2016 American College of Surgeons Trauma Quality Improvement Program data set and found a higher overall mortality rate in the REBOA group compared to the matched non-REBOA group (35.7% vs 18.9%, p = 0.01).[41] However, this study was criticised for not collecting and analysing data such as indication for REBOA placement, whether a protocol was used, whether REBOA was placed early or late in the patient's admission, REBOA inflation time and whether it was placed in a high volume centre or not. These criticisms are not unique to this study, with other studies also not routinely including this information. These all contribute to the discrepancy between studies looking at outcomes following REBOA. Unsurprisingly, due to the low quality of evidence of these studies, of the three systematic reviews carried out appraising these studies one found a survival benefit associated with REBOA whereas the other two were unequivocal or slightly favourable.[5,42,43] The completed UK-REBOA trial (publication of results pending) is the first randomised controlled trial examining outcomes following REBOA and will help provide higher level evidence to guide the use of REBOA in trauma.[44]

Higher volume centres have been shown to generally be more successful in accurate REBOA placement.[45] Theodorou et al. carried out a retrospective multi-centre study from the American Association for the Surgery of Trauma (AAST) Aortic Occlusion for Resuscitation in Trauma and Acute Care Surgery (AORTA) Registry from 11/2013–01/2018.[45] They defined high volume centres as those which inserted more or equal to 80 REBOA devices (two hospitals), mid volume as those that inserted 10-20 (four hospitals) and low volume centres as those that inserted less than 10 REBOA devices over this time period (14 hospitals).[45] No hospitals inserted between 21 to 79 REBOA devices. They found increased odds of successful REBOA placement (defined as haemodynamic improvement with balloon inflation) at high volume vs low volume hospitals (OR 7.50, 95% CI 2.10–27.29, p = 0.002) and mid volume vs low volume hospitals (OR 7.82, 95% CI 1.52–40.31, p = 0.014).[45] This may be due to multiple factors such as longer time in low and mid volume centres to achieve aortic occlusion, better familiarity with the REBOA insertion procedure at higher volume centres, as well as potentially superior simultaneous resuscitation at higher volume centres.[45] Specifically with regards to insertion times, low volume hospitals had a longer median time from admission to start of REBOA placement (low volume 45 minutes, mid volume 17 minutes, high volume 11.5 minutes, p <0.00001) and to aortic occlusion (low volume 45 minutes, mid volume 36 minutes, high volume 23 minutes, p = 0.00027).[45] Procedural time from initiation to successful aortic balloon inflation has been reported as between six to ten minutes in other studies.[27,46] In-hospital mortality rates and complications were however not different between low, mid or high volume centres.[45]

WA REBOA experience

An audit was recently carried out at Royal Perth Hospital (RPH) reviewing the outcomes following REBOA and EDRT over the past 10 years (January 2012 to September 2022). During this time period 11 REBOA devices were inserted and a 36 per cent mortality was reported, which compared favourably to other studies which report a mortality of 50-70 per cent in patients who had a REBOA.[29,47,48] This is despite the RPH patient population having a median injury severity score (ISS) of 50, higher than most other literature which report a median ISS of between 30 and 35.[29,47] Additional patient demographics such as age, sex, and mechanism of injury were similar to other studies.[29,47,48] Although direct comparisons are extremely difficult to do, we speculate that the lower mortality may be a result of the expertise of the trauma surgeons at RPH and the timing

of placement. Earlier placement may result in less haemorrhage with less volume resuscitation required and shorter balloon inflation times. These two factors have been associated with improved survival.[49,50]

Another interesting point is that in general the role of REBOA is slightly more limited in Australia than that of other countries. Due to the wide geographical nature of most Australian states (such as WA), patients often need to travel significant distances before reaching a trauma centre. Insertion of a REBOA device in a peripheral hospital in WA prior to transfer to the main trauma centre is not currently practiced. Thus, a significant percentage of critically unwell rural trauma patients may not be able to benefit from this intervention and will have to rely on traditional resuscitation measures. Four of the eleven study patients who had a REBOA, in the mentioned audit, were from a rural or remote area. This may have introduced a survival bias into the mortality rates and led them to appear higher than they may have otherwise been since these patients had to travel significant distances (increasing time to balloon placement). On the other hand, some critically unwell rural patients may have deceased prior to reaching a metropolitan trauma centre, leaving the more robust patients to be included in the audit, and thus influencing the mortality rate positively. Another consideration is the relatively small number of REBOA procedures done during the audit period and the effect each additional survivor would have on mortality data.

On admission to RPH, relative to patients who had an EDRT, patients who had a REBOA had a higher mean systolic blood pressure (mean ± standard deviation (SD), 18 ± 44 vs 96 ± 48 mmHg respectively), higher heart rate (beats per minute ± SD, 22 ± 46 vs 106 ± 43 respectively) and higher Glasgow Coma Scale (GCS) (GCS (interquartile range), 3 (3-3) vs 12 (11-14) respectively). This is in keeping with the trend of these procedures where EDRT is generally reserved as a "last ditch" resuscitative effort whereas REBOA is often placed before this point.[51] REBOA patients also had a significantly lower initial and peak lactate level compared to the EDRT group (lactate level ± SD, initial REBOA 7.3 ± 3.0, peak REBOA 9.8 ± 4.6 vs initial EDRT 13.0 ± 5.7, peak EDRT 16.8 ± 10.9).

EDRT

An EDRT is generally performed during peri-arrest or arrest scenarios and relies on an emergency thoracotomy and aortic cross clamp to achieve haemorrhage control.[52] Although both REBOA and EDRT result in aortic occlusion, their indications are different. For EDRT, the general indications include[52,53]:

- Non-compressible torso haemorrhage with imminent arrest.
- Persistent severe hypotension SBP less than 70mmHg, unresponsive to aggressive fluid resuscitation and/or inotropic support due to major intrathoracic haemorrhage (more than 1500ml from chest drain).
- Cardiac tamponade.
- Gas embolism with circulatory arrest.
- Massive haemothorax.
- Blunt extrathoracic trauma with witnessed cardiac arrest, less than 10 min CPR and signs of life (conditional recommendation).
- Penetrating extrathoracic trauma with witnessed cardiac arrest and less than 15 minutes of CPR (conditional recommendation).

Following the thoracotomy simple damage control manoeuvres (for example, direct pressure, packing, clamping) are used to manage visible haemorrhage and a pericardiotomy can be done to gain control of any cardiac injuries.[52] The aorta is then cross clamped followed by aggressive volume resuscitation, open cardiac massage and internal defibrillation, if required.[54] Exploration of thoracic structures to exclude other injuries will follow definitive surgical treatment.[54] An EDRT can be performed by any trained acute care physician, which at RPH is generally the trauma surgeons.[54] An EDRT procedure is discouraged in settings where an appropriately trained surgeon is not available to provide immediate definitive care, as opposed to REBOA insertion which can serve as a temporary bridge to definitive care in the appropriate patient.[52,53]

The mortality following EDRT is universally poor and survival is reported as less than 10 per cent in most studies.[7] Reasons for this include the poor patient prognosis at the time of EDRT and the invasive nature of the EDRT procedure resulting in severe physiological derangement, coagulopathy and hypothermia.[29] The highest survival rates are amongst patients with isolated penetrating cardiac injuries, followed by penetrating noncardiac thoracic injuries, penetrating abdominal and lastly multiple penetrating injuries.[7] Patients with blunt thoracic injury have a very low survival rate with EDRT, with one study reporting a survival rate of only 1.4 per cent.[7] Contra-indications to EDRT include trauma with prolonged cardiac arrest, nontraumatic arrest, severe head injury and multisystem injury.[52,53]

WA EDRT experience

The audit done at RPH reports 76 EDRTs over the past decade, with comparable age, sex and mechanisms of injury to other literature. Of note, 40 per cent of the EDRT procedures resulted from penetrating mechanisms of injury with the remaining 60 per cent due to blunt mechanisms of injury. The median ISS in this population was 30, similar to that of other literature. Twelve of these 76 patients were from a rural or remote area and only one of the 76 patients survived to discharge.

Factors influencing success with REBOA or EDRT

Whilst caseload is one component of success, there are many other factors which influence institutional success with REBOA or EDRT:

1. Multi-disciplinary leadership including representatives from emergency medicine, trauma surgery, vascular surgery and nursing. Of note, REBOA and EDRT should only be employed as part of a larger system of damage control resuscitation - it is not a definitive treatment. Twenty-four hour availability of interventional radiology, theatre and ICU should be present to facilitate definitive treatment.
2. Regular reviews of the trauma pathway to ensure key performance targets are being met (for example, time to REBOA insertion) and optimisation of care pathways.
3. Regular team based and operator skill training to ensure technical and non-technical skills are achieved and maintained.[46] Consideration should be given to requiring recognised course completion before being credentialled to carry out these procedures.
4. A quality assurance process which regularly conducts audits of trauma care in both patients who do and do not receive REBOA and EDRT procedures, to identify areas of improvement.
5. Audits, and any other future studies, should include information on the indication for REBOA insertion, the proceduralist, the time taken to insert the device, the inflation time and associated complications as a result of REBOA placement. For EDRT this includes information such as the specific indication, the proceduralist and duration of CPR pre-EDRT.

By addressing these pillars, hospital survival associated with the REBOA and EDRT procedures may be continually improved on. The positive outcomes RPH has had with REBOA have been attributed to several factors. The technique was first introduced in 2014 with a specific patient subgroup in mind; this subgroup was the peri-arrest trauma patient who needed to be stabilised to allow transfer from the emergency department to interventional radiology or theatres. Prior to implementation, two of the senior RPH trauma surgeons had training on how to insert REBOA devices. The presence of staff skilled at conducting the technique cannot be overstated. Another important consideration is the timely ability to conduct the procedures. For our local institution, the trauma surgeons who were trained in the technique and supportive of integrating it into the hospital's trauma services all lived close to the hospital, enabling a consultant trauma surgeon to be in the ED ready to place a REBOA within 10 minutes of being called in. Furthermore, prior to the introduction of REBOA, collaboration was done with other departments in the hospital (for example, interventional radiology) on efficient and accurate insertion and device troubleshooting. Pre-enrolment collaboration also included high fidelity simulations with the emergency department trauma multi-disciplinary team. These simulations are repeated on a continuous basis, to maintain familiarity and proficiency across the multitude of team members that are essential in effectively providing this intervention. With increasing familiarity over time, insertion became quicker, and the balloons are now only inflated for the minimum time necessary to allow for safe transfer. With time, our trauma surgeons have also become more experienced in rapidly assessing the patients suitable for a REBOA (age, co-morbidities), trauma (type, injury pattern) and appropriately selecting the supporting resources needed (trauma surgeon, theatre and ICU availability and expertise). Having hospital wide engagement in supporting this system is essential for appropriate insertion, management, and follow-up of REBOA devices.

CONTROVERSIES

REBOA as part of a damage control resuscitation package varies between hospitals and from case to case with regards to REBOA device use, triggers for insertion, insertion techniques, time taken to achieve aortic occlusion, methods of verifying REBOA position and inflation times.[5,42,43] This expected variability contributes to heterogeneity in the literature and may confound comparisons between different studies.[5,42,43] Detailed reporting of these variables should be done in future studies, aiming at technique standardisation which should result in improved patient survival.

Although attempts have been made to do so, it is extremely difficult to compare outcomes following EDRT and REBOA. EDRT is generally done in patients who are close to or have already arrested, whilst REBOA is generally utilised at an earlier stage.[51] Inherently this means that REBOA patients generally have less

physiological derangement than patients who require EDRT. Randomised controlled trials to compare the two have never been done and are unlikely to ever occur. There have however been several observational studies on the topic. Brenner et al. found a survival benefit in an unmatched observational study when comparing REBOA to EDRT, concluding that REBOA offered a survival advantage over resuscitative thoracotomy in patients not requiring cardiopulmonary resuscitation.[6] Furthermore, systematic reviews by Castellini et al and Borger van der Burg et al also found a survival benefit to REBOA when compared to EDRT.[5,44] However, the findings of these studies must be taken in the context of the low quality evidence they were based on and the inherent selection bias present in these studies. Additionally, the difference in indications and patient selection for EDRT and REBOA may make direct outcome comparisons inappropriate.

CONCLUSION

Management of trauma related haemorrhage has advanced significantly over the past few decades. New concepts such as damage control resuscitation and haemostatic transfusion have drastically improved patient outcomes. REBOA and EDRT are techniques which, when properly applied, may theoretically improve outcomes even further in a select group of patients. REBOA in particular has some promising low-quality evidence backing its use, however the studies forming the basis of these findings are mainly retrospective and non-randomised.[5,43,44] The UK-REBOA study will help determine future directions for this technique and may also help to elicit further specific indications for REBOA. For the time being, REBOA and EDRT both remain potentially useful tools in our arsenal against uncontrolled haemorrhage. In Western Australia the use of REBOA in a designated trauma centre which is proficient and experienced in its use, most likely leads to better patient outcomes. Regular future auditing and quality control procedures are essential to ensure the procedures being carried out are to a comparable standard to other high performing centres.

REFERENCES

1. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. J Trauma. 2006 Jun; 60:S3-11.
2. Rossiter ND. Trauma-the forgotten pandemic? Int Orthop. 2022 Jan; 46(1):3-11.
3. Hughes CW. Use of an Intra-aortic balloon catheter tamponade for controlling intra-abdominal hemorrhage in man. Surgery. 1954 Jul; 36(1):65–8.
4. Osborn LA, Brenner ML, Prater SJ, Moore LJ. Resuscitative endovascular balloon occlusion of the aorta: current evidence. Open Access Emerg Med. 2019 Jan; 11:29–38.
5. Castellini G, Gianola S, Biffi A, Porcu G, Fabbri A, Ruggieri MP, et al. Resuscitative endovascular balloon occlusion of the aorta (REBOA) in patients with major trauma and uncontrolled haemorrhagic shock: a systematic review with meta-analysis. World J Emerg Surg. 2021 Aug; 16(1):41.
6. Brenner M, Inaba K, Aiolfi A, DuBose J, Fabian T, Bee T, et al. Resuscitative endovascular balloon occlusion of the aorta and resuscitative thoracotomy in select patients with hemorrhagic shock: early results from the American Association for the Surgery of Trauma's aortic occlusion in resuscitation for trauma and acute care surgery registry. J Am Coll Surg. 2018 May; 226(5):730-40.
7. Rhee PM, Acosta J, Bridgeman A, Wang D, Jordan M, Rich N. Survival after emergency department thoracotomy: review of published data from the past 25 years. J Am Coll Surg. 2000; 190(3):288-98.
8. Rabinovici R, Bugaev N. Resuscitative thoracotomy: an update. Scand J Surg. 2014; 103(2):112-9.
9. Mercer S J, Kingston E V, Jones C P L. The Trauma call. Br. Med. J. 2018; 361:2272.
10. American Trauma Society. Trauma center levels explained [Internet]. Falls Church (VA): American Trauma Society; [cited 2023 May 24]. Available from: https://www.amtrauma.org/page/TraumaLevels
11. Victoria Department of Health. Code brown guidelines [Internet]. Melbourne (VIC): Victoria Department of Health; 2017 [cited 2023 May 24]. Available from: https://www.health.vic.gov.au/publications/code-brown-guidelines
12. Clarke JR, Trooskin SZ, Doshi PJ, Greenwald L, Mode CJ. Time to laparotomy for intra-abdominal bleeding from trauma does affect survival for delays up to 90 minutes. J Trauma. 2002; 52:420–5.
13. van Vugt AB, van Kampen A. An Unstable pelvic ring. J Bone Joint Surg Br. 2006; 88(4):427-33.
14. Spalding MC, Thomas PG, O'Mara MS, Ramirez CL, Yanagawa FS, Hon HH, et al. Evidence-based approach to the trauma patient in extremis: Transitioning from exclusive emergency department thoracotomy use to protocolized approaches incorporating resuscitative endovascular balloon occlusion of the aorta. Int J Crit Illn Inj Sci. 2018 Apr; 8(2):57-62.
15. Salcedo ES, Brown IE, Corwin MT, Galante JM. Angioembolization for solid organ injury: A brief review. Int J Surg. 2016; 33:225-30.
16. Duchesne JC, Pereira BM, Fraga GP. Damage control resuscitation. Trauma Surg. 2013 Aug 19:27–42.
17. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care. 2016 Apr 12; 20:100.
18. Cap AP, Pidcoke HF, Spinella P, Strandenes G, Borgman MA, Schreiber M, et al. Damage control resuscitation. Mil. Med. 2018 Sep; 183:36-43.
19. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery. 2017 Jan; 80(1):6-15.

20. Cotton BA, Reddy N, Hatch QM, LeFebvre E, Wade CE, Kozar RA, et al. Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. Ann Surg. 2011 Oct; 254(4):598-605.
21. Albreiki M, Voegeli D. Permissive hypotensive resuscitation in adult patients with traumatic haemorrhagic shock: a systematic review. Eur J Trauma Emerg Surg. 2018; 44:191–202.
22. Lamb CM, MacGoey P, Navarro AP, Brooks AJ. Damage control surgery in the era of damage control resuscitation. Br J Anaesth. 2014 Aug; 113(2):242-9.
23. Jackson K, Nolan J. The Role of hypotensive resuscitation in the management of trauma. J Intensive Care Soc. 2009; 10(2):109-14.
24. Wise R, Faurie M, Malbrain MLNG, Hodgson E. Strategies for intravenous fluid resuscitation in trauma patients. World J Surg. 2017 May; 41(5):1170-83.
25. Markov NP, Percival TJ, Morrison JJ, Ross JD, Scott DJ, Spencer JR, et al. Physiologic tolerance of descending thoracic aortic balloon occlusion in a swine model of hemorrhagic shock. Surgery. 2013 Jun; 153(6):848-56.
26. Stannard A, Eliason JL, Rasmussen TE. Resuscitative endovascular balloon occlusion of the aorta (REBOA) as an adjunct for hemorrhagic shock. J Trauma. 2011 Dec; 71(6):1869-72.
27. Sridhar S, Gumbert SD, Stephens C, Moore LJ, Pivalizza EG. Resuscitative endovascular balloon occlusion of the aorta: principles, initial clinical experience, and considerations for the anesthesiologist. Anesth Analg. 2017 Sep; 125(3):884-90.
28. Olsen MH, Thonghong T, Søndergaard L, Møller K. Standardized distances for placement of REBOA in patients with aortic stenosis. Sci. Rep. [Internet]. 2020 August 7 [cited 2023 Jun 16]; 10:13410. Available from: https://www.nature.com/articles/s41598-020-70364-9. doi: 10.1038/s41598-020-70364-9. Figure 1, Simplistic rendering of aorta.
29. Moore LJ, Martin CD, Harvin JA, Wade CE, Holcomb JB. Resuscitative endovascular balloon occlusion of the aorta for control of noncompressible truncal hemorrhage in the abdomen and pelvis. Am J Surg. 2016 Dec; 212(6):1222-30. Figure 2, REBOA algorithm; p. 1224.
30. Matsumoto S, Funabiki T, Kazamaki T, Orita T, Sekine K, Yamazaki M, et al. Placement accuracy of resuscitative endovascular occlusion balloon into the target zone with external measurement. Trauma Surg Acute Care Open [Internet]. 2020 Apr [cited 2023 May 24];5(1):e000443. Available from: https://pubmed.ncbi.nlm.nih.gov/32426527/. doi: 10.1136/tsaco-2020-000443
31. Wasicek PJ, Li Y, Yang S, Teeter WA, Scalea TM, Hu P, et al. Examination of hemodynamics in patients in hemorrhagic shock undergoing resuscitative endovascular balloon occlusion of the aorta (REBOA). Injury. 2019 May; 50(5):1042-8.
32. Borger van der Burg BLS, Kessel B, DuBose JJ, Hörer TM, Hoencamp R. Consensus on resuscitative endovascular balloon occlusion of the aorta: A first consensus paper using a delphi method. Injury. 2019 Jun; 50(6):1186-91.
33. Reva VA, Matsumura Y, Hörer T, Sveklov DA, Denisov AV, Telickiy SY, et al. Resuscitative endovascular balloon occlusion of the aorta: what is the optimum occlusion time in an ovine model of hemorrhagic shock? Eur J Trauma Emerg Surg. 2018 Aug; 44(4):511-8.
34. Russo RM, White JM, Baer DG. Partial resuscitative endovascular balloon occlusion of the aorta: A systematic review of the preclinical and clinical literature. J Surg Res. 2021 Jun; 262:101-14.
35. Tibbits EM, Hoareau GL, Simon MA, Davidson AJ, DeSoucy ES, Faulconer ER, et al. Location is everything: The hemodynamic effects of REBOA in zone 1 versus zone 3 of the aorta. J Trauma Acute Care Surg. 2018 Jul; 85(1):101-7.
36. Cantle PM. REBOA utility. Surg Open Sci. 2022 Mar 18; 8:50-6.
37. Morrison JJ, Galgon RE, Jansen JO, Cannon JW, Rasmussen TE, Eliason JL. A Systematic review of the use of resuscitative endovascular balloon occlusion of the aorta in the management of hemorrhagic shock. J Trauma Acute Care Surg. 2016; 80(2):324–34.
38. Harfouche MN, Madurska MJ, Elansary N, Abdou H, Lang E, DuBose JJ, et al. Resuscitative endovascular balloon occlusion of the aorta associated with improved survival in hemorrhagic shock. PLoS One [Internet]. 2022 Mar 24 [cited 2023 May 28];17(3):e0265778. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0265778. doi: 10.1371/journal.pone.0265778
39. 39. Yamamoto R, Cestero RF, Suzuki M, Funabiki T, Sasaki J. Resuscitative endovascular balloon occlusion of the aorta (REBOA) is associated with improved survival in severely injured patients: A propensity score matching analysis. Am J Surg. 2019 Dec; 218(6):1162-8.
40. Norii T, Crandall C, Terasaka Y. Survival of severe blunt trauma patients treated with resuscitative endovascular balloon occlusion of the aorta compared with propensity score-adjusted untreated patients. J Trauma Acute Care Surg. 2015 Apr; 78(4):721-8.
41. Joseph B, Zeeshan M, Sakran JV, Hamidi M, Kulvatunyou N, Khan M, O'Keeffe T, Rhee P. Nationwide analysis of resuscitative endovascular balloon occlusion of the aorta in civilian trauma. JAMA Surg. 2019 Jun 1; 154(6):500-8.
42. Manzano Nunez R, Naranjo MP, Foianini E, Ferrada P, Rincon E, García-Perdomo HA, et al. A Meta-analysis of resuscitative endovascular balloon occlusion of the aorta (REBOA) or open aortic cross-clamping by resuscitative thoracotomy in non-compressible torso hemorrhage patients. World J Emerg Surg [Internet]. 2017 Jul 14 [cited 2023 May 28];12:30. Available from: https://pubmed.ncbi.nlm.nih.gov/28725258/. doi: 10.1186/s13017-017-0142-5
43. Borger van der Burg BLS, van Dongen TTCF, Morrison JJ, Hedeman Joosten PPA, DuBose JJ, Hörer TM, et al. A Systematic review and meta-analysis of the use of resuscitative endovascular balloon occlusion of the aorta in the management of major exsanguination. Eur J Trauma Emerg Surg. 2018 Aug; 44(4):535-50.
44. Jansen JO, Cochran C, Boyers D, Gillies K, Lendrum R, Sadek S, et al. The Effectiveness and cost-effectiveness of resuscitative endovascular balloon occlusion of the aorta (REBOA) for trauma patients with uncontrolled torso haemorrhage: study protocol for a randomised clinical trial (the UK-REBOA trial). Trials. 2022 May 12; 23(1):384.
45. Theodorou CM, Anderson JE, Brenner M, Scalea TM, Inaba K, Cannon J, et al. Practice, practice, practice! Effect of resuscitative endovascular balloon occlusion of the aorta volume on outcomes: Data From the AAST AORTA registry. J Surg Res. 2020 Sep; 253:18-25.

46. Brede JR, Lafrenz T, Krüger AJ, Søvik E, Steffensen T, Kriesi C, et al. Resuscitative endovascular balloon occlusion of the aorta (REBOA) in non-traumatic out-of-hospital cardiac arrest: evaluation of an educational programme. BMJ Open [Internet]. 2019 May 9 [cited 2023 May 28];9(5):e027980. Available from: https://pubmed.ncbi.nlm.nih.gov/31076474/. doi: 10.1136/bmjopen-2018-027980
47. Moore LJ, Brenner M, Kozar RA, Pasley J, Wade CE, Baraniuk MS, et al. Implementation of resuscitative endovascular balloon occlusion of the aorta as an alternative to resuscitative thoracotomy for noncompressible truncal hemorrhage. J Trauma Acute Care Surg. 2015 Oct; 79(4):523-30.
48. Brenner M, Moore L, Teeter W, Hu P, Yang S, Wasicek P, et al. Exclusive clinical experience with a lower profile device for resuscitative endovascular balloon occlusion of the aorta (REBOA). Am J Surg. 2019 Jun; 217(6):1126-9.
49. Matsumura Y, Matsumoto J, Kondo H, Idoguchi K, Ishida T, Okada Y, et al. Early arterial access for resuscitative endovascular balloon occlusion of the aorta is related to survival outcome in trauma. J Trauma Acute Care Surg. 2018 Sep; 85(3):507-11.
50. Griggs JE, Jeyanathan J, Joy M, Russell MQ, Durge N, Bootland D, et al. Mortality of civilian patients with suspected traumatic haemorrhage receiving pre-hospital transfusion of packed red blood cells compared to pre-hospital crystalloid. Scand J Trauma Resusc Emerg Med. 2018 Nov 20; 26(1):100.
51. DuBose JJ, Scalea TM, Brenner M, Skiada D, Inaba K, Cannon J, et al. The AAST prospective aortic occlusion for resuscitation in trauma and acute care surgery (AORTA) registry: Data on contemporary utilization and outcomes of aortic occlusion and resuscitative balloon occlusion of the aorta (REBOA). J Trauma Acute Care Surg. 2016 Sep; 81(3):409-19.
52. Narvestad JK, Meskinfamfard M, Søreide K. Emergency resuscitative thoracotomy performed in European civilian trauma patients with blunt or penetrating injuries: a systematic review. Eur J Trauma Emerg Surg. 2016 Dec; 42(6):677-85.
53. Eidt JF, Foreman ML. Resuscitative thoracotomy: Technique. In: Bulger EM, Wolfson AB, Collins KA, editors. UpToDate [Internet]. Walters Kluwer (NE): UpToDate Inc; 2022 [cited 2023 May 25]. Available from: https://www.uptodate.com/contents/resuscitative-thoracotomy-technique

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Development of a massive transfusion protocol and cognitive aid

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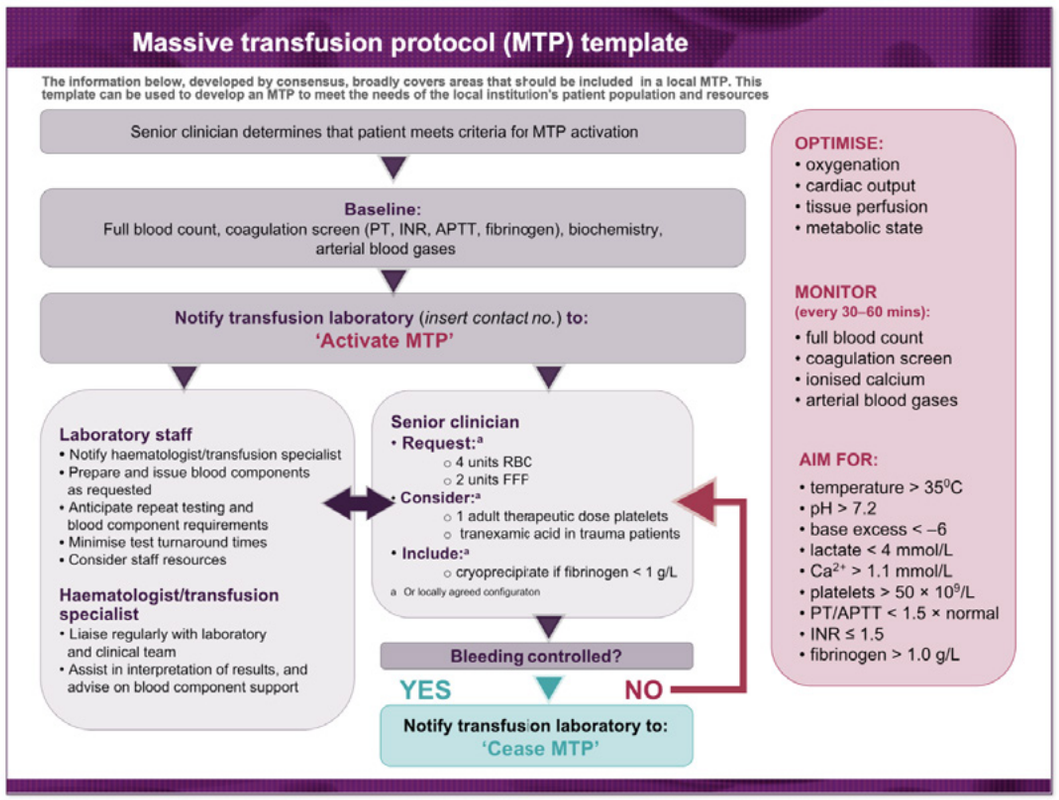
BACKGROUND

Massive Transfusion Protocols (MTPs) have been advocated by the National Blood Authority (NBA) to facilitate the logistic and clinical management of critical bleeding. The Patient Blood Management guidelines for Critical Bleeding[1] were published in 2011 and are currently under review. The MTP template proposed in the NBA Critical Bleeding document outlines the activation process by the senior clinician at the bedside and the responsibilities of the transfusion laboratory. The document also outlines some steps required to facilitate the co-ordination of this process between the clinical team and the transfusion laboratory. In addition, the Critical Bleeding document promotes the development of local MTPs. While "promoted," the development of a locally viable, safe and effective protocol is an important, complex, and collaborative process. Because of the time-critical nature of managing massive transfusion situations, hospitals should delineate the specific processes for MTP activation and management in accordance with the resources available to their institution. In this article, we work to delineate our local experience in undertaking this process, highlighting what our outcomes were, the integral aspects of a well-designed cognitive aid, as well as how and why we came to these determinations. The hope is this will provide support and insight for other institutions considering the same undertaking.

MTPs are designed to rapidly deliver a ratio of blood products mimicking reconstituted whole blood to the critically bleeding patient. The early administration of predefined and balanced ratios of RBC, FFP, and platelets has been shown to be associated with improved patient outcomes in adult trauma patients – the PROPPR trial demonstrated a reduction in mortality from exsanguination in trauma patients receiving 1:1:1 balanced transfusion.[2] Current clinical guidelines similarly promote the use of "1:1:1 ratios" of blood product administration.[3,4]

Clinical settings requiring MTP are time-critical situations, with significant contextual variability between individual hospital sites and Local Health Districts (LHDs). This means that the logistics for clinical management of critical bleeding should be customised into site-specific MTPs and cognitive aids.

Figure 1. The current MTP template from the NBA[1]



CLINICAL GUIDELINE DEVELOPMENT PROCESS

Committee engagement

Stakeholder selection, inclusion, and engagement are crucial to ensure locally effective solutions are developed. Many of the specialities and positions represented within our process will be relevant to your local institution but may vary as well.

The Patient Blood Management Clinical Nurse Consultant (CNC) was tasked by the Northern Sydney Local Health District (NSLHD) Blood Committee with updating the Adult MTP, and creating a NSLHD specific Paediatric MTP. The NSLHD encompasses both Tertiary and District hospitals, but not a dedicated paediatric tertiary referral hospital.

The working group for the revision of the MTP also sought to incorporate the development of a cognitive aid into the process – for both adult and paediatric patients. The vision was to create cognitive aids that were individualised to assist the clinical team at each hospital within the LHD.

It was envisaged the updated MTPs would embed decision support tools to extend the NBA MTP template, seeking to ensure that the appropriate clinical team and logistic resources were mobilised to treat the critical bleeding. The incorporation of the paired priorities of clinical and logistic concerns was an early decision – to ensure that medical management tasks would be completed appropriately, but in conjunction with, logistic considerations around resource mobilisation and coordination to optimise efficiency and minimise human error.

Separate MTP working groups were created to develop the Adult and Paediatric MTPS. This was led by clinicians from patient blood management, anaesthesia, intensive care and emergency medicine – with additional input from the trauma service, haematology, obstetrics, paediatrics, transfusion scientists, and the medical executive unit. The project co-ordinator was the Blood Management CNC, who researched adult and paediatric MTPs throughout Australia and internationally, disseminating the documents through the Blood Committee, and collating feedback. The cognitive aid was developed by anaesthetists with feedback from the working group. There was an early understanding that a single cognitive aid would not be functional across

all hospitals in our LHD. Instead, each individual hospital would be given the opportunity to review and adapt the primary cognitive aid to include local contact numbers and processes. This customisation of the MTP for individual institutions was considered essential to ensure effective clinical management at each site.

Development process

Due to the significant scope of both the proposed revision to the existing MTP and the creation of an accompanying cognitive aid, an iterative process was adopted by the working group. This helped to maintain momentum throughout the development process, and to minimise delays arising from a reluctance to commit to a final version. Instead, there was an understanding that there would be ongoing rounds of revision from user feedback and working group discussions, and subsequent releases of progressive versions.

We found that this approach was effective in mitigating the difficulty that often arises in achieving consensus agreement when creating clinical guidelines that involve multiple stakeholder opinions and viewpoints. It was pleasing to observe that each round of revisions in this iterative process produced cumulative improvements to the MTP and cognitive aids.

The organic process in developing, revising, and refining both the protocol and cognitive aids accommodated the diverse workloads and challenges that naturally arise in attempting to coordinate a large group of professionals across a range of specialties. This approach produced an efficient and consistent engagement, while minimising the need and difficulty involved with coordinating large-group meetings.

Activation criteria

One of the first adaptations to the NBA MTP template was the working group's decision to alter the wording of the activation criteria. We opted to list Major Traumatic Bleeding first, because our tertiary hospital has a trauma "Code Crimson" pathway. This change and comparison can be seen between Figure 1 (the NBA template) and Figure 2 (our first iteration in the development process). Trauma Code Crimson identifies exsanguinating trauma patients in the pre-hospital environment and outlines pre-hospital and in-hospital processes to streamline access to definitive intervention, including an operating theatre or interventional radiology suite.[5] Code Crimson activation occurs via the hospital switchboard for major trauma and mobilises surgical, anaesthesia, and emergency medicine teams. The wording was also simplified to "Major Traumatic Bleeding" from the NBA's "severe thoracic, abdominal, pelvic or multiple long bone trauma".[1]

Another decision was made to change the NBA activation criteria of "actual or anticipated 4 units of Red Blood Cells (RBC) in less than 4 hours".[1] It was determined by the working group that this bleeding rate might not require MTP activation – as this blood loss would usually be insufficient to cause coagulopathy requiring plasma transfusion. Instead, the activation criteria were revised to "actual or anticipated blood loss of greater than 2000 mL". This volume represents approximately 40% of the adult blood volume. While acknowledging the difficulty in estimating actual blood loss, it was considered important to prevent unnecessary MTP activation for lower volume blood loss not requiring plasma transfusion. The shift in wording also changed the assessment criteria from predicted blood replacement, to predicted blood loss – this change was felt to be a more approachable criteria by a broad number of staff. It is important to note that current guidelines discourage the use of plasma transfusion for indiscriminate volume replacement.[3]

LOGISTIC CO-ORDINATION

Massive transfusion situations require co-ordination of both clinical and logistic resources. Upon presentation of a critically bleeding patient, these resources must be rapidly mobilised to facilitate effective management to meet the patient's clinical needs.

Our LHD adopted the new clinical process of MTP activation through a call to switchboard utilising the state-wide 2222 number – as part of a global initiative to use "2222" as the standardised emergency number to activate all medical emergencies.[6] The hospital switchboard obtains details of the patient's location and the contact details of the designated blood co-ordinator (the medical or nursing liaison with Blood Bank). The next step is activation of the MTP paging system by the hospital switchboard – this notifies Blood Bank staff, nursing manager, and a support services officer ("blood runner") who is dispatched to the clinical area. Our institution has experienced problems with MTP activations without a dedicated blood runner to ensure efficient delivery of blood products to the clinical area, and pathology tests to the laboratory. A major advantage of implementing MTP activation via the hospital switchboard (instead of the previous method of directly calling the hospital Blood Bank) is the guaranteed allocation of this blood runner, and a consistent, centralised process for ensuring relevant team members are notified and activated en masse.

The next step is to mobilise the clinical team, which is led by the medical team leader, a critical care physician who assumes responsibility for clinical decision making in the MTP. It is preferable that this team leader is "hands off" – meaning that they are not physically involved in the resuscitation process, but instead physically positioned further back to maintain situational awareness and team oversight.

Additional medical officers (MO) are essential, including a Vascular Access MO to obtain reliable venous and/or arterial access to facilitate the resuscitation. If staffing permits, then an additional MO, or senior nurse delegate, may act as the blood co-ordinator to liaise with Blood Bank to ensure ongoing blood product supply. The appropriate surgical and/or paediatric medical officers must also be alerted, depending on the specific clinical situation. It is also important that sufficient nursing staff are allocated to the ongoing MTP – with at least one nurse allocated to each medical officer.

It is critical that the team leader determines the optimal location for the resuscitation and ensuing MTP. In smaller hospitals, or for paediatric patients, this may require urgent medical retrieval. This may also require transport of the patient to the operating theatre or angiography suite. In addition, all equipment necessary for the resuscitation – including warming devices, rapid infusers, and cell salvage – should be rapidly mobilised to the clinical area.

This discussion around logistics certainly highlights the significant practical differences that exist between individual hospital sites – specifically: personnel, contact numbers, locations, and available equipment. These variations reinforce the need for MTP cognitive aids to be customised for each facility.

CLINICAL MANAGEMENT

While all bleeding situations are different, our working group recognised that there are two essential decision points which must be clarified early in the MTP process. These are the blood volume deficit and the presence of coagulopathy. Following the identification and correction of these initial deficits, the clinical team then moves towards administering the MTP packs, as needed, to deliver reconstituted whole blood. These key decision points are expanded below.

Blood volume deficit

After preparation of the necessary personnel and equipment for resuscitation, the first clinical decision is to determine the estimated blood volume deficit. One of the weaknesses of the MTP process, is that the initial MTP pack may be insufficient to achieve euvolemia in haemorrhagic shock. The NBA has advocated for an MTP pack to contain 4 units of RBC and 2 units of Fresh Frozen Plasma (FFP).[1] This MTP pack only provides a total volume of approximately 1.5 litres. Additionally, at hospitals without Extended Life Plasma (ELP), the clinical team will initially only receive a delivery of 4 units of RBC – with a subsequent delay of up to 30 minutes to allow for thawing of the FFP. This initial volume of one litre of RBC would be inadequate to restore euvolemia in most MTP scenarios. Even accounting for the delayed arrival of the FFP, the standard MTP pack would likely fail to restore blood volume in advanced haemorrhagic shock.

It is also important to note that Blood Bank staff routinely prepare only one MTP pack at a time. Only after dispensing the initial MTP pack are they then required to start preparing the next MTP pack. This means that approximately 30 minutes (to allow for the thawing of FFP) would reasonably elapse before the next MTP pack can be dispensed. This situation emphasises that the standard release of MTP packs will be insufficient to keep pace with critical bleeding occurring at a rate greater than 2 litres in 30 minutes.

To address this logistical challenge, which is not uncommon in our clinical environment, we revised our MTP and proposed that – in critical bleeding situations involving patients with large blood volume deficits, or in situations with rapid rates of blood loss – that both MTP packs are prepared in tandem and dispensed. This adjustment results in the provision of a blood product volume nearing 4 litres – which should be sufficient to restore euvolemia.

Each hospital will have differing preparation and delivery times for MTP packs. It is essential to understand these constraints to ensure the appropriate timing and volume of blood product delivery. This may necessitate overriding the routine MTP pathway in circumstances where the actual blood loss exceeds the rate that blood products would be supplied. Identifying the potential for this need and agreeing on a process for communicating when overriding the routine pathway is needed is also a locally specific process.

Coagulopathy

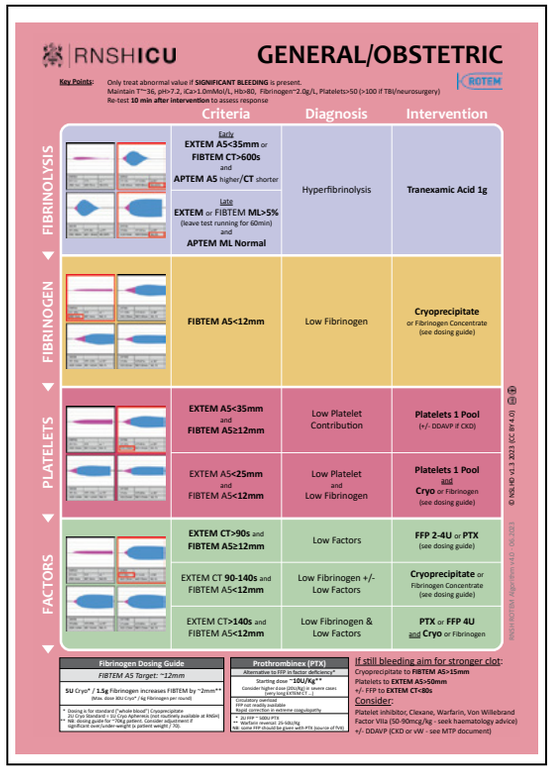
The presence of coagulopathy impacts the ratio of blood products that are necessary to support haemostasis. Clinical guidelines support the use of balanced transfusion ratios of RBC:FFP:Platelets at 1:1:1 for patients during haemorrhage.[3] However, for patients with coagulopathy, this product ratio may fail to restore a favourable coagulation profile.[4] Reconstituted whole blood utilising a 1:1:1 ratio will only have a coagulation factor activity

of 65% of whole blood and a platelet count approximating 88 x 10^9/L.[7] Patients with coagulopathy will likely require a higher proportion of clotting factors (particularly fibrinogen) and platelets – compared to RBC – in order to restore adequate coagulation.

Coagulopathy during massive transfusion can occur due to pharmacological or pathological reasons. Pharmacological coagulopathy occurring as a result of antithrombotic medications should be corrected during the initial phase of resuscitation. This may be with a specific antidote (for example, protamine for heparin, idarucizumab for dabigatran, or vitamin K and prothrombin complex concentrate for warfarin) or with non-specific reversal agents (for example, prothrombin complex concentrates (PCC) for Factor Xa inhibitors, or platelets for aspirin). Pathological coagulopathy may occur as a consequence of the disease process (for example, Trauma Induced Coagulopathy or Placental Abruption), or from consumptive and/or dilutional coagulopathy resulting from the administration of crystalloid, colloid, or RBC infusions. Assessment for pathological coagulopathy needs to be repeated during continued administration of blood products.

Assessment for coagulopathy should be undertaken early in the resuscitation – and be repeated every 30 to 60 minutes. Ideally, this assessment should utilise point-of-care coagulation tests (POCT) (for example, Rotational Thromboelastometry or Thromboelastography), as these provide clinical teams with more rapid results that may better represent in-vivo whole blood coagulation capacity. There was an existing ROTEM-guided pathway at our institution for the assessment and treatment of coagulopathy during critical bleeding (Figure 2). As access to, and clinical familiarity with, the use of ROTEM was already established at our institution, incorporation of this testing was felt to be appropriate for our local protocols.

Figure 2. RNSH ROTEM pathway



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This ROTEM pathway, based upon work disseminated by Fiona Stanley Hospital,[8] was updated and integrated into our new MTP documents. The ROTEM-guided approach is useful in identifying the cause of coagulopathy and guiding the use of clotting factor concentrates to correct for the specific coagulation deficiency. Clinical guidelines advocate the use of cryoprecipitate or fibrinogen concentrate to correct hypofibrinogenemia. They also support the use of PCC over FFP in situations where POCT testing demonstrates clotting factor deficiency.[3] Both of these considerations were subsequently incorporated into our final protocols.

ROTEM Sigma machines are available in both the intensive care unit and operating theatres at our institution. The benefits of utilising ROTEM for coagulation management (compared to standard coagulation testing) are the shorter time for test results and the ability to diagnose specific clotting factor deficiencies. The associated aspects of the cognitive aid included the most frequently utilised elements of these ROTEM pathways to correct coagulopathy – specifically, the dosing details for fibrinogen, platelets, and clotting factor replacement. However, other aspects of the ROTEM pathway pertaining to the assessment for fibrinolysis and residual heparin effect were excluded – instead, our cognitive aid prescribes tranexamic acid and reversal of pharmacological coagulopathy during the Initiation Phase of the MTP.

MTP pack design

General

Unlike the NBA MTP template, which only suggests RBC and FFP, we elected to embed platelets and fibrinogen supplementation into the MTP packs. The combined use of MTP packs 1 and 2 were designed to deliver Reconstituted Whole Blood (RWB) (Table 1). Repeated cycling between these two packs, would deliver an ongoing ratio of blood products approaching the 1:1:1 target for RBC:FFP:Platelets. Our local experience aligns with the findings during the PROPPR trial, where the average volume of RBC and FFP transfused was nine and six units respectively.[2]

Thus, most MTP activations utilise an average of two to three MTP packs. By alternating the presence of cryoprecipitate and platelets between MTP Pack 1 and 2 – with an appropriate ratio of RBC and FFP – we hoped to ensure that RWB would be delivered throughout the MTP activation.

Table 1. Blood products delivered after administration of both Pack 1 and Pack 2 in an adult patient[9]

Blood product	Number of units	Volume per unit	Total volume	Comments
RBC	6	259 mL	1554 mL	
FFP	6	278 mL	1668 mL	Contains 3-3.5 g fibrinogen
Cryoprecipitate	10	36 mL	360 mL	Contains 3-4 g fibrinogen
Platelets	4	273 mL	273 mL	One pack of pooled platelets
Total volume			**3855 mL**	Total fibrinogen ~ 6.5 g (1.7 g/L)

Our MTP packs sought to promote a RBC:FFP ratio of 1:1.[2-4] Consideration was given to the overall volume of blood products in each MTP pack. It was agreed that a total volume of 1.5 to 2 litres would be sufficient in each pack. Three units of RBC and FFP were thus included in each MTP pack.

Fibrinogen

Fibrinogen is the coagulation factor that falls to dangerous levels early in critical bleeding.[10] Current clinical guidelines promote a fibrinogen target of:

- 1.5-2 g/L during perioperative bleeding[3]
- > 1.5 g/L for trauma[4]
- > 1.5 g/L during cardiac surgery[11]
- > 2 g/L for obstetric bleeding[12]

Given these current recommendations, our working group decided to specify a fibrinogen target of 2 g/L across all patient populations. A single fibrinogen target has the benefit of being easily remembered. In addition, aiming for the higher end of the target range would permit a margin of safety, and reduce the likelihood of patients developing fibrinogen levels below 1.5 g/L. A single fibrinogen target also simplified the development of fibrinogen dosing algorithms utilising ROTEM and plasma Clauss fibrinogen concentrations. Our working group elected to incorporate cryoprecipitate into our first MTP pack as a systems-level step to ensure the maintenance of plasma fibrinogen during initial resuscitation in a massive transfusion setting. Plasma transfusion alone with FFP is insufficient to correct for hypofibrinogenemia.[3] Our MTP packs without cryoprecipitate would only result in a fibrinogen concentration of approximately 1.0 g/L (from Table 1). With the addition of cryoprecipitate, the final fibrinogen concentration is approximately 1.7 g/L.

Platelets

Platelet targets during critical bleeding are 50 x 10^9/L and 100 x 10^9/L in intracranial bleeding.[1,4] Given that most critical bleeding situations are resolved with the administration of 2 or 3 MTP packs,[2] it is unlikely that platelet levels will fall below those aforementioned thresholds, unless blood loss significantly exceeds one blood volume. The transfusion laboratory in our LHD provides pooled platelets (platelets from 4 individual donors). Our working group agreed that given the lower likelihood of platelet levels falling to critical levels during the early phases of resuscitation, an overall product ratio of 6 units RBC, 6 units FFP, and 1 Pooled Platelets would achieve an adequate approximation of 1:1:1 reconstituted whole blood. However, additional platelets may be required for patients taking antiplatelet medication, or when directed by ROTEM or formal full blood count.

ROTEM targets

Our working group established a FIBTEM A5 target of 12 mm for all patient groups during critical bleeding. We were not able to find evidence to routinely support a fibrinogen target greater than 2 g/L, nor a FIBTEM A5 target greater than 12 mm.[3] Fibrinogen dosing was thus designed to restore to a FIBTEM A5 of 12 mm, given that 10 units cryoprecipitate, or 3 g fibrinogen concentrate, are required to raise FIBTEM A5 by 4-5 mm.[13]

Platelet transfusion was recommended when poor platelet contribution was suggested by ROTEM (EXTEM A5 < 35 mm) or when thrombocytopenia was detected with formal laboratory testing. FFP or PCC was recommended when ROTEM clotting time was prolonged (EXTEM Clotting Time > 90 seconds), or formal coagulation tests (APTT or INR) were greater than 1.5 times normal.[4] Our ROTEM pathway recommends PCC over FFP in patients with severely prolonged EXTEM clotting times.

For the sites within our LHD without access to ROTEM, we embedded fibrinogen, platelet, and FFP replacement guidelines into their cognitive aids based upon standard coagulation tests. The adaptation and application of these recommendations at your local institution needs to consider a multitude of logistical factors, including the presence and ease of access to some of these POC testing modalities.

COGNITIVE AID DEVELOPMENT

Overview

The cognitive aid was designed to facilitate not only appropriate blood product delivery, but also clinical decision-making in patients with critical bleeding. Effective management of patients requiring massive blood transfusion involves both clinical and logistic considerations. The production of the cognitive aids was facilitated by ASCAR (Anaesthesia Cognitive Aids and Research Group), the organisation based at our institution with a keen interest in human factors and visual design.

The cognitive aid was developed to flow over two pages – initially to accommodate the necessary content, but this two-page design later provided the ability to demarcate the MTP into a two-stage process. The first stage (initiation phase) of the MTP is outlined on the first page. It includes the activation criteria and the logistic coordination tasks required to activate the MTP effectively. This co-ordination includes identifying the optimal location for resuscitation and mobilising the relevant team members and equipment required. It mandates early notification of Blood Bank and requesting the first pack of blood products and medications necessary to reverse pharmacological coagulopathy. Steps completed during this initiation phase are not required during the later phases of resuscitation.

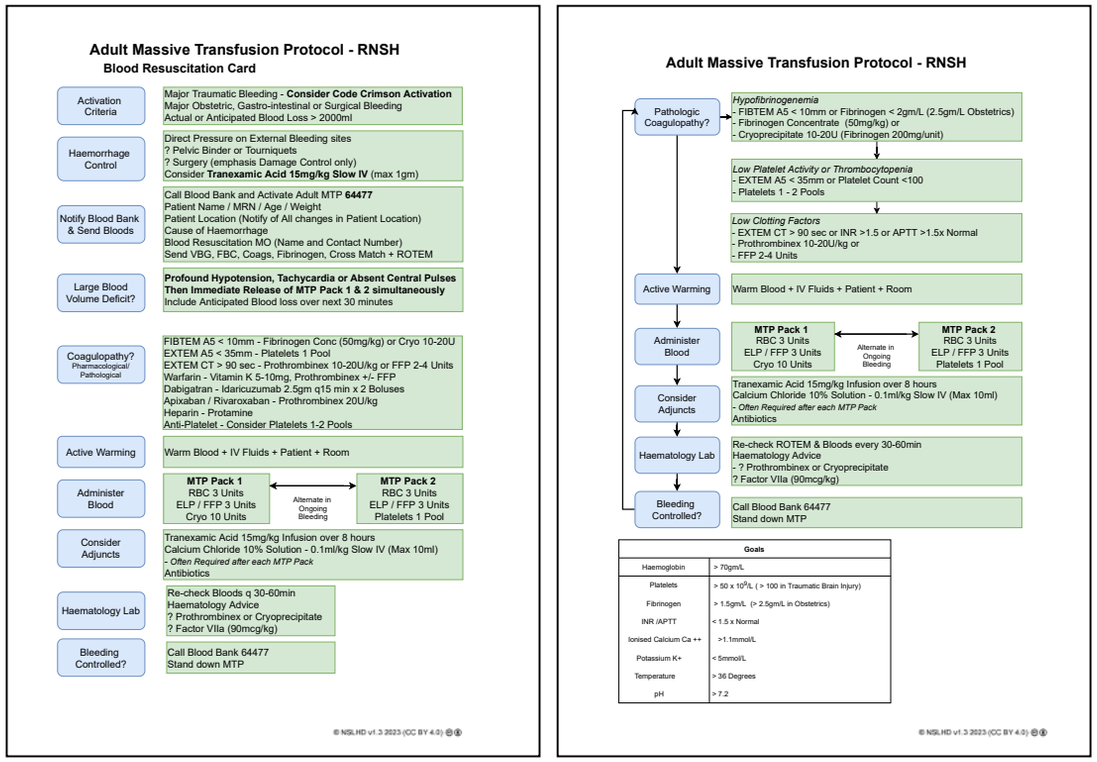
Once the initial phase of the MTP has been completed, clinical care moves into the subsequent cycling (or maintenance) phase until bleeding has been controlled. This is outlined on the second page, allowing clinicians to use a single page to guide this stage of the MTP – where the clinical priorities are to administer blood products and to treat hypothermia and ongoing coagulopathy.

Individualised MTP cognitive aids were created for each hospital within the LHD. The overall content and

visual design were retained, but site-specific customisations were made. This allowed locally relevant contact numbers and processes to be embedded within each cognitive aid. Cognitive aids need to strike a balance of being locally relevant, but also retaining consistent visual formatting to reduce the cognitive load for staff working at multiple locations.

Initial version

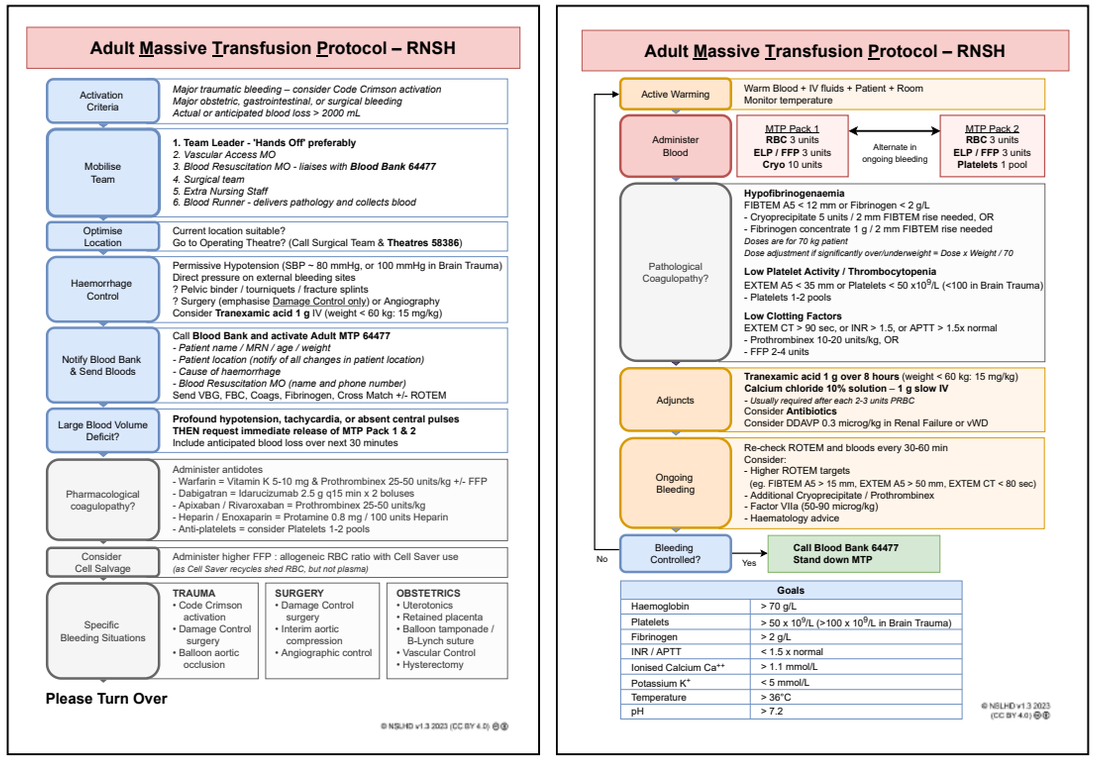
Figure 3. Development stage of MTP cognitive aid



There was an early consensus decision for a linear/flowchart visual layout for the cognitive aids, to harness the intuitive and familiar feel of this format. One of the first drafts for our cognitive aid highlights these components and is shown in Figure 3. The primary steps of the MTP are listed in separate panels on the left-hand side of the page to allow rapid scanning. Explanatory notes are included in a secondary panel on the right-hand side of the page, using succinct and clear language. The initial designs were deliberately simple, with minimal visual design input – instead, the focus was on refining the actual text – a "content-first" approach. This initial draft provided a platform for members of the working group to rapidly provide input and guidance that allowed for the final product to be achieved.

First release

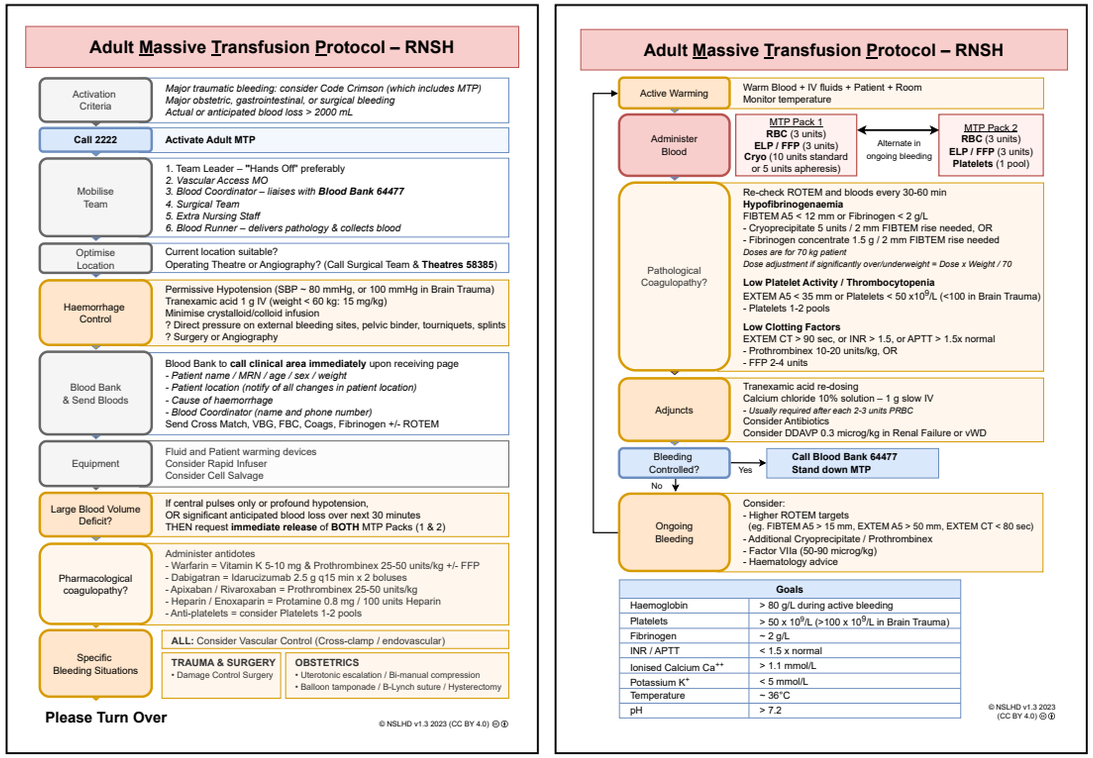
Figure 4. First release version (v1.0) of MTP cognitive aid



After several rounds of development and stakeholder feedback, the content was simplified to increase clarity and reduce duplication. With the content mostly finalised, the visual layout was then refined to improve usability – the size and shape of the panels were adjusted, a simple colour palette was introduced, version numbers were added to the footer, and a header was introduced (Figure 4). Short, numbered lists and dot points were implemented to improve the readability of the aids in a crisis situation. Overall, there were significant changes in both content and visual design between the initial drafts and the first production release (v1.0).

4.4 Current release

Figure 5. More recent version (v1.3) MTP cognitive aid



All clinical resources and publications need ongoing review from user feedback over the course of time and clinical use. This iterative process was continued after the release of v1.0 – with ongoing meetings and feedback discussion about the MTP and accompanying cognitive aids. Further refinements were made to the content and visual design, highlighting the value of the feedback process and engagement with both clinicians and our working group. Some examples include introduction of a new "Activation" panel to reflect this logistic change in our LHD, and the use of colour as a grouping tool for the panels (orange: clinical, grey: logistic, red: blood product administration) (Figure 5).

Production of a cognitive aid, especially for critical events, needs to embed pathways for receiving feedback and correcting errors or issues. Once refined to a functional state, regular reviews should be scheduled to assess its continued relevance, utility, and adherence to current standards. Accordingly, our MTP cognitive aids will continue to be adjusted and refined as this process continues.

PAEDIATRIC MTP

Paediatric MTPs are significantly different from Adult MTPs, both in logistic coordination and in clinical management pathways. Clearly, a cognitive aid designed for an Adult MTP would be inadequate to support clinicians involved in paediatric crisis situations. The development of a Paediatric MTP was novel in our institution, and its activation would likely be a rare occurrence. Hence, every effort was made to simplify the pathway and reduce the cognitive load for clinicians. The key differences in the Paediatric MTP for our institution are outlined below.

Logistics

Involvement of the Newborn and Paediatric Emergency Transport Service (NETS) was embedded early in the MTP management flow as our hospital is not a paediatric trauma nor a tertiary paediatric referral centre. NETS notification automatically activates both the patient retrieval process and access to a paediatric haematologist for telephone advice. Mobilisation of paediatric medical staff was also added to the MTP, to maximise appropriate clinical support for the resuscitation process.

Clinical management

The activation criteria for Paediatric MTP were modified to include weight-based criteria. This aligned the protocol with the Sydney Children's Hospital Network MTP,[14] which is the paediatric referral hospital for our institution. Similarly, all drug dosing was modified to use a weight-based approach, as is common practice for paediatric patients. The clinical signs for detection of significant blood loss in the paediatric population was also emphasised – focusing on the significance of profound tachycardia and late development of hypotension. A table with the clinical signs of paediatric haemorrhagic shock was added to the cognitive aid.

Product ratios

Our paediatric weight-based transfusion ratios were designed to also reconstitute whole blood, mirroring one of the goals in the Adult MTP. The Paediatric MTP differs from the Adult MTP as weight-based transfusion volumes are administered – and are likely to require partial transfusion of any blood product units supplied. Consequently, we de-emphasised the concept of alternating "packs" – Pack 1 and Pack 2, and instead implemented the concept of alternating "boluses" – Bolus A and Bolus B. A subsequent bolus should utilise remaining volume in the blood product bag prior to using blood from another donor. The working group again elected to place cryoprecipitate in MTP Bolus A, along with RBC and FFP boluses.

The weight-based transfusion rules in our Paediatric MTP are RBC 10 mL/kg, FFP 10 mL/kg, and Platelets or Cryoprecipitate at 5 mL/kg. Thus, representing an overall bolus of 25 mL/kg. The NBA promotes boluses of RBC 25 mL/kg, FFP 15 mL/kg, and Platelets 10-15 mL/kg.[15] However, our working group elected to give smaller boluses of RBC, that are balanced with FFP, cryoprecipitate, and platelets. A RBC 25 mL/kg bolus represents one third of total blood volume, and the working group believed that it would be preferable to incorporate FFP to avoid the development of coagulopathy associated with such a large RBC transfusion. After the administration of both Bolus A and Bolus B, the transfused volume closely reflects reconstituted whole blood, with a RBC:FFP:Platelets ratio approximating 1:1:1. The additional cryoprecipitate results in an overall fibrinogen concentration of approximately 1.7 g/L.A practical example of how this regimen would be applied in a 25 kg patient (the average weight of a 7-year-old) is demonstrated in Table 2.

An additional benefit in our final recommendations for the doses of blood products to be administered is the ease in remembering them: "10-10-5" – with Bolus A being RBC 10 mL/kg, FFP 10 mL/kg and cryoprecipitate 5 mL/kg, and Bolus B being RBC 10 mL/kg, FFP 10 mL/kg and platelets 5 mL/kg.

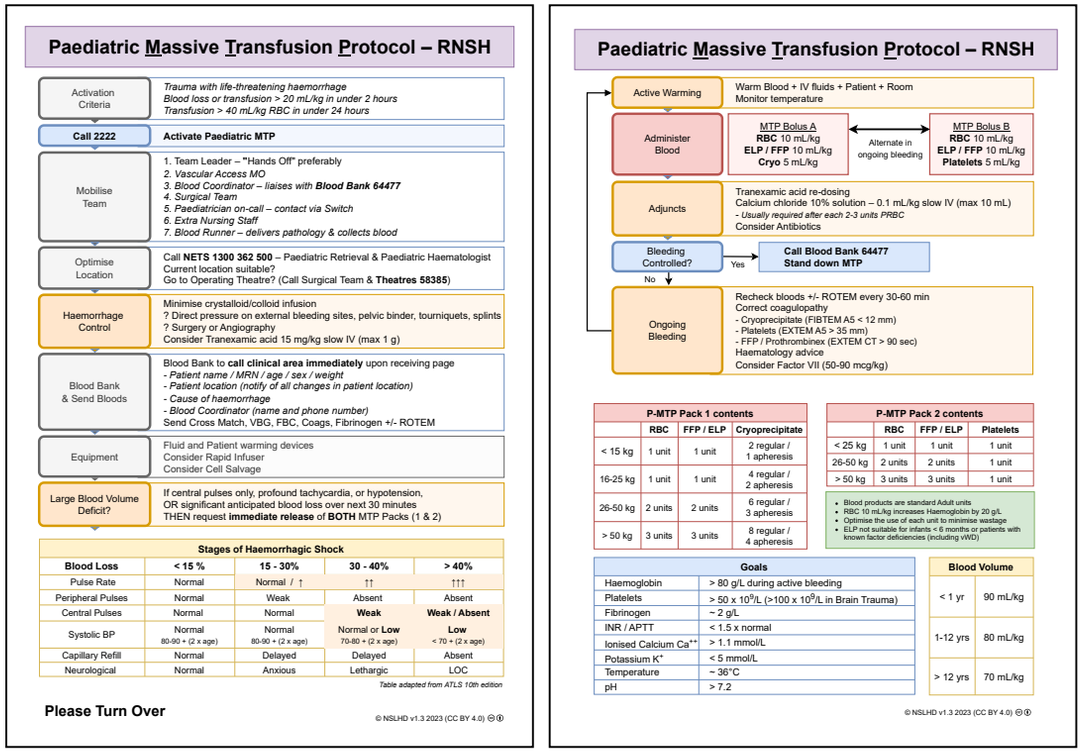
Table 2. Blood products delivered after administration of both Bolus A and Bolus B in a 25 kg paediatric patient

Blood product	Dosage	Volume delivered	Total units required	Comments
RBC	20 mL/kg	500 mL	~ 2 units	
FFP	20 mL/kg	500 mL	~ 2 units	Contains ~1 g fibrinogen
Platelets	5 mL/kg	125 mL	~ 2 units	
Cryoprecipitate	5 mL/kg	125 mL	~ 4 units	Contains ~1.2 g fibrinogen
Total		**1250 mL**		Total fibrinogen ~ 2.2 g (1.7g/L)

The working group elected not to incorporate ROTEM and formal guidance to correct coagulopathy into the Paediatric MTP. The frequency of paediatric MTP activation in our LHD is uncommon, and it was felt that such advice would best be delivered by the consulting NETS paediatric haematologist. However, hospitals with greater experience with paediatric resuscitation may elect to incorporate specific advice for correction of coagulopathy in their MTP pathway.

Cognitive aid

Figure 6. Current version (v1.3) of the Paediatric MTP cognitive aid



Paediatric Massive Transfusion Protocol – RNSH

Activation Criteria	*Trauma with life-threatening haemorrhage* *Blood loss or transfusion > 20 mL/kg in under 2 hours* *Transfusion > 40 mL/kg RBC in under 24 hours*
Call 2222	**Activate Paediatric MTP**
Mobilise Team	1. Team Leader – "Hands Off" preferably *2. Vascular Access MO* *3. Blood Coordinator – liaises with **Blood Bank 64477*** *4. Surgical Team* *5. Paediatrician on-call – contact via Switch* *6. Extra Nursing Staff* *7. Blood Runner – delivers pathology & collects blood*
Optimise Location	Call **NETS 1300 362 500** – Paediatric Retrieval & Paediatric Haematologist Current location suitable? Go to Operating Theatre? (Call Surgical Team & **Theatres 58385**)
Haemorrhage Control	Minimise crystalloid/colloid infusion ? Direct pressure on external bleeding sites, pelvic binder, tourniquets, splints ? Surgery or Angiography Consider Tranexamic acid 15 mg/kg slow IV (max 1 g)
Blood Bank & Send Bloods	Blood Bank to **call clinical area immediately** upon receiving page *- Patient name / MRN / age / sex / weight* *- Patient location (notify of all changes in patient location)* *- Cause of haemorrhage* *- Blood Coordinator (name and phone number)* Send Cross Match, VBG, FBC, Coags, Fibrinogen +/- ROTEM
Equipment	Fluid and Patient warming devices Consider Rapid Infuser Consider Cell Salvage
Large Blood Volume Deficit?	If central pulses only, profound tachycardia, or hypotension, OR significant anticipated blood loss over next 30 minutes THEN request **immediate release** of **BOTH** MTP Packs (1 & 2)

Stages of Haemorrhagic Shock

Blood Loss	< 15 %	15 - 30%	30 - 40%	> 40%
Pulse Rate	Normal	Normal / ↑	↑↑	↑↑↑
Peripheral Pulses	Normal	Weak	Absent	Absent
Central Pulses	Normal	Normal	**Weak**	**Weak / Absent**
Systolic BP	Normal 80-90 + (2 x age)	Normal 80-90 + (2 x age)	Normal or **Low** 70-80 + (2 x age)	**Low** < 70 + (2 x age)
Capillary Refill	Normal	Delayed	Delayed	Absent
Neurological	Normal	Anxious	Lethargic	LOC

Table adapted from ATLS 10th edition

Please Turn Over

Page 1

Paediatric Massive Transfusion Protocol – RNSH

Active Warming	Warm Blood + IV fluids + Patient + Room Monitor temperature
Administer Blood	MTP Bolus A **RBC** 10 mL/kg **ELP / FFP** 10 mL/kg **Cryo** 5 mL/kg Alternate in ongoing bleeding MTP Bolus B **RBC** 10 mL/kg **ELP / FFP** 10 mL/kg **Platelets** 5 mL/kg
Adjuncts	Tranexamic acid re-dosing Calcium chloride 10% solution – 0.1 mL/kg slow IV (max 10 mL) *- Usually required after each 2-3 units PRBC* Consider Antibiotics
Bleeding Controlled?	Yes → **Call Blood Bank 64477** **Stand down MTP**
	No
Ongoing Bleeding	Recheck bloods +/- ROTEM every 30-60 min Correct coagulopathy - Cryoprecipitate (FIBTEM A5 < 12 mm) - Platelets (EXTEM A5 > 35 mm) - FFP / Prothrombinex (EXTEM CT > 90 sec) Haematology advice Consider Factor VII (50-90 mcg/kg)

P-MTP Pack 1 contents

	RBC	FFP / ELP	Cryoprecipitate
< 15 kg	1 unit	1 unit	2 regular / 1 apheresis
16-25 kg	1 unit	1 unit	4 regular / 2 apheresis
26-50 kg	2 units	2 units	6 regular / 3 apheresis
> 50 kg	3 units	3 units	8 regular / 4 apheresis

P-MTP Pack 2 contents

	RBC	FFP / ELP	Platelets
< 25 kg	1 unit	1 unit	1 unit
26-50 kg	2 units	2 units	1 unit
> 50 kg	3 units	3 units	1 unit

- Blood products are standard Adult units
- RBC 10 mL/kg increases Haemoglobin by 20 g/L
- Optimise the use of each unit to minimise wastage
- ELP not suitable for infants < 6 months or patients with known factor deficiencies (including vWD)

Goals

Haemoglobin	> 80 g/L during active bleeding
Platelets	> 50 x 10^9/L (>100 x 10^9/L in Brain Trauma)
Fibrinogen	~ 2 g/L
INR / APTT	< 1.5 x normal
Ionised Calcium Ca^{++}	> 1.1 mmol/L
Potassium K^+	< 5 mmol/L
Temperature	~ 36°C
pH	> 7.2

Blood Volume

< 1 yr	90 mL/kg
1-12 yrs	80 mL/kg
> 12 yrs	70 mL/kg

Page 2

The Paediatric MTP cognitive aid (Figure 6) was designed to complement and resemble the visual flow of our Adult MTP cognitive aid. As with the adult document, it was designed to flow over two pages – with the first page outlining the initiation phase of MTP, and the second page outlining the cycling (or maintenance) phase of resuscitation. A deliberate effort was made to maintain visual consistency between the two aids – to maximise familiarity and minimise cognitive load for the end user.

The key differences for the paediatric cognitive aid are:

- Colour palette: a different colour was used for the header to help distinguish between the two aids, but the remaining panels retain the same colour scheme.
- Removal of panels that were more relevant for Adult MTP
  - Pharmacological coagulopathy
  - Specific bleeding situations
  - Pathological coagulopathy.
- Addition of panels to assist clinical management of Paediatric MTP
  - Stages of haemorrhagic shock (adapted from ATLS 10th edition)[16]
  - Paediatric MTP pack contents
  - Paediatric blood volume formulas
  - Supplementary notes on blood product administration.

FUTURE DIRECTIONS

There are ongoing regular committee meetings regarding the ongoing refinement and optimisations to both the MTP process and MTP cognitive aids at our LHD. There are post-implementation quality assurance plans to review the effectiveness, strengths, and weaknesses of these systems – and their impact on the delivery of safe and quality healthcare in patients requiring massive blood transfusion. These steps of auditing both the MTP process and the utility of the associated cognitive aid are imperative steps at any institution to ensure issues are addressed and content is kept up to date.

CONCLUSION

The process of updating the existing Adult and Paediatric MTPs at our institution has been a valuable and rewarding experience. Early and active engagement of key stakeholders is an essential step to ensuring a relevant and functional collection of resources and recommendations. The additional development of an accompanying cognitive aid to assist the management has been a very worthwhile asset to help translate the MTP into clinical practice. Effective management requires consideration of both clinical and logistic domains, and cognitive aids are an excellent tool to assist clinicians involved in managing an MTP. We hope that this article has been useful in describing the processes and practicalities to consider when implementing similar endeavours at your institution.

REFERENCES

1. National Blood Authority Australia. Patient Blood Management Guidelines: Module 1 Critical Bleeding/Massive Transfusion: National Blood Authority Australia; 2011. Available from: https://www.blood.gov.au/pbm-module-1.
2. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015;313(5):471-82.
3. Kietaibl S, Ahmed A, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, et al. Management of severe peri-operative bleeding: Guidelines from the European Society of Anaesthesiology and Intensive Care: Second update 2022. Eur J Anaesthesiol. 2023;40(4):226-304.
4. Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. Crit Care. 2019;23(1):98.
5. Agency for Clinical Innovation, Institute of Trauma and Injury Management. Trauma code crimson pathway [Internet]. NSW Health; 2017 [cited 2023 July 3]. Available from: https://aci.health.nsw.gov.au/networks/trauma/resources/trauma-code-crimson-pathway.
6. European Society of Anaesthesiology and Intensive Care. 2222 Cardiac Arrest Call [Internet]. European Society of Anaesthesiology and Intensive Care; 2016 [cited 2023 July 3]. Available from: https://www.esaic.org/patient-safety/2222-cardiac-arrest-call/.
7. McCoy CC, Brenner M, Duchesne J, Roberts D, Ferrada P, Horer T, et al. Back to the Future: Whole Blood Resuscitation of the Severely Injured Trauma Patient. Shock. 2021;56(1S):9-15.
8. Mace H, Khanna M. Fibrinogen concentrate for acquired hypofibrinogenaemia. In: Riley R, editor. Australasian Anaesthesia 2017: Australian and New Zealand College of Anaesthetists; 2017. p. 105-16.
9. Australian Red Cross Lifeblood. Blood components [Internet]. Australian Red Cross; 2023 [cited 2023 July 03]. Available from: https://www.lifeblood.com.au/health-professionals/products/blood-components.
10. NSW Institute of Trauma and Injury Management. Fibrinogen administration in prehospital trauma [Internet]. Agency for Clinical Innovation; 2022 [cited 2023 July 03]. Available from: https://aci.health.nsw.gov.au/__data/assets/pdf_file/0004/716566/ACI-Fibrinogen-administration-in-prehospital-trauma.pdf.
11. Pagano D, Milojevic M, Meesters MI, Benedetto U, Bolliger D, von Heymann C, et al. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. Eur J Cardiothorac Surg. 2018;53(1):79-111.
12. Drew T, Carvalho JCA. Major obstetric haemorrhage. BJA Educ. 2022;22(6):238-44.
13. Winearls J, Wullschleger M, Wake E, Hurn C, Furyk J, Ryan G, et al. Fibrinogen Early In Severe Trauma studY (FEISTY): study protocol for a randomised controlled trial. Trials. 2017;18(1):241.
14. The Sydney Children's Hospital Network. Massive Transfusion Protocol (MTP) - Paediatric [Internet]. The Sydney Children's Hospital Network; 2022 [cited 2023 July 03]. Available from: https://www.schn.health.nsw.gov.au/policies/14-7000.
15. National Blood Authority Australia. Patient Blood Management Guidelines: Module 6. Neonatal and Paediatrics: National Blood Authority Australia; 2016. Available from: https://www.blood.gov.au/pbm-module-6.
16. American College of Surgeons. Advanced trauma life support. 10th edition. Chicago: American College of Surgeons, Committee on Trauma; 2018.

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Vasoconstrictors – friend or foe?

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Edited by Dr Alex Yartsev

INTRODUCTION

The use of vasoconstrictors in the management of intraoperative hypotension (IOH) is ubiquitous and associated with a not insignificant cost.

The purpose of this article is to explore the rationale for administering vasoconstrictors to treat IOH and whether their administration may be associated with complications. Comparisons of outcomes with and without administration of vasoconstrictors may prove challenging in the current setting, where blood pressure (BP) control is regarded as paramount and withholding vasoconstrictors may not receive approval from ethics committees.

There are many definitions of IOH but no agreed standard definition.[1-3] Nonetheless, vasoconstrictors are commonly used to restore BP to within variable pre-determined limits. The reason used as justification is to maintain "perfusion pressure" based on the premise that BP drives flow. The dogma behind such reasoning may trigger an inappropriate use of vasoconstrictors, which may adversely affect tissue blood flow as well as cause harm. As a simple example, cases of vasopressor-induced digital ischaemia in the context of haemorrhage and attempts to restore blood pressure are evident in the literature.

The author questions the logic and potential reflexive action of "treating a number" without considering the true outcomes desired and inadequately engaging with an understanding of the factors contributing to the blood pressure reading.

A systematic review of the literature was undertaken with respect to the complications attributed to IOH having specific regard to stroke, myocardial ischaemia, and postoperative cognitive dysfunction (POCD). Possible mechanisms for these are considered and whether the associated complications of IOH are caused by hypotension.

DISSECTING BLOOD PRESSURE VERSUS PERFUSION

Regulation of regional blood flow

The combined effects of neurohumoral and local metabolites are responsible for altering vessel calibre, and hence resistance with consequent effects on distribution of blood flow at the tissue level.

The effect of vascular resistance is highlighted when comparing the systemic circulation with the pulmonary circulation,[4] which is a low resistance circulation. In the normal heart, cardiac output from both left and right ventricles is the same, but because of the lower resistance in the pulmonary vasculature, this output is achieved at only one-fifth of the pressure of the systemic side. It is difficult to reconcile this observation if pressure is a driver of flow.[5]

There are multiple postulated mechanisms for regulation of blood flow across the microcirculation demonstrating increasing sensitivity from small arteries to terminal arterioles.[6] The metabolic theory proposes that as flow exceeds local tissue needs the washout of metabolites stimulates contraction of the vascular smooth muscle leading to constriction of the vessels.[7] The corollary being that where flow is inadequate to meet local demands there is a local build-up of metabolites that provokes relaxation of the vascular smooth muscle leading to vasodilatation.

Hypertension

Hypertension is a clinically well-established and well-studied disease associated with recognised complications including, but not limited to, cerebral and cardiac events.[8-10]

Normotension and blood pressure control

In the context of circulatory homeostasis, BP has been credited with a central role. Maintenance of normotension is considered to be the goal. Part of the reason for this is historical, in that the ability to measure blood pressure preceded the ability to measure flow by two hundred years.[21,22]

Notwithstanding the acceptance that tissue perfusion is the critical function of the circulation, the inability to directly measure flow led to BP becoming the surrogate for flow. The focus in medicine on targeting the metrics of a situation while losing sight of the intended outcome is a rampant problem that is often propagated by the overwhelming number of responsibilities each of us are constantly tasked with.

Hales is reputed to be the first to have measured BP by cannulating an artery in 1733.[11] Non-invasive techniques were used in the early 1800s, and in 1901 Harvey Cushing is reputed to have instituted BP monitoring as a regular feature during anaesthesia. It was not until the mid-1900s that the Fick Principle was first used to deduce flow, and it was significantly later that doppler technology matured sufficiently to be an accurate tool for measuring blood flow. It is not surprising then that blood pressure became so ingrained as an indicator of perfusion, and that circulatory function is centred on BP.

While the population mean systolic BP is around 120 mmHg, the range of "normal" is variable, with the "normal" resting systolic BP for some people being as low as 80 mmHg systolic.[12] This raises the question as to why there is such variability and how the body sets its baseline.

The existence of stretch receptors, which in the circulation have been termed baroreceptors, fuels the perception that the body controls BP. However, this warrants further consideration. For example, what is actually being sensed? Is there some kind of manometer in the circulation and if so, what is the baseline? In his article, Raven[13] poses several questions and suggests that changes in mean arterial pressure are accompanied by a resetting of the baroreceptor reflex function curve with preservation of sensitivity to acute changes in BP. While this explanation reflects neural adaptation to stimuli and re-setting of thresholds, it does not exclude the primary stimulus being volume rather than pressure.

Baroreceptors, located in the aortic arch and the carotid sinus, derive their name on the presumption that they sense pressure. However, they are stretch receptors and as such are sensitive to volume change, which is determined by stroke volume. In her article, Lau[14] correctly identifies uniaxial stretching of baroreceptor neurons mimicking the *forces* exerted on blood vessels that elicit an increase in intracellular Ca^{++} in baroreceptor neurons, but then goes on to consider pressure as if the two are interchangeable. Despite identifying that stretch reflects the forces acting on the receptors the subsequent discussion reverts to current views, centring on pressure.

The baroreceptor reflex invokes inotropic responses designed to alter contractility as well as invoking chronotropic responses affecting heart rate, the combination of which determines cardiac output. It could be argued then, that the body's primary circulatory aim is to control cardiac output and any BP changes are coincidental to alterations in cardiac output and vascular resistance.

Autoregulation

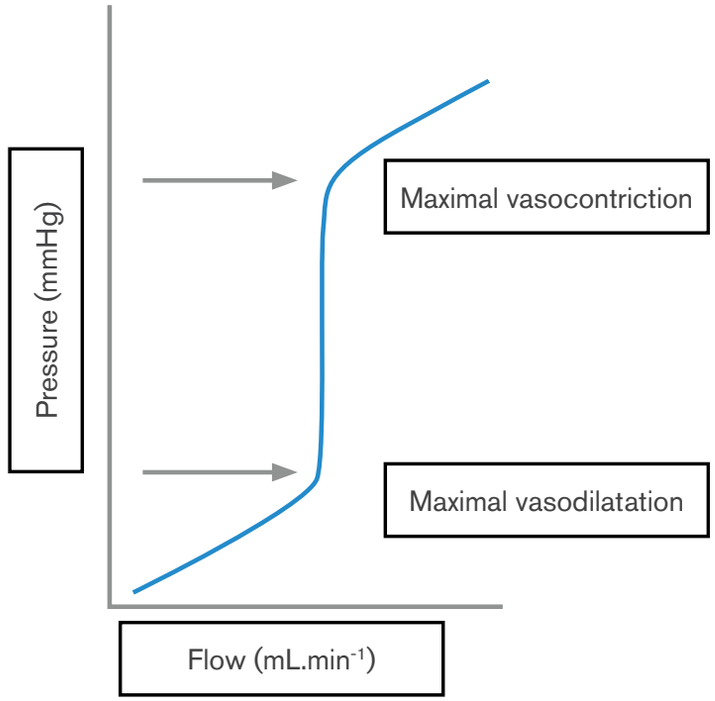
Autoregulation is described as the ability of tissues to maintain a relatively constant local regional flow within a range of "global" BP such as measured in the arm or leg.[15,16] BP measured in this way bears little resemblance to pressures and flows at the tissue level. At any given BP reading, regional flows and pressures may vary significantly depending on local tissue needs.

There are several postulated theories for the mechanism of autoregulation that include the myogenic theory, tissue metabolic theory, tissue fluid pressure theory, and renin-angiotensin theory (in the kidney only).[17] They all have in common the fact that local tissue demands invoke changes in vessel resistance to adjust flow and ensure their localised needs are met. This occurs independently of global pressure measured at any distant site.

The autoregulation argument is predicated on the assumption that pressure drives flow, which begs the question that if BP drives flow, why doesn't flow increase with increasing BP, and instead remains constant over a wide range of pressures? Could it be that BP is not the independent variable?

To illustrate this, the author has taken the liberty of interchanging the axis variables as normally depicted for autoregulation, with blood flow as the independent variable on the X-axis and pressure as the dependent variable in the Y-axis (Figure 1). This allows an alternative perspective.

Figure 1. Plot of autoregulation curve with pressure as the dependent variable



With maximal vasodilatation (minimal resistance), pressure changes little in parallel with an increase in flow and reflects changes in preload. Once flow exceeds the tissue's needs it induces increasing local vasoconstriction to progressively increase local resistance, thereby maintaining constant flow to the tissue despite the rise in BP. Finally, when the tissue has reached its maximum capacity for vasoconstriction, local flow becomes predominantly dependent on cardiac contractility.

IOH

Given the lack of an agreed definition of IOH, it is difficult to reconcile the real incidence of complications and the variable levels at which interventions occur.

Sequelae attributed to hypotension include, cerebral,[18-20] cardiac,[21] increased 30-day mortality,[22-24] and postoperative cognitive dysfunction (POCD).[25-27] The inference is that BP needs to be maintained in order to perfuse tissues and prevent these events. However, at the local tissue level, regional pressures will vary with changes in regional flow, yet the BP measured in the arm may remain constant.

Hypoperfusion secondary to hypotension is regarded as the underlying mechanism causing these outcomes. Consequently, the almost ubiquitous response to managing hypotension is to administer vasoconstrictors in order to elevate the BP back to "normal," on the assumption that flow (and thus perfusion) will increase in response. However, Newton's second law of motion reveals that a force must be applied to a body to change its momentum or direction or both. It is considered to be one of the most important laws in all of physics.[28] In determining the motion of a mass (blood), it is clear that only a force is capable of influencing the motion of any mass, and not pressure.

The interaction and balance of forces within the circulatory system determine the magnitude and direction of blood flow.[5] In this context, the administration of vasoconstrictors has a detrimental effect on blood flow[29,30] despite any rise in BP.

Another factor considered to drive flow is the pressure gradient. Vasoconstriction results in elevated pressures in vessels proximal to the constriction but a fall in pressure distally, which is observed as an increase in pressure gradient. Despite the increase in pressure gradient, flow decreases and is accompanied by an increase in flow velocity, which may of itself be detrimental.

Stroke associated with IOH

Embolism is considered the primary cause of postoperative ischaemic stroke,[31] which may be related to presence of atrial fibrillation or surgery-induced hypercoagulability in combination with vulnerable plaques in carotid or major cerebral arteries.[17,18]

IOH is considered a major contributor to hypoperfusion and cited as a factor associated with postoperative stroke,[21-23] however, no association has been found between IOH and postoperative stroke in patients undergoing non-cardiac surgery.[32-34]

On the other hand, studies have demonstrated that increased blood velocity and turbulence can damage intimal cells and dislodge plaques.[35] Consequently, it could be that in those studies where a positive association between IOH and stroke exists, that vasoconstrictors were administered resulting in increased blood velocity/momentum and turbulence promoting plaque dislodgement with subsequent embolisation.

Surgery in the beach chair position is regarded as a particular risk to cerebral hypoperfusion with dependency on adequate BP. However, the administration of vasoconstrictors may not be the solution, and indeed may be the enemy. Cho's paper[36] in which prophylactic administration of vasoconstrictors to patient undergoing shoulder surgery in the beach chair position was associated with regional cerebral oxygen desaturation on upright positioning,[36] casts doubt on the merits of vasoconstriction to maintain cerebral perfusion.

Regarding haemorrhagic stroke, the administration of vasoconstrictors could conceivably be a contributory factor by promoting velocity-related turbulence to disrupt cerebral microaneurysms and subsequent rupture.

For a description of the physics and biophysical mechanisms underpinning these processes the author directs readers to Hademenos and Massoud's book.[37]

Myocardial ischaemia associated with hypotension

Walsh et al,[24] in their retrospective analysis of 33,000 patients, examined mean arterial pressure to determine predictors of postoperative morbidity and mortality. They concluded that mean arterial pressure (MAP) less than 55 mmHg predicted adverse cardiac and renal outcomes.

The risk of myocardial injury rose markedly with duration of hypotension when MAP was less than 55 mmHg in comparison with MAPs above this level. This association is clearly demonstrated in their paper. However, these findings warrant further consideration. Those patients in ASA categories III and IV constituted the greater proportion of patients with MAP < 55 mmHg at all durations. Such patients are at higher risk as predicted by their ASA status, which may include morbidity such as pre-existing poor cardiac function, or alternatively a reflection of more extensive major surgery with accompanying hypovolaemia.

The study by Walsh et al does not consider whether vasoconstrictors were administered, and if so, at what point. Administration of vasoconstrictors may have provoked adverse effects on blood flow and contributed to increased morbidity and mortality. It needs to be established whether vasoconstrictors were used and then compare outcomes with and without vasoconstrictors.

In an article by Howell, they propose that high arterial pressures are associated with high levels of afterload and cardiac work.[10] This serves as a logical explanation for the mechanism responsible for cardiac complications observed with hypertension. The combination of the need to meet tissue oxygen demand along with vessel rigidity and narrowing, results in hypertrophy of the myocardium with subsequent impairment of critical sub-endocardial blood flow. If myocardial demand exceeds reserves, and the ability to provide the necessary flow, then susceptible patients are at risk of developing ischaemia.

While this provides an explanation in patients with chronic hypertension, the same mechanism may contribute to similar outcomes when treating BP with vasoconstrictors. Overzealous or injudicious use of vasoconstrictors intraoperatively may precipitate a cardiac event in those prone to developing ischaemia due to the increase in afterload and therefore myocardial work and myocardial oxygen demand.

Aside from the increased afterload accompanying vasoconstriction, but equally important, is the effect of increased velocity of blood flow as vessels narrow, resulting in turbulent flow with intimal stress/disruption, and potential dislodgement of plaque within the coronary circulation.

Postoperative cognitive dysfunction

Deterioration in cognitive function following anaesthesia is the subject of considerable investigation and continues to be a focus as a major health concern. Several factors have been implicated, with anaesthesia being one of the most recently identified.[26]

One of the mechanisms under investigation is adequacy of cerebral perfusion and the need to maintain BP levels, although there is little evidence to indicate the appropriate level or target BP.[11] Hirsch et al concluded that absolute or relative hypotension was not predictive of postoperative delirium but rather it was the fluctuations in BP.[26]

Fluctuations in BP under anaesthesia arise because of numerous factors, including the administration of anaesthetic medications and other vasoactive drugs, including vasoconstrictors.

Further research comparing bolus administration of vasoconstrictors with infusions may shed some insight into whether it is the swings resulting from bolus administration that are the problem, or whether such problems occur even with constant infusions, in which case vasoconstrictors may be implicated irrespective of the means of their administration.

While earlier research suggested that the anaesthesia technique used, and selection of general anaesthesia was a contributing factor to POCD, more recent research is favouring other mechanisms on the basis that there appears to be no difference in the incidence of postoperative cognitive dysfunction between general anaesthesia and spinal or epidural techniques.[38,39] One of the hypotheses used to explain this observation is that regional techniques are often supplemented by the administration of sedative medications or sub-hypnotic doses of hypnotics.

However, another factor common to both general anaesthesia and regional anaesthesia is the intention to control BP, which is essentially achieved through the use of vasoconstrictors. This may explain the absence of any difference between general anaesthesia and central neural blockade, as vasoconstrictor administration is known to be associated with swings in BP irrespective of the anaesthesia technique.

VASOCONSTRICTORS – FRIEND OR FOE?

There is undoubtedly a place for the judicious use of vasoconstrictors, such as their direct and localised application to minimise blood flow to a region. This may include their local administration to minimise surgical bleeding, as with endoscopic sinus surgery,[40] for example. Administration of vasoconstrictors to the local surgical site increases local vascular resistance and, along with concomitant administration of vasodilators, systemically reduces systemic resistance thereby diverting flow away from the surgical site.

Alternatively, vasoconstrictors may be beneficial when aiming to reduce regional flow to minimise capillary leakage, as occurs with anaphylaxis and septic shock.

However, for control of trauma or damaged organ bleeding, any increase in generalised vascular resistance tends to aggravate blood loss due to the diversion of blood flow away from the general circulation to the damaged organs, which have lost the ability to alter their local vascular resistance. Use of vasodilators is often helpful in these settings by producing generalised vasodilatation, which facilitates diversion of blood flow away from the surgical site or damaged organ.

The assumption that BP determines flow promotes the intraoperative use of vasoconstrictors to treat hypotension and restore blood pressure back to "normal," for which there are consequences.

Arguments that have been proposed to support the use of vasoconstrictors include:

- Vasoconstriction diminishes peripheral flow with consequent diversion of blood volume centrally to maintain flow to brain, heart, and kidney. However, this is not supported by the distribution of alpha-1 receptors within the circulation. These receptors are widespread in the vascular smooth muscle of genitourinary, intestinal, cardiac,[41] and brain[42] and consequently, these organs are subject to the effects of alpha-1 agonists. While vasoconstriction aims to support BP on the premise that blood flow will be maintained to the central organs, this may not be the case, and in fact may prove to be harmful.
- Diastolic filling of coronary arteries can be maintained or improved as a result of vasoconstriction, which may have a beneficial effect on cardiac output. While coronary blood flow is maximal during diastole, it is also true that any increase in afterload results in an increase in wall tension, which decreases subendocardial flow and may precipitate an ischaemic event. Furthermore, the determinants of cardiac output are preload, afterload, and contractility. Administration of vasoconstrictors increases cardiac work and consequently may disproportionately increase oxygen/blood flow demand with likely adverse effects.
- Increasing afterload leads to an increase in left ventricular end-diastolic volume (LVEDV), with consequent increase in stroke volume and cardiac output. However, any increase in the LVEDV secondary to an increase in afterload has to be the consequence of reduced systolic emptying, which suggests that cardiac output is in fact diminished. This will then be compensated by an increase in contractility (and myocardial work) resulting from the increased myocardial muscle fibre length but represents an encroachment on myocardial physiological reserves.

- Administration of vasoconstrictors to avoid reductions in blood pressure in patients with left ventricular outflow tract obstruction is thought to be of benefit with regard to maintaining cardiac output in these patients. The problem with outflow tract obstruction being a resistance to flow is that it acts as a force opposing the propulsive force of myocardial contraction. Adding any additional opposing resistive force, in series with the outflow tract obstruction, despite the aim of maintaining blood pressure on the premise that this drives flow, can only have deleterious effects on cardiac output.
- Not all vasoconstrictors are the same and demonstrate varying alpha and beta receptor effects. This is indeed a valid argument to support the judicious use, which suggests that beta receptor agonists are indicated to support cardiac contractility where this is compromised. However, the use of pure alpha receptor agonists to manipulate blood pressure is regarded by the author as dubious.

CONCLUSION

IOH is not an uncommon event under anaesthesia, predominantly being attributable to changes in vascular resistance and to some degree, myocardial depression.

Vasodilatation under anaesthesia, with concomitant hypotension, presents a low resistance circulation with blood flow accompanied by reduced myocardial work. What then is the true benefit of administering vasoconstrictors to rectify a BP reading that may not in fact reflect flow?

Vasoconstrictors have an important application in surgery to reduce blood flow to surgical areas, with the aim of minimising bleeding and optimising the surgical field. However, intravenous administration to manage BP is another matter.

Regarding the effects of vasoconstrictors in increasing vascular resistance, increasing blood flow velocity with subsequent turbulence and intimal capillary damage, fluctuations in BP, or all of these combined, further research is required to establish the risks of vasoconstrictors and whether IOH is an indication for their use.

Hopefully, challenging accepted thinking and asking questions will provoke the research necessary to support further investigation and more refined answers.

REFERENCES

1. Lonjaret L, Lairez O, Minville V, Geeraerts T. Optimal perioperative management of arterial blood pressure. Integrated Blood Pressure Control. 2014:7; 49-59
2. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. Incidence of IOH as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. Anesthesiology. 2007;107(2):213-220
3. Klohr S, Roth R, Hofmann T, Rossaint R, Heesen M. Definitions of hypotension after spinal anaesthesia for caesarian section: literature search and application to parturients. Acta Anaesthesiol Scand. 2010;54(8):909-921
4. Pinsky MR. The right ventricle: interaction with the pulmonary circulation. Critical Care. 2016;20:266-274
5. Roessler P. Myths surrounding the relationship between blood pressure and blood flow. SIIC. 2017http://dx.doi.org/10.21840/siic/153992
6. Purkayastha S, Raven PB. The functional role of the alpha-1 adrenergic receptors in cerebral blood flow regulation. Indian J Pharmacol. 2011 Sep;43(5):502-6
7. Jacob M, Chappell D, Becker B F. Regulation of blood flow and volume across the microcirculation. Critical Care (2016) 20:319
8. Phillips SJ. Pahtophysiology and Management of Hypertension in Acute Ischaemic Stroke. Hypertension. 1194;23(1):131-136
9. Li C, Engström G, Hedblad B, Berglund G, Janzon L. Blood Pressure Control and Risk of Stroke. A Population-Based Prospective Cohort Study. Stroke. April 2005;36;725-730
10. Howell SJ,Sear JW, Foëx P. Hypertension, hypertensive heart disease and perioperative cardiac risk. BJA. 2004;92(4):570-583
11. Ward M, Langton JA. Blood pressure measurement. Continuing Education in Anaesthesia, Critical Care & Pain. 2007;7(4):122-126
12. Owens PE, Lyons SP, O'Brien ET. Arterial hypotension: prevalence of low blood pressure in the general population using ambulatory blood pressure monitoring. J Hum Hypertens. 2000 Apr;14(4):243-7
13. Raven P, Chapleau MW. Blood Pressure Regulation XI: Overview and Future Research Directions. Eur J Appl Physiol. 2014;114(3):579-586
14. Lau EOC, Lo CY, Mak AFT, Jiang L, Huang Y, Yao X. Aortic Baroreceptors Display Higher Mechanosensitivity than Carotid Baroreceptors. Frontiers in Physiol. 2016;7(Article 384):1-8
15. Cupples WA, Braam B. Assessment of renal autoregulation. Am J Renal Physiol. 2007;292:F1105-F1123
16. Olufsen MS, Ottesen JT, Tran HT, Ellwin LM, Lipsitz LA, Novak V. Blood pressure and blood flow variation during postural change from sitting to standing: model development and validation. J Appl Physiol. 2005;994(4):1523-1527

17. Johnson PC. Autoregulation of Blood Flow. Circulation Research. 1986;59(5):483-495
18. Bijker JB, Persoon S, Peelen LM, Moons KG, Kalman CJ, Kappelle LJ, van Klein WA. IOH and Perioperative Ischemic Stroke after General Surgery: A Nested Case-control Study. Anesthesiology. 2012;116(3):658-664
19. Bijker JB, Gelb W. The role of hypotension in perioperative stroke. Can J Anaesth. 2013;60:159-167
20. Kam PCA, Calcroft RM. Peri-operative stroke in general surgical patients. Anaesthesia. 1997;52:879-883
21. Lindop MJ. Complications and Morbidity of Controlled Hypotension. BJA. 1975;47:799-803
22. Enderby GEH. A Report on Mortality and Morbidity Following 9,107 Hypotensive Anaesthetics. BJA. 1961;33:109-113
23. Monk TG, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping STJ, Bentt DR, Nguyen JD, Richman JS, Meguid RA, Hammermeister KE. Association between IOH and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. Anaesthesiology. 2015;123(2):307-319
24. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI. Relationship between Intraoperative Mean Arterial Pressure and Clinical Outomes after Noncardiac Surgery. Toward an empirical Definition of Hypotension. Anaesthesiology. 2013;119(3):507-515
25. Brown C, Deiner S. Perioperative cognitive protection. BJA. 2016;117(S3):iii52-iii61
26. Fodale V, Santanaria LB, Schifilliti D, Mandal PK. Anaestheitics and postoperative cognitive dysfunction: a pathological mechanism mimicking Alzheimer's disease. Anaesthesia.2010;65:388-395
27. Hirsch J, DePalma G, Tsai TT, Sands LP, Leung JM. Impact of IOH and blood pressure fluctuations on early postoperative delirium after non-cardiac surgery. BJA. 2015:418-426
28. Britannica, The Editors of Encyclopaedia. "Newton's laws of motion". Encyclopedia Britannica, 27 Mar. 2023, https://www.britannica.com/science/Newtons-laws-of-motion. Accessed 8 April 2023.
29. Levy MN. The Cardiac and Vascular Factors That Determine Systemic Blood Flow. Circulation Research. 1979;44(6):739-747
30. Peterson LH. The Dynamics of Pulsatile Blood Flow. Circulation Research. 1954;2:127-139
31. Semat H, Katz R. Physics, Chapter 9: Hydrodynamics (Fluids in Motion). Robert Katz Publications. 1958:164-181
32. Selim M: Perioperative stroke. N Engl J Med 2007; 356:706–13
33. Limburg M, Wijdicks EF, Li H: Ischemic stroke after surgical procedures: Clinical features, neuroimaging, and risk factors. Neurology 1998; 50:895–901
34. Hart R, Hindman B: Mechanisms of perioperative cerebral infarction. Stroke 1982;13:766 –73
35. van Wermeskerken GK, Lardenoye JW, Hill SE, Grocott HP, Phillips-Bute B, Smith PK, Reves JG, Newman MF: Intraoperative physiologic variables and outcome in cardiac surgery: Part II.Neurologic outcome. Ann Thorac Surg 2000; 69:1077–83
36. Fry DL. Acute Vascular Endothelial Changes Associated with Increased Blood Velocity Gradients. Circulation Research 1968;22:165-197
37. Cho SY, Kim SJ, Jeong CW, Jeong CY, Chung SS, Lee J, Yoo KY. Under general anaesthesia arginine vasopressin prevents hypotension but impairs cerebral oxygenation during arthroscopic shoulder surgery in the beach chair position. Anaesth Analg. 2013;117(6):1436-1443
38. Hademenos GJ, Massoud TF. The Physics of Cerebrovascular Disease. Biophysical Mechanisms of Development, Diagnosis and Therapy. Springer-Verlag NY Inc. 1998: pp145-149
39. Tzimas P, Samara E, Petrou A, Korompilias A, Chalkias A, Papadopoulos G. The influence of anesthetic techniques on postoperative cognitive dysfunction in elderly patients undergoing hip fracture surgery: genera vs spinal anesthesia. Injury 2018;49(12):2221-2226
40. Higgins, T.S., Hwang, P.H., Kingdom, T.T., Orlandi, R.R., Stammberger, H. and Han, J.K. (2011), Systematic review of topical vasoconstrictors in endoscopic sinus surgery. The Laryngoscope 2018;121: 422-432.
41. Bacal F, et al. Heart failure: Influence of drug interventions on vessels. Endothelium and Cardiovascular Diseases, Vascular Biology and clinical Syndromes. 2018;Chap 39:575-588
42. Davis N, Lee M, Lin AY, Lych L, Monteleone M, Falzon L, Ispahany N, Lei S. Post-operative cognitive dysfunction following general versus regional anesthesia, a systematic review. J Neurosurg Anesthesiol. 2014;26(4)369-376

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Magical distraction for induction of paediatric anaesthesia

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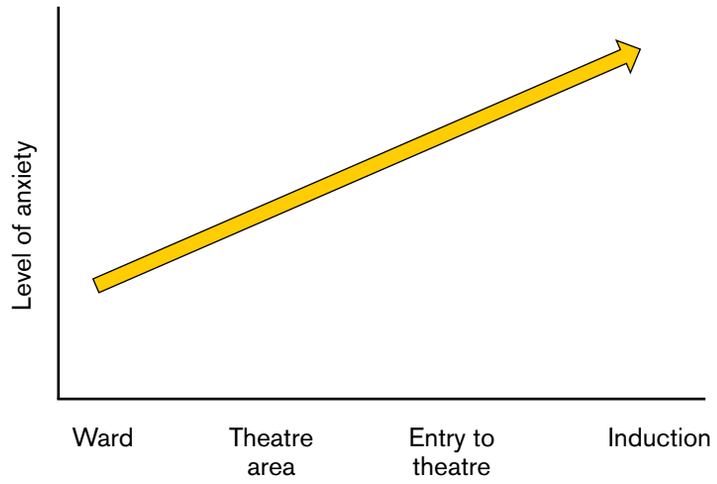
INTRODUCTION

Between 40 and 60% of children are anxious before anaesthesia and surgery, resulting in some becoming uncooperative at induction but also having effects persisting after anaesthesia. Anxiety can be reduced with a combination of education, behavioural and pharmacological techniques. Research shows the child's experience of anxiety is greatly affected by the anaesthetist's choice of words and behaviour. Distraction is a very important behavioural technique the anaesthetist can use at the time of induction to reduce a child's anxiety by keeping their focus away from the procedure. Current research focuses on virtual reality as a form of distraction, although this may involve complex and expensive systems. After a brief overview, this article will give a practical approach to managing induction by taking advantage of the powerful distraction from three simple magic tricks suitable for children aged four years and older. Magical distraction is so strong, that children can be thrilled and laughing as they fall asleep, perhaps reducing the likelihood of emergence delirium. It also distracts and relaxes the parent at the time of induction. After using this technique over the past twenty years and for thousands of children, the author has lost count of the number of frightened children assisted, and of the grateful words and notes of thanks.

ANXIETY AT INDUCTION OF ANAESTHESIA

A child's anxiety increases as they progress towards surgery, with induction of anaesthesia being the most stressful part of hospital admission[1] (Figure 1). Signs of anxiety include crying, screaming, becoming quiet and withdrawn, expressing fear or sadness or lack of cooperation. These signs of anxiety are very common: One sign is present in 42% of 2 to 10-year-olds, and three or more signs detected in 17% at induction.[2] Anxiety is more common in children aged one to five years, those who have a shy, inhibited, or anxious temperament, have had a difficult or 'stormy' induction before, or have very anxious parents.[3]

Figure 1. A child's anxiety increases during their journey towards theatre and induction, although there is variation between children depending on their temperament, past experiences, and other factors. Based on Chorney and Kain.[2]



CONSEQUENCES OF ANXIETY AT INDUCTION

Anxiety can reduce cooperation at induction, with up to 25% of young children who have not received a sedative premedication requiring restraint at this time[1]. However, the effects of this anxiety persist beyond induction. Children who have a difficult induction that necessitates restraint are more likely to be agitated when awakening, have increased pain and behavioural changes after surgery, and may become more anxious about future anaesthetics (Figure 2).

Behavioural changes include clinginess and separation anxiety, sleep disturbances and night terrors, food refusal, temper tantrums, and enuresis. Up to 60% of children have behavioural changes on the first postoperative day.[1,4,5] They commonly persist for three days after discharge, but sometimes for a few weeks or even months (Figure 3). Of the children who have emergence delirium, one in four have an increased incidence of behavioural changes one week postoperatively.[6]

Figure 2. Preoperative anxiety may affect emergence from anaesthesia and cause dysfunctional behaviour in the postoperative period. This experience may then increase the child's anxiety at the next anaesthetic.

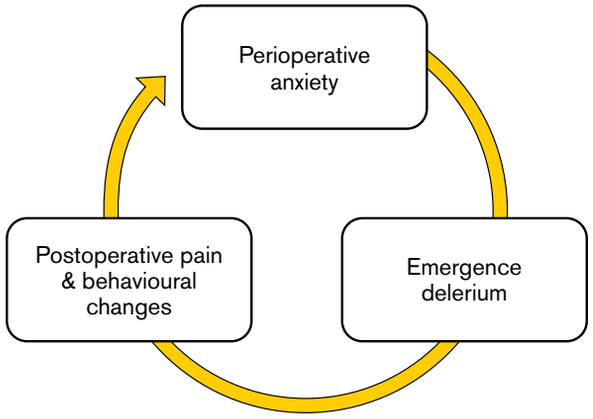
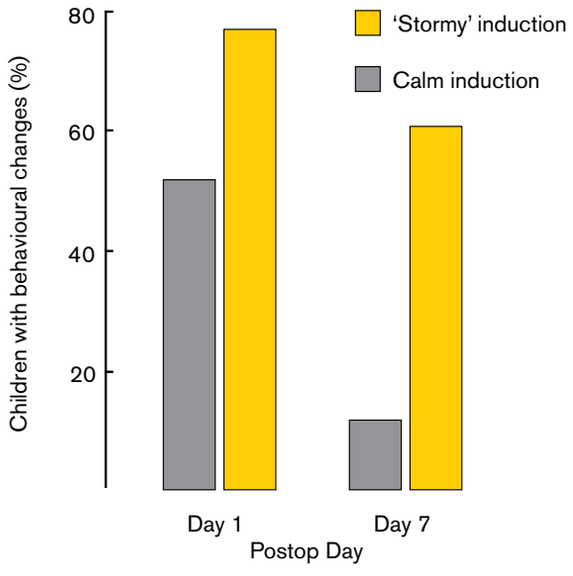


Figure 3. A difficult or 'stormy' induction is associated with an increased incidence of behavioural changes after anaesthesia. Based on Kain et al.[1]



REDUCTION OF ANXIETY AT INDUCTION

Reducing a child's anxiety leading up to and including induction reduces pain and behavioural disturbances in PACU and later. A small group of children will be calm and cooperative at induction no matter what strategies the anaesthetist employs. There is also a small group of children who will likely be unhappy and uncooperative no matter what the anaesthetist does. In the middle is a large group whose anxiety can be managed, and their cooperation maintained. The aim in this group is to maintain a low level of anxiety and prevent tipping into a frightened and uncooperative state. It is important to prevent tipping, because once this has happened it can be very difficult to reduce the child's anxiety and regain their cooperation. The techniques to reduce a child's anxiety at the time of surgery include those educating and preparing the child and parent before admission, pharmacological premedication, and behavioural techniques in hospital.

Education techniques

Preparation programs are optimal if they teach the child coping skills to deal with their anxiety. This requires significant resources, and these programs are not commonly used.[7] The use of individualised video and virtual reality technology may make these programs common again. For the time being, information brochures and websites are the commonest form of education, though they are the least effective. The preoperative phone call to the carer and assessment of the child remains the commonest individualised education and preparation.

The preoperative period is also the time to introduce to the child any distraction technique planned, such as a video or a story. Finally, assessing the child before theatre also gives time for pharmacological premedication, when required.

Pharmacological techniques

Premedication effectively reduces preoperative anxiety. Its use should be targeted however to allow for risk factors such as the child's age, the duration of surgery and the potential for delayed recovery. When pharmacological premedication is needed, the commonest agents are clonidine 60 minutes before induction or midazolam 30 minutes before induction. Comparisons of the two premedications in preschool age children give diverging results when the effect on anxiolysis is the primary study outcome. A recent study of children between the ages of 2-6 years old showed midazolam gave better anxiolysis and less sedation than clonidine or dexmedetomidine.[8] Midazolam may sometimes cause dysphoria and amnesia after waking though, which should be taken into consideration. However, midazolam does not have to be rigidly dosed at 0.5mg/kg. The dose can be between 0.25 and 0.5mg/kg, administered 30 minutes before induction.[9] It seems plausible that titrating the dose according to the age of the child and their level of anxiety would reduce the likelihood of postoperative dysphoria.

Behavioural techniques

Parental presence at induction is a standard role in caring for children. Even though it does not reduce the child's anxiety at the time of induction, it avoids separation from their carer and increases parental satisfaction. It is part of modern 'family-centred' care.

The anaesthetist can use positive reinforcement and distraction to reduce the child's anxiety at induction. The behaviour of the anaesthetist – what they say and do – can worsen or lessen the child's anxiety.[10,11] Distraction, humour, and talking about something other than the procedure help the child cope with their situation and reduces their anxiety. On the other hand, reassuring, apologising, empathising, criticising, or allowing the child too much control over the procedure focuses them internally, and on their situation, increasing their anxiety and possibly making them inaccessible due to fear (Table 1a and 1b).

Table 1a. Staff and anaesthetist behaviours that reduce a child's anxiety at induction. Distraction shifts attention away from the induction and reduces anxiety. Based on Martin et al.[9]

Anaesthetist behaviours that reduce the child's anxiety	
Staff behaviour	**Example**
Non-procedural, distracting talk	Magic Talking about toys, pets, favourite movies Story telling
Humour	Jokes Funny story
Clear choices that do not allow avoidance of procedure	"Do you want me to hold the mask or your dad (or insert name of parent or carer) to hold it?" "Strawberry or chocolate mask?" "Walk or ride on the trolley?" "Do you want to climb onto the bed or mum to lift you?"
Medical play and describing visible equipment in no threatening terms	Astronaut space mask Green balloon bag
One adult talking	Only one person distracting the child
Firm warm confidence	Speaking with calm clear voice with sense of leadership
Good word choice	Metal tube, plastic straw, perfume smell. Focusing on what child can do rather than not do

Table 1b. Staff and anaesthetist behaviours that increase a child's anxiety at induction. Reassuring, empathic statements focus the child on their feelings of distress and increase anxiety. Based on Martin et al.[10]

Anaesthetist behaviours that increase the child's anxiety	
Staff behaviour	**Example**
Reassurance, empathy, and apologising	"You'll be OK", "Don't worry", "I know it's hard", "I'm sorry"
Excessive technical or medical talk	Too much information about the procedure or equipment, especially immediately before theatre
Suggesting control when the child actually has none	"Can I put the mask on now?" "Are you ready to come to theatre now?" "Do you want to climb up on the bed?"
Multiple adults talking	Child not focused on interacting with one person
Allowing child to delay	"Just a minute", or "Wait, I just want to…"
Poor word choice	Needle, sting, hurt, smelly. Focusing on what child can't do

The words chosen by the anaesthetist also affect the child's behaviour. Framing discomfort using playful, imaginative, or abstract language is helpful – "sparkles" up the arm rather than "this may sting a little", or "a beautiful perfume" rather than "this gas might smell". Speaking in a slow rhythmic manner can be somewhat hypnotic and help hold a child's attention. The choice of words and phrases used at this time are important and have been well discussed by Allan Cyna and his group in Adelaide.[12] Finally, the anaesthetist's posture, facial expression and where they stand relative to the child may also affect the child's anxiety.

Distraction is a very important technique in reducing the child's anxiety. The aim is to get the child's attention and keep their focus away from the procedure. Distraction can be achieved many ways, and although some children will be relaxed with simple non-procedural talk about school or toys, other children are more anxious and benefit from stronger distraction. Various techniques have been studied and assessed in a Cochrane review.[13] Current research tends to focus on electronic devices such as videos, handheld games, and virtual reality headsets.[14] Some of these techniques are complex, expensive, or cumbersome. Furthermore, it seems the child is better distracted if they are actively participating with the technique. One comparison showed actively playing a video game distracted the child and reduced anxiety, but just watching a video did not.[15] The novelty of the device is also important. Passively attempting distraction by just showing a video on a phone might not have enough impact.[16]

Strong, effective distraction starts early, is continuous, and increases as induction progresses, (Table 2) with a goal of preventing the child 'tipping' to an uncooperative state. A distraction is made powerful by its novelty and by building a sense of anticipation so the child is looking forward, or even excited, to find out what will happen. For a story, this might mean beginning it in the preoperative area. For a video or game, it might mean starting to watch it or choosing aspects of the game in the preoperative area. The distraction is maximised if the child's interest is held while they enter theatre, rather than their focus shifting to looking around and becoming worried.

Simple magic tricks are a powerful distraction because they are novel, colourful, and partly performed by the child. Unlike videos, children don't often see or experience them. Magical distraction has the practical benefits of being cheap, mobile, reliable, and easily accessed in theatre. Although some tricks need some skill, this form of distraction removes the need for the anaesthetist to make up stories, sing, remember jokes, or think of topics for conversation.

Table 2. The effectiveness of any distraction used by the anaesthetist can be maximised.

Effective distraction
Is interesting and new to the child
Gets child's attention as soon as they enter theatre
Begins with a sense of anticipation to build excitement
Increases as induction approaches and anxiety increases
Is continuous with no pauses or gaps that might lose child's attention
Has the strongest distraction saved for the time of mask acceptance or cannula insertion when anxiety is maximal

MAGICAL DISTRACTION

The author was fortunate to have learnt magical distraction from Professor Chris Abajian in Vermont, about 20 years ago.[17] Since then, he has employed three simple tricks at induction of children aged four years and older.

These simple tricks are easily carried, perhaps in a pocket, and are easy to clean and reuse. The overarching story presented to the child is that they will be able to colour-in with their finger by magic, immediately building a sense of anticipation (or disbelief) for them to look forward to. The three tricks used by this author are the zig zag pencil, a simple sponge ball trick, and a magic colouring book. They are used in this order, as they become more impressive and more distracting, flowing nicely to the start of induction. They are also effective tricks because the child is actively involved in doing them, rather than just watching. The details of the three tricks are in the Appendix, but an overview of what they are and how they help the child is given below.

Zig zag pencil in the waiting area

The idea of the child being able to colour-in by magic with their finger is discussed at the preoperative assessment. The zig zag pencil is used to reinforce the idea of magic, and to give some proof that the child really will have magical powers. This trick requires zero skill and takes 30 to 60 seconds, during which a pencil appears to be chopped into three pieces, then magically re-joined.

Sponge balls in the preoperative area

The second trick uses sponge balls and is performed immediately before the child is taken to theatre, so its distraction power is maximal. It is an impressive trick that first makes one ball become two, and then two become three, all in the child's hand. The child is then left holding the three balls and is challenged to turn them into four. The child becomes distracted right up to entering theatre, excited at the thought of learning how to make four balls. This trick is sophisticated enough to distract some anxious teenagers, as they can become very nervous at the time of induction even though they usually maintain their cooperation.

Magic colouring book in theatre

As the child enters theatre, their attention is immediately grabbed by the anaesthetist holding up the colouring book to show them. This maintains their focus, as they look at it and not around the theatre environment. Now is also the time to make the fourth ball appear. Either as the trolley is brought into the induction room, or positioned beside the operating table, or as the child walks up to the table to climb onto it. The fourth ball appearing is a 'wow' moment for the child (and parent) and makes them happy to climb onto the operating table or be in the induction room.

Maintaining the flow and without pauses, the colouring trick is begun. The magic colouring book first has outlines, then becomes coloured, then becomes blank, then the outlines reappear.

What happens after the magic?

The child is impressed and excited. They did magically colour-in like you said they would. Now they are much more likely to comply with the next stage of induction. They are even perhaps looking forward to what happens next and if there is another trick. The magical distraction is best maintained when flowing into an inhalational induction. It is also helpful with an intravenous induction, but it is more difficult for the anaesthetist to maintain distraction while concentrating on the IV insertion. There are many ways to proceed from here, and each anaesthetist will have their preferred approach.

To maintain the flow of the induction, this author introduces the mask by touching it on the child's hand where they can see and feel it, then places the mask onto the bridge of the nose. The lower portion of the mask is kept off the mouth at first, so the child doesn't feel a change in their breathing while getting used to the mask in their personal space.

The mask is lowered on to the mouth as the rebreathing bag is held up and the child challenged to blow it up in five breaths. There could be lots of different stories or words that are used at this point, but here is one of them: After the bag has been blown up by the child, relate a simple story about their magic powers making the balloon get bigger and smaller. Touching the bag on their hand adds another sensory input and is a new distraction to the child. As the sevoflurane is introduced, the child is asked to hold the parent's hand because they might get dizzy, like being on a merry-go-round. This focuses the child on the touch of the hand rather than the smell of the gas. If the mother is present, it's nice to say the smell might be like a perfume mum wears when she goes out, which often gets a laugh from the mother and perhaps relaxes the child further. The anaesthetist holds the child's other hand, and it is gently rotated around and around, like a merry-go-round. Thus, the anaesthetist has control of that hand, the parent has the other hand, and the child is distracted in a new way.

This author prefers to give nitrous oxide in oxygen for about 20 seconds before sevoflurane is begun, and until the sevoflurane has begun to have an effect. There is no need to incrementally increase sevoflurane as opposed to beginning at 8 per cent, especially if the circle circuit is being used.[18]

SUMMARY

Distraction is the most important and effective way of reducing a child's anxiety at the time of induction. Distraction using three simple magic tricks has been presented. This is a powerful form of distraction since children don't usually see or experience magic close up. The zig zag pencil, sponge balls, and magic colouring book require little skill or effort, but will distract patients, who will be much more likely to remain cooperative at induction. Magical distraction is so powerful, children can be thrilled and laughing as they fall asleep, which would be expected to reduce the likelihood of emergence delirium. The tricks also distract and relax the parent, are enjoyed by staff, and will have children asking if they can please have the 'magic doctor' next time they have an anaesthetic.

REFERENCES

1. Kain Z, Mayes L, Caramico L, Hofstadter M. Distress during induction of anesthesia and postoperative behavioral outcomes. Anesth Analg 1999;88:1042–7.
2. Chorney JM, Kain ZN. Behavioral analysis of children's response to induction of anesthesia. Anesth Analg 2009;109:1434-40.
3. Kain ZN, Caldwell-Andrews AA. Preoperative psychological preparation of the child for surgery: An update. Anesthesiol Clin N Am 2005;23:597-614
4. Kotiniemi LH, Ryhanen PT, Moilanen IK. Behavioural changes in children following day-case surgery: a 4-week follow-up of 551 children. Anaesthesia 1997;52:970–6.
5. Aono J, Mamiya K, Manahe M. Preoperative anxiety is associated with a high incidence of problematic behavior on emergence after halothane anesthesia in boys. Acta Anaesthesiol Scand 1999;43:542-4.
6. Kim J, Byun SH, Kim JW, Kim J, Kim YJ, Choi N et al. Behavioral changes after hospital discharge in preschool children experiencing emergence delirium after general anesthesia: A prospective observational study. Ped Anesth 2021;31:1056-64.
7. Kain ZN, Caramico LA, Mayes LC, Genevro JL, Bornstein MH, Hofstadter MB. Preoperative preparation programs in children: a comparative examination. Anesth Analg. 1998;87:1249-5.
8. Bromfalk A, Myrberg T, Wallden J, Engstrom A, Hultin M. Preoperative anxiety in preschool children: A randomized clinical trial comparing midazolam, clonidine and dexmedetomidine. Ped Anesth 2021;31:1225-33.
9. Cote CJ, Cohen IT, Suresh S, Rabb M, Rose JB , Weldon C et al. A comparison of three doses of commercially prepared oral midazolam syrup in children. Anesth Analg 2002;94:37-43.
10. Martin S et al. Changing healthcare providers' behavior during pediatric inductions with an empirically based intervention. Anesthesiol 2011;115:18-27
11. Litman RS. Allaying anxiety in children: When a funny thing happened on the way to OR. Anesthesiol 2011;115:4-5.
12. Laing R, Cyna A. Hypnosis and communication in paediatric peri-operative care. In: Riley R (Ed) Australasian Anesthesia. Melbourne: Aust NZ College Anesthetists, 2017. pp 273-9.
13. Manyande A, Cyna AM, Yip P, Chooi C, Middleton P. Non-pharmacological interventions for assisting the induction of anaesthesia in children. Cochrane Database Syst Rev. 2015 Jul; 2015(7): CD006447.
14. Rodriguez S, Caruso TJ. What every anesthesiologist should know about virtual reality. Ped Anesth 2022;32:1276-7.
15. Sakizci Uyar B, Polat R, Bolat M, Donmez A. Which is good for pre-operative anxiety? Midazolam, video games or teaching with cartoons. EJA 2021;38:744-50.
16. Rodriguez S, Caruso TJ, Tsui B. Bedside entertainment and relaxation theatre: size and novelty does matter when using video distraction for perioperative pediatric anxiety. Ped Anesth 2017;27:668-9.
17. Abajian JC. Magical Distractions. Presented at the Society for Pediatric Anesthesia Annual Scientific Meeting, Chicago, October 2006. Available at http://www2.pedsanesthesia.org/meetings/2006annual/syllabus/MagicalDistractions-Abajian.pdf (Accessed Aug 2023)
18. Lerman JL. Induction of anesthesia with sevoflurane in children: Curiosities and controversies. Ped Anesth 2022;32:1100-3.

APPENDIX

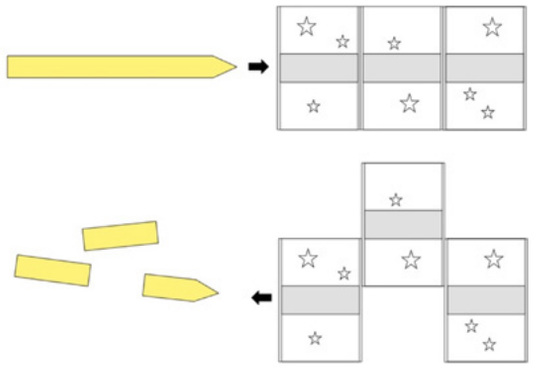
This section describes the three distraction tricks in detail. All three are available online from magic shops.

The zig zag pencil

A pencil is cut into three pieces, then 'glued' back together (Figure 1). The instructions supplied with the pencil are easy to follow, and the device can be easily cleaned between uses. The child can be involved with the trick rather than just watching, asking them to put the pieces back into the device and push it shut.

Video at https://www.youtube.com/watch?v=H5GFCGwUuTQ (accessed August 2023)

Figure 1. The zig zag pencil, which magically cuts and re-joins a pencil.



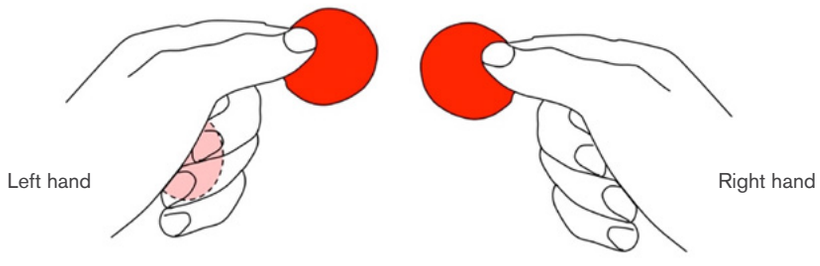
Sponge balls

Sponge balls are soft, compressible red foam balls, 1.5 inches in diameter, that come in packs of four. There are many brands, including 'Magic by Gosh'. They can be cleaned using some types of hand sanitiser.

Children need to be at least four years old to be able to do this trick. The child begins with one red ball, which turns into two, then three. The magic happens in their hand, making it a strong distractor shortly before anaesthesia. The child is left with the three balls and challenged to make four, either just before going to theatre, or while being taken around to theatre. The child is focused on trying to make the fourth ball appear when they enter theatre, taking their attention off the theatre environment. The anaesthetist makes the fourth ball appear in the child's hand upon entry to theatre, amazing the child and helping make them happy to climb onto the operating table, or just being within the induction room.

Step 1. In the right hand, the anaesthetist holds one ball between thumb and index finger and clenches the remaining fingers. In the left hand, a ball is also held between thumb and index finger, but a third ball is hidden in the clenched fist (Figure 2). The anaesthetist secretly gives the child both balls from their left hand, getting the child to clench their fist around the balls so their presence is not revealed. It's easy to hide the other ball in this move so the child thinks they have only been given one ball. Meanwhile, the anaesthetist has a fourth ball hidden in their left scrubs pocket for future use.

Figure 2. The anaesthetist's view of the first step. A ball is between the fingertips of both hands, but another is within the clenched left hand. Both hands need to be clenched to avoid suspicion.



Step 2. This step is the most difficult part. It is usual to feel self conscious when doing it, but the audience is a young child, not a live TV audience! The anaesthetist now has a ball visible in their right hand, and this needs to disappear. This is done by quickly 'palming' the ball into the left hand (Figure 3). The ball in the fingertips of the right hand is poked into the palm of the left hand, and is held there by bringing the thenar and hypothenar eminences together, puckering the palm and gripping the ball. As soon as the ball is within the left hand, the right hand is taken away and clenched in a fist. At the same time, the left hand with the palmed ball is kept facing down to conceal the ball, and placed flat on a surface so it doesn't look like anything is in it. This flat surface can be the bed sheet (Figure 4), or the knee or thigh (if the anaesthetist is crouching), or within the hand clenched around the railing of a patient trolley. Clenching the left hand or looking at it gives away the secret.

At this stage, the child believes they have a ball in their fist and the anaesthetist has a ball in their clenched right fist, when in fact the anaesthetist's ball is in their flat left hand.

Figure 3. The anaesthetist's view of the second step. The ball between the fingertips of the right hand is poked into the palm of the left hand and held there by puckering the hand. The right hand is immediately clenched into a fist while the left hand, with the ball, is lain flat on a surface.

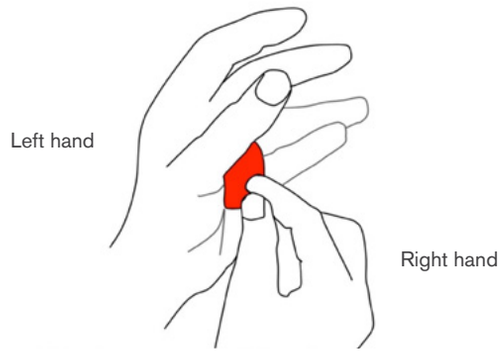
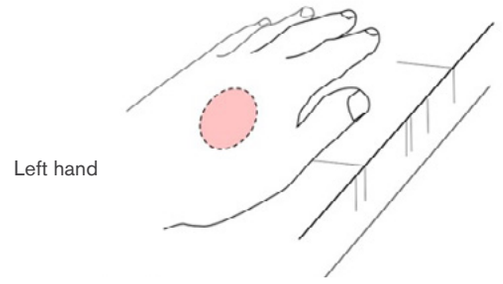


Figure 4. The anaesthetist's view of the third step. The ball is squashed under the hand, held against the bed sheet. This hides it and makes the child think the ball is the anaesthetist's clenched right hand.



Step 3. After an 'abracadabra', or blowing magic, the anaesthetist and child open their hands. The child is amazed they have two balls and the anaesthetist has none!

Step 4. Next, the third ball will be revealed. This ball is currently in the anaesthetist's left hand. The anaesthetist uses the right hand to take the two balls from the child, then places them into their left hand where the third ball already is, then gives the child all three balls into their clenched fist.

Step 5. After another 'abracadabra' or blowing magic, the child is asked to open their hand, revealing three balls this time. The child is now challenged to turn them into four while the anaesthetist either leaves to ready theatre, or escorts the child around to theatre.

Step 6. Immediately upon entry to the induction room or theatre, the fourth ball is made to appear. The fourth ball from the scrubs pocket is hidden in the anaesthetist's left hand before the child enters the room. Similar to step 5, the three balls are taken from the child, added to the fourth within the left hand, then all four are given to the child.

This might seem a complicated trick to carry out, but after several times it becomes easy and natural. The magical distraction is impressive and powerful for both child and parent, and is a great reward for doing it. It is also a useful distractor for nervous teenagers, who can be challenged to work out how it is done and how to make a fourth ball. A phrase like "You're way too old for this trick, but your mum will like to watch it" also makes it more acceptable to a teenager.

Video of a similar routine https://www.youtube.com/watch?v=iiegjl46pPk (accessed August 2023)

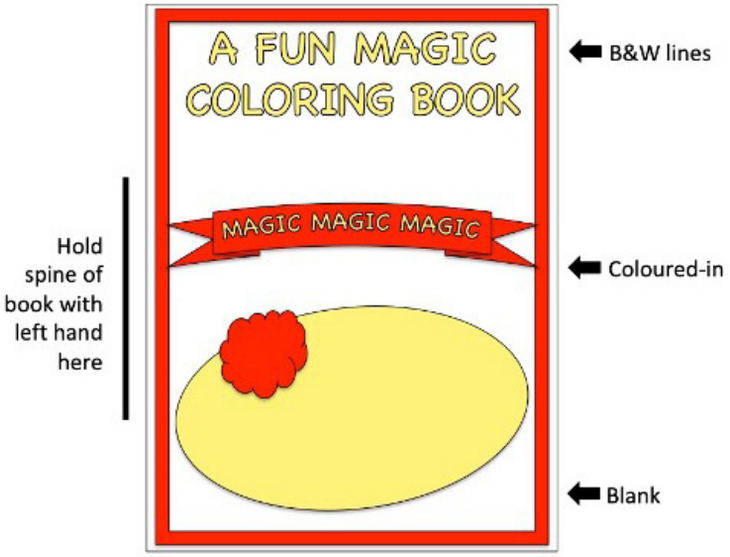
The magic colouring book

This is the final trick that the anaesthetist has been telling the child they will be able to do all along, building anticipation and distraction power. The book pages alternate between simple outlines, coloured-in, or blank, depending on where the right-hand side of the book is held while turning the pages (Figure 5). If the book is protected by a clear plastic book covering, it can be wiped over to clean.

Children aged about three and a half years and older can do this trick. After demonstrating the outline drawings inside, the anaesthetist can ask the child to press some part of the front cover and say 'abracadabra', before making the coloured pages appear. The child can then be asked to turn the pictures back, but the pictures mysteriously become blank. Finally, the child can make the outlines come back as at the beginning.

Video at https://www.penguinmagic.com/p/73 (accessed August 2023).

Figure 5. The magic colouring book.



The spine of the book is held in the left hand, and the pages flipped using the thumb and forefinger of the right hand. The arrows show the effect of flipping the pages with the fingers in the three positions.