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Editor-in-Chief Introduction

Dr Mabel Leow, MD PhD
Editor-in-Chief, AMSJ

Welcome to Volume 11, Issue 2 of the Australian Medical Student Journal.

After battling the Covid-19 for more than 2 years, we are glad to be moving into a new norm of living with the virus. As countries lift their restrictions, everyone is looking forward to travelling, resuming overseas placements, and research work. However, do take extra vigilance when you are in the clinical setting. Practicing good hygiene and wearing a mask will keep you safe! Also, don't forget to practice self-care (physical and mental) in the midst of the busy study-load and clinical placements.

This issue consists of 11 articles with a mix in variety of styles – One original article, two literature reviews, three case studies, two featured articles, one letter, and two covid-19 reflections. The topics ranged from diagnosis and treatment of specific diseases, to medical education and regulations. Papers on specialisation preferences and regulations will provide students with updated information of current trends.

As research activities resume, we look forward to receiving more article submissions. To ease the process of submission, we have finally managed to acquire the Open Journal System (OJS). In future, you can submit your manuscript through the OJS. We are constantly exploring ways to improve the journal, and we look forward to your feedback.

Finally, I'm grateful to the entire AMSJ team who have made this issue possible. Much thanks to the internal who have helped with putting together the manuscripts to form the issue and doing the artwork, and external team with their ongoing help with publicity and seeking for fundings. I also appreciate the editors in the editorial team who work tirelessly to maintain the quality of the manuscripts, and proofreaders who check for language errors.

We hope that this issue will inspire you to get involve in research activities, and broaden your knowledge in the field of Medicine.

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Feature Article

Unique opportunities as an Assistant in Medicine during COVID-19 pandemic.

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Dr. Madison Boot graduated from medicine at the University of Wollongong. She previously completed a Bachelor of Biomedical Science at the University of Notre Dame Australia. She is currently completing her internship at Wagga Wagga Base Hospital. Dr. Boot has a personal interest in surgical oncology. **Dr. Pippa Burns** completed a Bachelor of Science (Honours), Master's in Public Health (distinction) and went onto do a PhD.

Key learning points

- This feature article is a reflection on my time as an Assistant in Medicine during the COVID-19 pandemic. It is also a review of similar pre-internship models and their outcomes for professional development leading into internship.

Abstract

Introduction: In Australia, the coronavirus disease of 2019 (COVID-19) pandemic led to the formation of a new and unique role within the medical system, known as the Assistant in Medicine. The Assistant in Medicine program involved a group of selected final-year medical students joining the workforce as a government initiative to expand and reallocate hospital resources.

Discussion Overview: This reflection explores the unique opportunities in professional development as an Assistant in Medicine. Similar pre-internship models seen in New Zealand reported higher levels of competence and preparedness for internship compared to other final-year medical student placement models (92% in New Zealand, compared to 58% and 64% in the UK and Australia, respectively). These positive outcomes lead to an interesting question: could the Assistant in Medicine placement or a modified version be integrated into Australia's final-year medical student curriculum?

Keywords: medical education; pre-internship training; professional development; Assistant in Medicine; COVID-19

Introduction

The COVID-19 pandemic has had a devastating impact worldwide, with over 3.9 million lives lost. In anticipation of a COVID-19 outbreak, the Australian government implemented many strategies to protect and support our healthcare system. These included international and interstate border closures, lockdowns, health education, and reallocation of hospital resources, including the 'Assistant in Medicine' (AiM) program. The Australian government implemented the AiM role as part of the COVID-19 medical surge workforce to supplement existing junior medical officers (JMOs). The purpose of the position was to provide medical care and support as part of the multidisciplinary team (MDT) while working under supervision. This reflection explores the unique professional development opportunities that the AiM position provides and its comparison to other pre-internship programs. In particular, New Zealand's 'trainee intern' program leads to higher rates of preparedness for internship compared to current Australian and British medical schools.

Discussion

The Assistant in Medicine role

Final-year medical students were selected based on a combination of medical school grades, an AiM specific exam, and a written expression of interest. A training intensive boot camp was conducted before selection; this covered standard ward calls, training in basic and advanced life support, and everyday JMO tasks. Roughly 200 candidates across New South Wales (NSW) were selected.

I was assigned to the radiation oncology team within a regional hospital and assisted in outpatient and inpatient medical care. The AiMs worked at a similar level to a JMO under the supervision of a placement supervisor and had most privileges of a JMO, excluding prescribing and admitting rights. A typical day would include ward rounds, reviewing sick patients and completing ward jobs (for example, ordering investigations, scripts, consulting teams). The AiM would complete documentation (such as discharge summaries, consult and admission notes) and procedures (for example, cannulas, venepunctures, nasogastric tubes, and catheter insertions). I worked closely with my supervising doctors, other JMOs, registrars, and the multidisciplinary team (MDT). We worked 32 hours a week in 12-week rotations for up to six months while also studying for our final-year examinations.

Personal and Professional Development Opportunities

My clinical experience before the AiM program was similar to many other medical students, mainly observational learning. As we progressed through medical school, there were more opportunities to get involved in ward rounds, including writing notes and helping with simple procedures. However, there was minimal interaction with the consultants, other members of the

MDT, and the patient's follow-up. The AiM program provided added responsibilities and the opportunity to be a valued member of the patient's healthcare team.

My responsibilities as an AiM included working with consultants and registrars to document ward rounds, requesting consults, and performing handovers. As a medical student, I occasionally performed a handover, but this was usually only once a week under strict supervision. However, as an AiM, I communicated regularly with JMOs, registrars, and consultants regarding patient progress and outcomes. This process allowed me to refine my handovers and improve my clinical communication skills, an opportunity that was not as readily available as a medical student.

The AiM program also allowed me to work more closely with members of the MDT, including Aboriginal Liaison Officers, Nurses, Social Workers, Physiotherapists, Occupational Therapists, Speech Pathologists, and Psychologists compared to my previous medical student placements. I attended MDT meetings, where we reviewed patients' goals of care, and addressed medical and allied health staff concerns. This experience gave me a better understanding of the importance of working within an MDT to develop holistic patient-oriented care plans and help patients be discharged safely.

Understanding medical uncertainty and developing coping strategies is a core clinical competency for medical graduates and trainees. Intolerance to uncertainty can increase stress, lead to burnout, and affect patient safety. The AiM program gave me more independence in managing unwell patients, including attending clinical reviews, participating in after-hours shifts, and acting as the first responder to rapid response calls.

I have now completed my first term as a medical intern, and my transition into the role has been extremely smooth. I feel comfortable assisting in ward rounds, consulting other teams, communicating with the MDT, and assessing unwell patients. Upon reflection, I believe the AiM program was very similar to my current role as a JMO, except for prescribing rights. The AiM role allowed senior medical students to practice working at the level of a JMO in a supported environment.

Challenges as an AiM

As one of the first participants of the AiM program, the most significant challenge was trying to fit into a new and undefined role. By communicating my abilities and limitations with the team, I clearly defined my professional and personal boundaries which allowed me to provide an appropriate standard of care to patients. As the team developed, we became more comfortable and confident about the AiM role, leading to more responsibility and autonomy.

A similar 'trainee intern' model

Transitioning from medical school to internship can be a challenging time in junior doctors' training. Many medical schools across Australia have tried to ease the transition by offering short 'pre-internship' placements. However, more can be done to help final-year medical students prepare for this transition. Pre-internship placements are only for a few weeks and mainly involve passively shadowing interns rather than taking responsibility. Enabling students to engage authentically in clinical environments will increase their preparedness for internship by promoting understanding of their role and responsibility. I believe the AiM role allowed for independence, autonomy, and responsibility while being supervised.

Interestingly, New Zealand has a transitional year within its undergraduate medical curriculum known as a 'trainee intern'. Introduced in 1972, final year medical students are employed to work in the hospital under the supervision of the medical team [1]. An evaluation of the program found that in comparison to year five medical students, (year six) trainee interns reported significantly greater competence and improvement in procedural skills (trainee interns: 77%, year five: 35%) and clinical tasks (trainee interns: 94%, year five: 56%) [2]. This evaluation also found that trainee interns felt significantly more prepared to work as junior doctors (trainee interns: 92%, year five: 53%) [1]. New Zealand trainee interns reported substantially higher levels of preparedness to work as a JMO than other pre-intern placements, with 92% of New Zealand trainee interns reporting adequate preparedness for internship compared with 38% in Ireland, 58% in the UK, and 64% in Australia [1,2].

There are many similarities between the Australian AiM program and the 'trainee intern' program in New Zealand. Both programs provide students with an increased level of responsibility and autonomy in appropriate clinical settings, a greater focus on MDT involvement, and direct patient care, albeit without prescribing rights. The program's main difference was duration, with New Zealand's program running for 12 months while the AiM ran over three to six months.

Ultimately, most students in medical school will become doctors. However, it is important to explore how to best prepare medical students for the transition into the workforce. An Australian study found that more hands-on experience, patient contact, and responsibility as medical students lead to greater confidence as JMOs [3]. Greater student participation, ownership, and responsibility for patient care and decision-making are vital for preparing junior doctors [4].

Conclusion

The AiM program was a COVID-19 initiative to increase medical resources by deploying final-year medical students into the medical workforce. This provided a unique opportunity for students to engage authentically in clinical environments while working under supervision. This program developed students' independence, autonomy, and responsibility while increasing their preparedness for internship. The AiM program has many similarities to the New Zealand pre-internship model, which reports a higher level of preparedness amongst JMOs compared to other countries' JMOs. Perhaps Australia can mirror the New Zealand initiative of employing final-year medical students to bridge the gap between students and effective, prepared doctors.

References

[1] Dare A, Fancourt N, Robinson E, Wilkinson T, Bagg W. Training the intern: the value of a pre-intern year in preparing students for practice. Med Teach. 2009;31(8):345-50.

[2] Abuhusain H, Chortirmall S, Hamid N, O'Neill SH. Prepared for internship? Ir Med J. 2009;102(3):82-4

[3] Eley DS. Postgraduates' perceptions of preparedness for work as a doctor and making future career decisions: support for rural, non-traditional medical schools. Educ Health (Abingdon). 2010;23(2):374.

[4] Hall K, Schneider B, Abercrombie S, Gravel J, Hoekzema G, Kozakowski S, et al. Hitting the ground running: medical student preparedness for residency training. Ann Fam Med. 2011;9(4):375.

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Feature Article

Electives closer to home: pre-hospital and retrieval medicine at MedSTAR, South Australia

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Mark is a final year medical student at the University of NSW, currently based at Albury-Wodonga Health. He has a particular interest in critical care medicine, specifically anaesthetics, and is looking to pursue a career in pre-hospital and retrieval medicine. In December 2020, he undertook an elective placement with the South Australian Ambulance Service MedSTAR pre-hospital and retrieval unit based at Adelaide Airport in South Australia.

Key learning points

- Pre-hospital and retrieval medicine is a growing subspecialty within critical care medicine that has proven benefits in improving morbidity and mortality for critically unwell patients.
- Pre-hospital and retrieval medicine is of particular importance in Australia because of the vast size of the country and the isolated nature of certain communities.
- MedSTAR is unique with respect to its broad range of capabilities, presenting the opportunity for students to observe a wide variety of pre-hospital and retrieval experiences from a single elective placement.

Abstract

Introduction: The COVID-19 pandemic radically changed the nature of elective placements undertaken over the summer of 2020/2021. With an international travel ban in place, students were forced to cancel overseas placements and look closer to home to find opportunities. This resulted in the discovery of world-class elective experiences within Australia that may have otherwise been overlooked by the allure of international travel. This was the case with the placement I undertook at the Medical State-wide Trauma/Transport Advice and Retrievals (MedSTAR) service in South Australia. **Summary**: MedSTAR is unique amongst pre-hospital and retrieval units, given the breadth of opportunities available to medical students. Participants have full access to both adult and paediatric cases across all three forms of transport: road, helicopter, and fixed-wing aircraft. The high-acuity nature of the patient population seen by MedSTAR guarantees access to numerous interesting, complex, and unusual cases that are typically not seen by medical students, providing fantastic educational experiences. This article will introduce the subspecialty of pre-hospital and retrieval medicine, detail the work undertaken by MedSTAR in delivering care to critically ill patients across South Australia, and provide an account of the student experience undertaking an elective placement in such a unique environment.

Keywords: Pre-hospital and Retrieval Medicine; Aeromedical Retrieval; Elective; Critical Care; MedSTAR

Introduction

The COVID-19 pandemic, international travel ban, and ever-changing state border restrictions made elective placements over the summer of 2020/2021 very different from previous years. Being forced to look closer to home resulted in the discovery of valuable opportunities that may have otherwise been overlooked, such as my elective placement with the South Australian Ambulance Service (SAAS) Medical State-wide Trauma/Transport Advice and Retrievals (MedSTAR) service. The breadth of opportunities available to students at MedSTAR is unique, encompassing exposure to critically ill adult and paediatric patients via road, helicopter, and fixed-wing aircraft. This article seeks to introduce the subspecialty of pre-hospital and retrieval medicine (PHRM) and document the student experience of PHRM during an elective placement with MedSTAR.

Electives closer to home

For junior medical students, the prospect of an elective term is exciting, with an enormous breadth of opportunities available across the world. Since my first year in 2016, I listened with anticipation to final year students speaking about their experiences and began to plan how I would spend my own elective in the summer of 2020/2021.

The expanding discipline of PHRM immediately drew my attention as an exciting placement option. Attracted by the opportunity for international travel whilst on placement, I began researching opportunities around the world and, by the start of 2020, I had my sights on a PHRM placement in London.

Then the COVID-19 pandemic hit. With an indefinite ban on international travel, constantly changing state border restrictions, and a reluctance of many health facilities to accept extra students due to COVID-19, it seemed that the class of 2021

would miss out on the elective experience of previous years. Like many of my colleagues, I watched my plans for an international placement crumble due to the restrictions necessitated by the pandemic.

Instead of gravitating overseas, students were forced to look closer to home for elective experiences. For some, this meant working with their favourite team at their home hospital. For others, it unearthed local opportunities that may have otherwise been overlooked. The latter was certainly the case for me, as I undertook a four-week placement at MedSTAR, South Australia's PHRM service.

Pre-hospital and retrieval medicine in Australia

PHRM is increasingly recognised as an important critical care subspecialty. It exists in the pre- and inter-hospital environment, providing treatment to critically ill patients before and during transport for definitive care. Between 2010 and 2014, Queensland's PHRM services responded to 73 042 cases, an average of 40 per day, with an increasing trend from 13 833 cases in 2010 to 15 064 cases in 2014 [1]. Over 80% of cases required transport from remote or regional locations, highlighting the particular significance of PHRM in Australia due to the vast size of the country and the isolated nature of certain communities [1,2].

Each state and territory in Australia have their own PHRM units, with the exception of the Australian Capital Territory which is included within the New South Wales (NSW) retrieval jurisdiction (Table 1). All states and territories other than the Northern Territory have separate adult and paediatric retrieval teams, with larger states such as NSW, Queensland, and Western Australia operating out of multiple bases. South Australia is the only state where both adult and paediatric teams are operated by the same organisation from a single base covering the entire state.

PHRM brings critical care services to the patient, resulting in improved morbidity and mortality due to both the earlier provision of life-saving interventions by critical care teams and reduced transport time to hospital [2]. The provision of blood transfusions by retrieval teams, for example, has repeatedly demonstrated an improvement in mortality in major trauma [3-5]. A retrospective study of all blood transfusions provided by NSW Ambulance retrieval teams between 2009 and 2018 revealed significantly improved haemodynamic stability for transfusion patients upon arrival at hospital [6]. Additionally, one study in Western Australia found a 5.1% decrease in mortality for major trauma patients transported directly to a tertiary hospital by helicopter compared to those transported indirectly by road via a local hospital [7].

PHRM teams generally consist of a doctor partnered with a critical care nurse or paramedic [8]. The doctors are usually drawn from the three main critical care specialties: emergency, anaesthetics, and intensive care medicine. In 2021, the Australasian College of Emergency Medicine, in conjunction with other critical care colleges, commenced the Graduate Diploma of Pre-Hospital and Retrieval Medicine (DipPHRM) in recognition of the growing need for formal training and

Table 1: Pre-hospital and retrieval units in Australia. *Pre-hospital and retrieval units operating in each state and territory of Australia, with South Australia's MedSTAR being the only unit to contain both adult and paediatric teams.*

State/Territory	Population	Service
New South Wales and Australian Capital Territory	Adult	Aeromedical and Medical Retrieval Service (AMRS)
	Paediatric	Newborn and paediatric Emergency Transport Service (NETS)
Victoria	Adult	Adult Retrieval Victoria
	Paediatric	Paediatric Infant Perinatal Emergency Retrieval (PIPER)
Queensland	Adult	Retrieval Services Queensland (RSQ)
	Paediatric	Children's Health Queensland Retrieval Service
Western Australia	Adult	Royal Flying Doctor Service Western Operations (RFDSWO) Emergency Rescue Helicopter Service (ERHS)
	Paediatric	Neonatal Emergency Transport Service of Western Australia (NETS WA)
South Australia	Adult	MedSTAR
	Paediatric	MedSTAR Kids
Tasmania	Adult	Aero-Medical and Medical Retrieval Division (AMMRD)
	Paediatric	Neonatal Emergency Transport Service (NETS)
Northern Territory (NT)	Northern NT	CareFlight
	Southern NT	Royal Flying Doctor Service Central Operations

qualification in PHRM [9]. This mirrors a similar program established in the United Kingdom (UK) in 2012 [10].

Traditionally, the high-acuity nature of the patient population, alongside space and weight restrictions on aircrafts, has limited medical student exposure to PHRM. Most budding retrievalists have to wait until senior registrar level before experiencing PHRM, with only a small number of units, including MedSTAR, offering elective placements to medical students.

MedSTAR

MedSTAR is the PHRM unit for South Australia (SA). Based in a purpose-built facility at Adelaide Airport, it is a fully integrated component of SAAS and functions alongside standard ambulance crews. From this single base, specialised adult and paediatric retrieval teams respond to critically ill patients of all ages across SA, covering an area of approximately 983 000 km^2 with a population of 1.7 million people [11]. This is unique amongst PHRM units in Australia.

MedSTAR taskings fall into one of two categories: primary or secondary. During primary responses, the MedSTAR team will travel directly to the incident site, for example, a motor vehicle accident (MVA) or other major trauma. For these taskings, the team is joined by a specialist rescue paramedic to assist with any extraction or difficult entry requirements.

Secondary responses, or inter-hospital transfers, involve patient transport from one health facility to another. This includes transport from remote or regional hospitals to a tertiary facility in Adelaide or transfer from one Adelaide hospital to another. Secondary responses involve both medical cases, with patients requiring an escalation of care, as well as major trauma necessitating transfer from a regional hospital to a tertiary centre (Figure 1). Secondary responses are attended only by a two-person team, with no requirement for a rescue paramedic, and comprise 70% to 80% of all MedSTAR taskings.

Figure 1 The MedSTAR team working alongside volunteer SAAS crews on the sports oval of a regional town to load a patient onto the helicopter for transport to a tertiary facility in Adelaide.

MedSTAR possesses a uniquely broad range of transport options from the one facility. Within the Adelaide metropolitan area, MedSTAR has a fleet of four rapid response vehicles and two fully equipped ambulances for MedSTAR Kids. These ambulances can be quickly reconfigured to carry either a stretcher or neonate transport system, depending on the age and requirements of the patient.

For taskings beyond Adelaide, MedSTAR utilises two dedicated Bell-412 rescue helicopters (Figure 2). These helicopters are able to respond to any incident within a 200-kilometre radius of Adelaide and allow for rapid transfer directly from the incident site to the helipad of major Adelaide hospitals.

Figure 2. One of the two Bell-412 helicopters used by MedSTAR to respond to cases within a 200-kilometre radius of Adelaide on the helipad of the Royal Adelaide Hospital.

For responses beyond a 200-kilometre radius, the Royal Flying Doctor Service supplies Pilatus PC-12 turboprop aeroplanes and a Pilatus PC-24 jet from their facility located 300 metres from the MedSTAR base (Figure 3). This enables teams to respond to taskings across SA and provide interstate transfers to Melbourne or Sydney. The ability to respond by road, helicopter or fixed-wing aircraft from the one facility is unique to MedSTAR among Australian PHRM units.

Figure 3. One of the RFDS Pilatus PC-12 turboprop aeroplanes used by MedSTAR to respond to cases beyond a 200-kilometre radius of Adelaide.

MedSTAR elective experience

MedSTAR allows students full access to all forms of transport and taskings where space and weight restrictions allow, offering students a broad range of experiences during their elective placement. Over the course of four weeks, I went on 37 separate taskings: 23 by road, eight by helicopter, and six by fixed-wing aircraft.

Having both paediatric and adult retrieval teams operate out of the one base further increases the range of experiences available to students. Seven of the cases I was involved with were for paediatric patients, including neonates only a few hours old with congenital cardiac abnormalities, babies with severe sepsis, pyloric stenosis, or congenital hypoventilation syndrome, and a teenager in a MVA with a significant intracranial haemorrhage.

One particularly memorable case that demonstrated the value of the retrieval team was a road response to a neonate only a few hours old. Upon our arrival, the baby was in severe respiratory distress with reduced oxygen saturations, pallor, and absent femoral pulses. The neonatal retrieval team managed to stabilise the baby by establishing a prostaglandin infusion, intubating and ventilating via rapid sequence induction, and providing ongoing care during transport to the hospital. The rapid provision of definitive care demonstrated by the retrieval team was essential in saving the baby's life.

The adult cases were equally varied, including severe diabetic ketoacidosis, subarachnoid and intraparenchymal haemorrhages, aortic dissection, acute respiratory failure, psychosis, significant gastrointestinal bleeding, and cardiac arrest and coagulopathy resulting from a snake bite. High acuity cases occasionally seen by medical students on normal placements are commonplace occurrences in PHRM.

The critically ill patient population of MedSTAR results in the provision of significant interventions, often conducted in unusual environments. The unique requirements of non-invasive ventilation during flight, for example, where atmospheric and oxygen partial pressures are reduced, are unique to this field of medicine. Additionally, although students may be familiar with the use of ketamine infusions to manage acutely psychotic and aggressive patients, it is not commonplace to witness this occurring while locked in a small turboprop aircraft several thousand feet in the air.

Life-saving interventions performed by MedSTAR often occur in out-of-hospital settings, where additional challenges including the uncontrolled environment, reduced availability of resources, and the weather come into play. During one case, a teenage boy who had been in a MVA required intubation for reduced conscious state and respiratory drive. This was conducted by the MedSTAR team at the incident site on the side of the road whilst light rain fell around them. Witnessing how such situations are managed in these circumstances is very rare and valuable for students, particularly those interested in critical care.

MedSTAR has regular team training and education sessions, providing an opportunity for students to learn more about the delivery of critical care services in PHRM. During my placement, this included information on the use of cardiac-pacing and balloon pumps in out-of-hospital settings, the management of facial fractures with significant epistaxis, and how to survive in the event of a bushfire burnover. Furthermore, as fully integrated members of the retrieval team, students participate in day-to-day activities essential to PHRM, such as equipment and pack checks and patient follow-up.

Given the high-acuity patient population, there are some limitations to what can be done as a student, including not being allowed to perform any interventional procedures on patients. Students can, however, assist with these procedures and be highly involved with tasks such as setting up equipment, taking vital sign observations, and preparing patients for transport.

Students are also not permitted to attend helicopter primary responses. This is due to space restrictions from the addition of a rescue paramedic to the team, taking up the third seat in the helicopter that is available for students in secondary responses. This excludes students from a significant portion of the major trauma seen by MedSTAR as they can only attend primary taskings reached by road within metropolitan Adelaide. As a result, during my four weeks, I attended only two primary taskings.

A further difference between a PHRM placement and a normal hospital position is the reduced patient numbers. Owing to the time required to travel to an incident, stabilise and package the patient for transport, and travel back to the destination hospital, each case takes several hours to complete. This results in a reduced caseload being seen by students during the placement, as a maximum of two or three cases can be completed per day.

The caseload of PHRM is also extremely dependant on what incidents occur throughout the state. It is not uncommon to spend many hours on base waiting to be tasked, including days with no cases at all. This is balanced, however, by the intensity of the cases when they do arrive and the ability to focus entirely on a single case and therefore learn a great deal about the pathology and its management.

Conclusion

MedSTAR is the only PHRM unit in Australia with both adult and paediatric retrieval teams responding via road, helicopter, and fixed-wing aircraft to cases across the state from a single base. This presents an exceptionally broad range of educational opportunities for medical students, including the management of critically ill patients in the out-of-hospital environment, exposure to a variety of complex and high acuity cases, and experience in a growing field of medicine that is not usually accessible to students. With the COVID-19 pandemic continuing to restrict elective placements, MedSTAR offers a unique elective experience located a little closer to home.

References

[1] Franklin RC, King JC, Aitken PJ, Elcock MS, Lawton L, Robertson A, *et al.* Aeromedical retrievals in Queensland: a five-year review. Emerg Med Australas. 2021;33(1):34-44.

[2] Ting J. Retrieval medicine and pre-hospital care in remote Australia. Intern Med J. 2020;50(6):763-6.

[3] Heelan Gladden AA, Peltz ED, McIntyre RC, Jr., Vega S, Krell R, Velopulos C, *et al.* Effect of pre-hospital use of the assessment of blood consumption score and pre-thawed fresh frozen plasma on resuscitation and trauma mortality. J Am Coll Surg. 2019;228(2):141-7.

[4] Sperry JL, Guyette FX, Brown JB, Yazer MH, Triulzi DJ, Early-Young BJ, *et al.* Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. N Engl J Med. 2018;379(4):315-26.

[5] Holcomb JB, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, *et al.* The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg. 2013;148(2):127-36.

[6] Shand S, Curtis K, Dinh M, Burns B. Prehospital blood transfusion in New South Wales, Australia: a retrospective cohort study. Prehosp Emerg Care. 2021;25(3):404-11.

[7] Ford D, Mills B, Ciccone N, Beatty S. Does direct helicopter retrieval improve survival of severely injured trauma patients from rural Western Australia? Air Med J. 2020;39(3):183-8.

[8] Kennedy M, Elcock M, Ellis D, Tall G. Pre-hospital and retrieval medicine: clinical governance and workforce models. Emerg Med Australas. 2017;29(4):467-9.

[9] Bertenshaw C, Dubash R, Kozlovski J, Ho JH. Pre-hospital and retrieval medicine: special skills placements and subspecialty training. Emerg Med Australas. 2020;32(4):667-9.

[10] Mackenzie R. Brief history of pre-hospital emergency medicine. Emerg Med J. 2018;35(3):146-8.

[11] [Alderson S, Paddock S, West N, Pearce A, Martin D, Keir A. Responding to the COVID-19 pandemic: the experiences of South Australia's rescue, retrieval and aviation services. Emerg Med Australas. 2021;33(2):375-8.

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E-Cigarettes in the Workplace – Past, Present and Future

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Wai Kit is a penultimate year medical student with an interest in Preventive Medicine. He is an avid researcher and writer, and has been working on projects related to improving population health in between his studies. He is also an active member in international student societies and hopes to use his knowledge as a medical student to raise awareness on issues involving the wider community.

Key learning points

- The prevalence of e-cigarette use or vaping is increasing, especially after association with smoking cessation and frequent promotion as an alternative to tobacco smoking.
- E-cigarettes can cause vaping-induced lung injuries and evidence on its efficacy for smoking cessation is conflicted.
- Like tobacco smoking, e-cigarettes use should be tightly regulated, for instance with workplace restrictions.

Abstract

Electronic cigarette (e-cigarette) smoking, also known as vaping, is a trend that has proliferated rapidly in the last decade. Initially heralded as a "better" replacement for the "more dangerous" tobacco smoking, we are starting to see several potential harms in the use of these devices. These include inflammatory lung damage from novel inhaled toxins and subsequent addiction to smoking. The workplace, where many spend a large part of their days at, may hold the key to controlling e-cigarette use – just as it did in Australia's successful campaign against tobacco smoking. Several stakeholders such as the government and worker unions are essential in making the necessary changes, amidst resistance by e-cigarette manufacturers and users.

Keywords: E-Cigarette, Vaping, Smoking, Workplace, Youth

Introduction

Tobacco smoking was once seen as a widely acceptable and popular habit, growing rapidly in the mid-20th century and promoted even by doctors as part of a reassuring image which tobacco companies aimed to portray [1]. Tobacco companies such as Marlboro even included supposed "medical benefits" from their use, including treatment of colds or stimulating digestive fluids. Following the 1964 US Surgeon General's report for tobacco control however, tobacco smoking has been condemned as a widely recognised health risk [2]. Yet, there is a new epidemic that has emerged from the shadows of its former counterpart; electronic cigarettes, or more colloquially known as vaping.

Electronic cigarettes (e-cigarettes) are devices that vaporise an added liquid solution to produce aerosols which are inhaled by the user. Propylene glycol in the solutions create the aerosol, which are frequently mixed with attractive flavours that make vaping so appealing and popular, especially among youths [3]. These solutions may also contain nicotine or other addictive substances such as cannabinoids. However, the health effects of many of these inhaled mixtures are not well-established.

There have been increasing concerns regarding potentially harmful effects associated with long-term use of e-cigarettes, such as inflammatory responses similar to tobacco use [4]. In the Unites States , e-cigarette use has been associated with acute severe respiratory distress, known as e-cigarette, or vaping associated lung injury (EVALI) [5]. Several mechanisms have been postulated for EVALI, including e-cigarette induced airway remodelling and impaired mucociliary clearance [6]. It now appears likely that EVALI is associated with vitamin E acetate added to solutions containing cannabinoids [7].

There is an upward trend in e-cigarette usage worldwide, with the sales of vaping products expected to more than double from 2018 to 2023 [8]. In Australia, 11% of the general population above 14 years old reported ever having used e-cigarettes. Among them, the younger age group tends to be more involved in vaping. 26.1% of adults between 18 to 24 years reported having ever used e-cigarettes in 2019, up from 9.5% in 2013. Use among adult smokers and non-smokers also increased between 2013 and 2019, from 17.9% to 38.4% and 1.8% to 6.8% respectively [9].

According to Australian laws, e-cigarette products containing nicotine are prohibited for sale or use, except for therapeutic reasons such as assistance in cessation of smoking [10]. Despite this legislation, reports about the true efficacy of e-cigarettes in smoking cessation have been conflicting. E-cigarettes have also not been approved by the Therapeutic Goods Administration (TGA). Nonetheless, Australian consumers have been purchasing the devices via alternative routes such as over the internet.

The debate around e-cigarettes

E-cigarette use appears to exacerbate existing respiratory diseases. A nation-wide study in the United States investigating e-cigarette use in those who had never smoked combustible cigarettes found increased odds of asthma among e-cigarette users [11]. It can also create respiratory symptoms in those without previous respiratory conditions, with a study in Hong Kong investigating e-cigarette use among 45 000 Chinese adolescents reporting increased odds of chronic cough or phlegm [12]

While it has been frequently heralded as a ground-breaking tool in smoking cessation, there has been conflicting evidence among various research groups. A 2020 Cochrane study involving 50 studies concluded that nicotine containing e-cigarettes are more effective in smoking cessation than non-nicotine e-cigarettes or behavioral support alone [13]. Of these 50 studies, only two were based in Australia and more than half were at risk of biases.

However, a meta-analysis of 20 studies showed that the odds of smoking cessation were lower among e-cigarette users compared to non-users [14]. Eight studies showed a significant decline for non-users, whereas only 2 studies showed a significant decline in smoking cessation rates among e-cigarette users. The remaining studies reported a non-significant difference between e-cigarette and non-users. Of note, e-cigarette use was found to be associated with smoking initiation rather than cessation, especially among non-established tobacco smokers. Soneji et al. reported that among adolescents and young adults, e-cigarette use was associated with an increased risk of subsequent smoking initiation and past 30-day cigarette smoking [15]. A recent report by the Australian National University (ANU) also claims that e-cigarette use can triple the chances of non-smokers taking up traditional cigarette smoking [16].

This trend has been further promoted by aggressive advertising from industry via price promotions and themes appealing to youth [17]. Furthermore, the e-cigarette scene is constantly evolving with new devices being regularly marketed. This makes it difficult to regulate, but trendy and futuristic to younger generations [19]. Part of this also involves e-cigarette flavours, with some containing traditionally addictive substances such as nicotine [19] while others seek to include other chemicals to create new and more appealing flavours. Many of these chemicals are unregulated and not well-proven in terms of safety to users. For example, components that make up these flavours, including diacetyl and 2,3-pentanedione, have shown to impair airway ciliary function [20].

Smoking regulations in the workplace

Over the past 50 years, Australia has seen a successful eradication of tobacco smoking in the workplace. Australia is considered an exemplary country in this aspect, with the first smoke-free work environment policy being adopted in the public service in 1988. The National Tobacco Strategy was also introduced to promote non-smoking environments in workplaces as well as enclosed public spaces. This has had the effect of all states and territories taking legislative steps to reduce tobacco smoking exposure [21]. On the ground, there has been a significant decrease in observed smoking or smoking in the workplace. When several states introduced a total ban on smoking in enclosed licensed premises, more than 90% of smokers reported compliance with the ban, with positive attitudes towards the ban more than doubling during the year of implementation [22]

The restrictions on smoking in the workplace have had positive effects on smoking behaviours in general. In adult smoking, there are reductions in cigarette consumption and increased rates of self-reported cessation. Smoke-free workplaces are currently responsible for an annual reduction of some 602 million cigarettes, or 1.8% of all cigarettes that might otherwise be consumed, in Australia, and an annual reduction of 9.7 billion cigarettes (2%) in the United States [23].

There are also some links to reduced youth cigarette smoking. In Australia, a 15-year longitudinal study showed that tobacco control policies including clean indoor air schemes have significantly reduced youth smoking prevalence [24]. In terms of air quality, there has been a drastic reduction in level of poor air quality markers such as nicotine, dust, benzene, and particulate matter [22]. This is likely to further improve with the implementation of smoke-free areas in cities such as Melbourne, under its own Activities Local Law 2019 [25].

There are however far less restrictions on e-cigarettes. Given the unclear evidence over the efficacy of e-cigarettes as well as the potential health effects they can have, a wary stance is expected of the government. The Department of Health has presented a joint statement confirming this, amidst lobbying from commercial interests [26]. Various non-governmental organisations such as Cancer Council Australia and the Australian Medical Association have also advocated for stronger regulations on e-cigarette use.

Yet, efforts to curb the sale and use of e-cigarette are still in its infancy, contrary to the tight legislations regulating nicotine use. There are clear regulations on nicotine-containing e-cigarettes and products, which treats nicotine as a poison unless it has been designated as therapeutic. Hence, it is an offence to manufacture, sell, or supply nicotine e-cigarettes without an appropriate licence or authorisation. However, there are no clear restrictions on non-nicotine containing e-cigarettes.

The Tobacco Amendment Act 2016 added e-cigarettes to the list of other tobacco products regulated under the Tobacco Act [27]. However, there are many variations in restrictions on e-cigarette use among the different states. The sale of e-cigarettes

with nicotine is banned across all states, in line with the Therapeutic Goods Act. However, most allow the sale of e-cigarettes not containing nicotine, with South Australia, Western Australia, and New South Wales adding that they are not allowed to resemble cigarettes. Vaping is also generally not allowed in smoke-free areas except in Northern Territory and Western Australia. These inconsistencies might reflect a lack of a collated effort in reducing e-cigarette use [27].

There are also no clear regulations on e-cigarettes in workplaces. In Western Australia, the Occupational Safety and Health Regulations 1996, repeated on 31 March 2022, addressed smoking in enclosed workplaces but do not address the use of e-cigarettes in workplaces [28]. This has not been updated since to reflect the new trends of e-cigarette use. There are also no specific workplace regulation changes pertaining to vaping in the other states.

Workers' unions usually play a large part in advocating for the benefits and rights of workers across the different sectors. Historically, they have had a part to play in some of the occupational hazards identified in the past, such as asbestos (by Australian Manufacturing Workers' Union) and silica dust (by the Australian Workers' Union). However, unions have been relatively quiet on the issue of e-cigarettes – possibly due to it being an increasingly popular trend as well as the lack of compelling evidence on its short and long-term risks.

The future of e-cigarettes in the workplace

E-cigarettes are on track to accompany tobacco smoking in their rise in popularity, and it is unsafe for such a practice to proliferate so rapidly when there are still many untold dangers. There has been compelling evidence that it can also result in increased rates of tobacco smoking in future. A study in Japan showed that workplace smoke-free policies that allow heated tobacco products and e-cigarettes are associated with higher rates of their use, along with that of conventional cigarette smoking [29].

On the ground, certain populations may be more susceptible to e-cigarette use. Workers that are traditionally more likely to engage in tobacco smoking, such as blue-collar workers, may form a large proportion of those who are currently using e-cigarettes as means to continue or cease their old habits [30]. However, a study done showed that workplace smoking-cessation programs that offer free e-cigarettes did not increase abstinence compared to smokers who were merely given access to information on smoking cessation – raising the importance for us to rethink the need for e-cigarettes in helping smoking cessation [31]. An association between depression and e-cigarette use has also previously been found, suggesting that those with a mental health diagnosis may be more engaged in e-cigarette use – a trend found in cigarette users as well [32]. Riehm et al. reported that externalizing problems such as rebelliousness and substance use symptoms predicted the use of e-cigarettes in a group of US adolescents [33]. These are vulnerable groups which the Australian government has to place extra attention on and who are the most vulnerable to risks posed by e-cigarette use.

While the recent COVID-19 pandemic has changed the dynamics of workplaces with many now working from home, there is still yield in targeting workplaces – the most vulnerable populations tend to still be working physically such as the blue-collared workers. Most parts of Australia are also beginning to return to life before the pandemic especially when the virus is under control.

Recommendations

Recently, New Zealand announced a ban of e-cigarettes beginning 11 November 2020, across all locations where tobacco smoking is banned as well. The Thoracic Society of Australia and New Zealand has also recently released a position statement stating that e-cigarettes are unsuitable for recreational use and no e-cigarettes can be safely recommended for smoking cessation [34]. These would certainly push for the Australian government to increase regulations on these products. While a total ban may be difficult to enforce, there could be laws on use among youths especially when they are more likely to engage in these activities and develop smoking behaviours in future. E-cigarette users in Australia are also in favour of e-cigarettes being regulated as long as those regulations do not impede their ability to obtain devices and refill solutions, which they view as important for them to remain smoke free [35]. There is a less enthusiastic response however, among the Australian youths, with oppositions against outright bans and need for prescription from a medical practitioner [36]. This is especially worrying given their susceptibility to smoking initiation and thus it might be wise to increase awareness of the harms of e-cigarette use among this group which may require non-traditional media such as social media [37].

The introduction of flavours has also been shown to influence vaping rates significantly with the more popular flavours roping in more users. Hence, harm reduction can be achieved by restricting more popular e-cigarette flavours [38]. Illegal substances such as cannabis, when found in flavours, should also be strictly prohibited. Further studies by regulating bodies should also be conducted on each brand and type of flavouring to explore any potential harms they may have as well as guide approval of flavours in Australia.

The government should employ a cautious stance against these products, and should any compelling evidence emerge, be ready to act in line with their strong opposition to tobacco smoking. Taking a similar approach to the fight against tobacco smoking by banning their use in the workplace would be a vital step to start with. As medical students, we should also be aware

of such a trend amongst the general population and consider incorporating e-cigarette counselling as part of our daily interactions with patients.

Conclusion

The safety of e-cigarettes is poorly studied and there have been many reports of lung injury secondary to vaping. There are also several conflicting evidence on its efficacy in smoking cessation. Recommendations to regulate e-cigarette use should be strongly considered, and various stakeholders including worker unions should collaborate with the government to establish restrictions on e-cigarettes. It is wise to start limiting the popularity of e-cigarettes, at least until more reliable evidence has been found.

References

[1] Gardner MN, Brandt AM. "The doctors' choice is America's choice": the physician in US cigarette advertisements, 1930-1953. Am. J. Public Health. 2006;96(2):222-32.

[2] Fifty Years of Change 1964–2014. The health consequences of smoking—50 years of progress: a report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US): National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health; 2014.

[3] Goldenson NI, Leventhal AM, Simpson KA, Barrington-Trimis JL. A review of the use and appeal of flavored electronic eigarettes. Curr Addict Rep. 2019;6(2):98-113.

[4] Reinikovaite V, Rodriguez IE, Karoor V, Rau A, Trinh BB, Deleyiannis FW-B, et al. The effects of electronic cigarette vapour on the lung: direct comparison to tobacco smoke. Eur. Respir. J. 2018;51(4):1701661.

[5] Christiani DC. Vaping-Induced acute lung injury. N. Engl. J. Med. 2019;382(10):960-2.

[6] National Academies of Sciences E, Medicine, Health, Medicine D, Board on Population H, Public Health P, et al. In: Eaton DL, Kwan LY, Stratton K, editors. Public Health Consequences of E-Cigarettes. Washington (DC): National Academies Press (US); 2018.

[7] Blount BC, Karwowski MP, Shields PG, Morel-Espinosa M, Valentin-Blasini L, Gardner M, et al. Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. N. Engl. J. Med. 2019;382(8):697-705.

[8] Besaratinia A, Tommasi S. Vaping: A growing global health concern. EClinicalMedicine. 2019;17.

[9] Greenhalgh E, Jenkins, S & Scollo, MM. 18B.3 Extent of use. Melbourne: Cancer Council Victoria; 2020 2020.

[10] Department of Health AG. Smoking and tobacco laws in Australia [internet]. 2020. [Available from: https://www.health.gov.au/health-topics/smoking-and-tobacco/about-smoking-and-tobacco/smoking-and-tobacco-laws-in-australia#ecigarette-laws.

[11] Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Uddin SMI, Dardari ZA, et al. The association between e-cigarette use and asthma among never combustible cigarette smokers: behavioral risk factor surveillance system (BRFSS) 2016 & 2017. BMC Pulm Med. 2019;19(1):180.

[12] Wang MP, Ho SY, Leung LT, Lam TH. Electronic cigarette use and respiratory symptoms in chinese adolescents in Hong Kong. JAMA Pediatrics. 2016;170(1):89-91.

[13] Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, et al. Electronic cigarettes for smoking cessation. Cochrane Database of Systematic Reviews. 2020(10).

[14] Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. Lancet Respir Med. 2016;4(2):116-28.

[15] Soneji S, Barrington-Trimis JL, Wills TA, Leventhal AM, Unger JB, Gibson LA, et al. Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: a systematic review and meta-analysis. JAMA Pediatr. 2017;171(8):788-97.

[16] Banks E, Beckwith K, Joshy G. Summary report on use of e-cigarettes and impact on tobacco smokng uptake and cessation, relevant to the Australian context.: Commissioned Report for the Australian Government Department of Health; 2020.

[17] Mitchko J, Lewis S, Marynak KL, Shannon C, Burnette D, King BA. E-Cigarettes and young people: communicating an emerging public health risk. American Journal of Health Promotion. 2019;33(6):955-7.

[18] Fadus MC, Smith TT, Squeglia LM. The rise of e-cigarettes, pod mod devices, and JUUL among youth: Factors influencing use, health implications, and downstream effects. Drug Alcohol Depend. 2019;201:85-93.

[19] Drazen JM, Morrissey S, Campion EW. The dangerous flavors of e-cigarettes. N. Engl. J. Med. 2019;380(7):679-80.

[20] Park HR, O'Sullivan M, Vallarino J, Shumyatcher M, Himes BE, Park JA, et al. Transcriptomic response of primary human airway epithelial cells to flavoring chemicals in electronic cigarettes. Sci Rep. 2019;9(1):1400.

[21] Organization WH. Report on smoke-free policies in Australia. University of California at San Francisco, Center for Tobacco Control Research and Education. 2003.

[22] Greenhalgh E, Jenkins, S & Scollo, MM. 15.8 Immediate impact of smokefree legislation in improving air quality. Melbourne: Cancer Council Victoria 2020.

[23] Chapman S, Borland R, Scollo M, Brownson R, Dominello A, Woodward S. The Impact of Smoke-Free Workplaces on Declining Cigarette Consumption in Australia and the United States. Am. J. Public Health. 1999;89:1018-23.

[24] White VM, Warne CD, Spittal MJ, Durkin S, Purcell K, Wakefield MA. What impact have tobacco control policies, cigarette price and tobacco control programme funding had on Australian adolescents' smoking? findings over a 15-year period. Addiction. 2011;106(8):1493-502.
[25] Melbourne City Council. Activities Local Law 2019.
[26] Policy and regulatory approach to electronic cigarettes (e-cigarettes) in Australia. In: Department of Health AG, editor. 2019.
[27] Douglas H, Hall W, Gartner C. E-cigarettes and the law in Australia. Australian Family Physician. 2015;44:415-8.
[28] Clearing the air on e-cigarettes. Parliament of Western Australia; 2017. Report No.1.
[29] Siripongvutikorn Y, Tabuchi T, Okawa S. Workplace smoke-free policies that allow heated tobacco products and electronic cigarettes use are associated with use of both these products and conventional tobacco smoking: the 2018 JASTIS study. Tobacco Control. 2020:tobaccocontrol-2019-055465.
[30] Ham DC, Przybeck T, Strickland JR, Luke DA, Bierut LJ, Evanoff BA. Occupation and workplace policies predict smoking behaviors: analysis of national data from the current population survey. J Occup Environ Med. 2011;53(11):1337-45.
[31] Halpern SD, Harhay MO, Saulsgiver K, Brophy C, Troxel AB, Volpp KG. A Pragmatic Trial of E-Cigarettes, Incentives, and Drugs for Smoking Cessation. N. Engl. J. Med. 2018;378(24):2302-10.
[32] Obisesan OH, Mirbolouk M, Osei AD, Orimoloye OA, Uddin SMI, Dzaye O, et al. Association Between e-Cigarette Use and Depression in the Behavioral Risk Factor Surveillance System, 2016-2017. JAMA Netw Open. 2019;2(12):e1916800.
[33] Riehm KE, Young AS, Feder KA, Krawczyk N, Tormohlen KN, Pacek LR, et al. Mental Health Problems and Initiation of E-cigarette and Combustible Cigarette Use. Pediatrics. 2019;144(1).
[34] McDonald CF, Jones S, Beckert L, Bonevski B, Buchanan T, Bozier J, et al. Electronic cigarettes: A position statement from the Thoracic Society of Australia and New Zealand. Respirology. 2020;25(10):1082-9.
[35] Fraser D, Weier M, Keane H, Gartner C. Vapers' perspectives on electronic cigarette regulation in Australia. International Journal of Drug Policy. 2015;26(6):589-94.
[36] Jongenelis MI, Kameron C, Rudaizky D, Pettigrew S. Support for e-cigarette regulations among Australian young adults. BMC Public Health. 2019;19(1):67.
[37] Collins L, Glasser AM, Abudayyeh H, Pearson JL, Villanti AC. E-Cigarette Marketing and Communication: How E-Cigarette Companies Market E-Cigarettes and the Public Engages with E-cigarette Information. Nicotine Tob Res. 2019;21(1):14-24.
[38] Litt MD, Duffy V, Oncken C. Cigarette smoking and eectronic cigarette vaping patterns as a function of e-cigarette flavourings. Tobacco Control. 2016;25:ii67-ii72.

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Case Report

Metastatic Cutaneous Prostate Cancer – A case report of a rare presentation

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Key learning points

- Although cutaneous metastatic lesions are rare, their presence warrants prompt assessment. These lesions are associated with dedifferentiated pathology, high burden of the disease, and poor prognosis. Therefore, prompt diagnosis and treatment are necessary to minimise associated morbidity and mortality.
- Biopsy of lesions allows for definitive diagnosis and can guide treatment in variant histology which may respond to certain chemotherapies. Other useful investigations include PSMA-PET scans, restaging CTs, and PSA markers.
- Prostate specific membrane antigen TRT is a relatively new therapy that may be offered as treatment for metastatic prostate cancer and is predominantly used when other treatments fail.

Introduction

Prostate cancer is one of the most commonly diagnosed cancers in Australia and is the second most common cause of cancer-related death in males [1]. Approximately one third of patients with localised disease will progress to locally advanced and metastatic disease, commonly spreading to bone and lymphatics and rarely to cutaneous tissue [2]. Prostate carcinoma is reported to metastasise to skin in 0.06% to 0.3% of cases [3]. The skin lesions are usually asymptomatic involving the lower abdomen, genitalia, thigh, and sometimes chest, head, and neck [3]. Few cases of skin metastases from prostate cancer have been reported in the literature but it usually occurs in advanced disease states and is associated with a poor prognosis [3]. In this report, we discuss an 83-year-old male with metastatic castration-resistant prostate cancer presenting with asymptomatic nodular lesions over his right pectoral tissue.

The case

An 83-year-old male with a background history of castrate-resistant metastatic prostate cancer presented to an outpatient cancer centre due to concerns about nodular chest lesions. Over eight weeks, he had developed multiple lesions circumferentially over his right pectoral tissue. The lesions were 10 mm by 5 mm, firm, raised, flesh-coloured nodules that were non-tender, non-pruritic, and without discharge or necrotic tissue (Figure 1). During this time, the patient also noted a decrease in functionality, including increasing fatigue and dyspnoea. His past medical history included anaemia of chronic disease requiring blood transfusions, right-sided

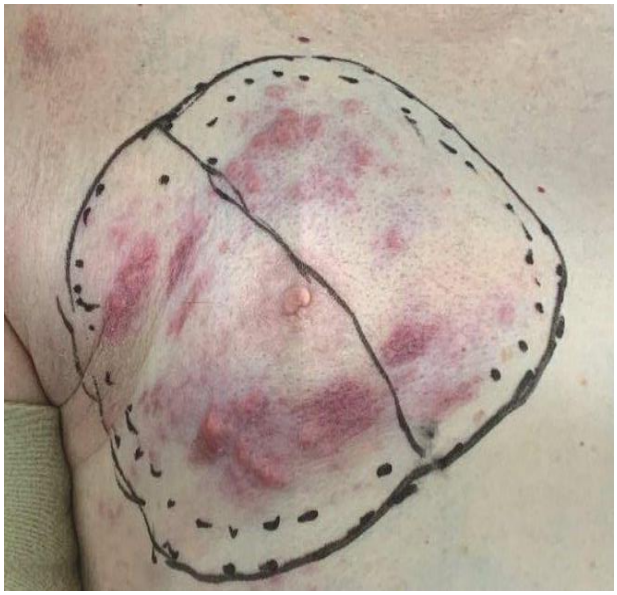
Abstract

Introduction: Prostate cancer is a leading cause of cancer morbidity and mortality in Australian men. Though prostate cancer is common, rarely does it present with cutaneous manifestations. Metastatic cutaneous prostate cancer represents less than 1% of all cutaneous metastatic disease and occurs in 0.06% to 0.3% of prostate cancer cases. This case report explores the rare presentation of cutaneous metastatic prostate cancer. **Case overview:** An 83-year-old male with a history of metastatic castration-resistant prostate cancer presented with nodular chest lesions. The patient had been diagnosed with prostatic adenocarcinoma eight years earlier, and had received a radical prostatectomy, adjuvant radiotherapy, palliative chemotherapy, and androgen deprivation therapy. He was receiving palliative treatment at the time of presentation. The patient reported an eight-week history of firm, fast-growing flesh-coloured nodules over his right pectoral region which were otherwise asymptomatic. A prostate specific membrane antigen positron emission tomography scan demonstrated avidity within cutaneous lesions and was highly suspicious for cutaneous metastatic castration-resistant prostate cancer. The patient declined targeted radionuclide therapy and was managed with palliative superficial radiotherapy. The patient passed away six weeks after diagnosis of cutaneous metastases. **Discussion overview:** Metastatic cutaneous lesions can result in diagnostic dilemmas for clinicians due to the rarity of presentations. Most cases will present with a known history of metastatic disease, however, a small number of cutaneous metastases may be the first indication of a clinically silent prostate cancer. Cutaneous metastasis is associated with a poor prognosis as there is often systemic disease present. Treating clinicians, including radiation oncologists, medical oncologists, dermatologists, urologists, and general practitioners, should consider the diagnosis of cutaneous metastasis in the case of skin lesions in prostate cancer patients.

Keywords: Prostate cancer; Metastasis; Cutaneous metastasis; Radiotherapy (Source: MeSH-NLM).

hydronephrosis secondary to extrinsic ureteric obstruction by metastatic lymphadenopathy requiring an intra-uretic stent, lumbo-sacral back pain and lymphoedema of the legs and right arm. The patient was a non-smoker and drank minimal alcohol on social occasions. He was a retired geochemical engineer and widowed father of four children, who lived with his son and required assistance completing activities of daily living. On examination the patient was hemodynamically stable, afebrile, had signs of anaemia (pallor of the skin, palmar creases and conjunctiva) and bilateral pleural effusions. The patient's Eastern Cooperative Oncology Group (ECOG) status was three.

Figure 1 Multiple flesh-coloured firm nodular lesions circumferential pattern on right pectoral region.

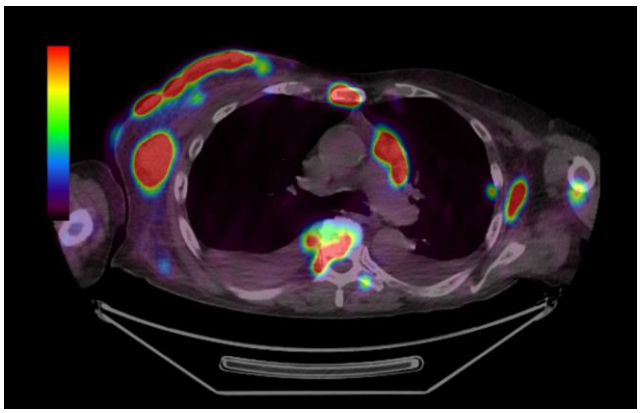


The patient had a strong family history of prostate cancer and was diagnosed with localised prostate cancer in 2012 after PSA monitoring. A radical prostatectomy and six weeks of adjuvant pelvic radiotherapy were performed due to his high-risk profile and the patient went into remission. In 2015, his PSA levels became detectable and staging investigations revealed the presence of skeletal metastases. The patient was commenced on androgen deprivation therapy (ADT) with degarelix and bicalutamide. Due to continually rising PSA levels, the patient was started on docetaxel for castration-resistant disease. Enzalutamide was trialled but it led to low mood, a recognised adverse effect [4]. In 2017, restaging scans showed extensive bony and lymph node progression for which he received palliative radiotherapy to the lower spine, right humerus, and right axillary lymph nodes.

In light of the patient's prostate cancer history, new skin lesions, and recent functional decline, a prostate specific membrane antigen positron emission tomography (PSMA-PET) scan was performed. The scan revealed extensive nodal PSMA-avid disease both above and below the diaphragm, together with extensive osseous metastatic disease and right chest wall cutaneous lesions (Figure 2). The PSMA PET avidity within cutaneous lesions was highly suspicious for cutaneous metastatic castration-resistant prostate cancer.

The patient received palliative superficial radiation therapy of 900 cGy over two fractions to the right chest lesions to prevent fungation. Though there was improvement with the radiation therapy, the lesion remained. The option of actinium-PSMA (a targeted radionuclide therapy) was discussed, however, the patient's general functional status deteriorated markedly due to progressive metastatic disease in his liver and bilateral lungs, and further treatment was considered too burdensome. The patient received a blood transfusion for symptomatic management of anaemia as an outpatient. The patient passed away peacefully at home with family six weeks later from progressive metastatic liver disease.

Figure 2 PSMA PET scan showing high avidity in accordance to right chest wall cutaneous lesions. (PSMA, prostate specific membrane antigen; PET, positron emission tomography)



Discussion

Cutaneous metastases from visceral malignancies are uncommon, occurring in 2% to 9% of cases [5]. This infrequent phenomenon is more commonly seen in breast, lung, renal, stomach, uterine, and colon malignancies, but rarely seen in prostate cancer [5]. Metastases usually occur in the advanced stage of malignancy and are associated with a poor prognosis [3,5,6]. In recent years, there have been more case reports of cutaneous metastasis of prostate cancer, possibly due to the aging population, new treatment methods lengthening survival, as well as better recognition by clinicians [7]. However, cutaneous metastatic prostate cancer is still very rare, representing less than 1% of all cutaneous metastatic disease and occurring in only 0.06% to 0.3% of prostate cancer cases [6,8].

Clinically, cutaneous metastatic disease presents with abrupt skin eruption which progressively worsens [7,8]. It can occur at any point of prostate cancer progression, with most cases presenting four years after the primary diagnosis [7,8]. The most common presentations include multiple asymptomatic firm flesh-like papules, nodules, or occasionally, sclerodermoid lesions [7-10]. Other variants of the disease include violaceous

or erythematous plaques and, rarely, necrotic skin [10-13]. These lesions commonly occur over the suprapubic region, lower abdominal area, medial thigh, and genitalia [3,5,8,10]. Rare sites of cutaneous metastasis include the chest, scalp, and face [6,8,9]. However, a recent literature review has shown that presentations of chest wall metastases are increasing [7].

The pathophysiology of the spread from the primary tumour to the skin is complex and not fully understood [7,8]. The cells must acquire the ability to evade the primary site, enter the lymphatics or the blood stream, survive in the circulation, extravasate to dermal tissue, and proliferate [7,8]. New research has hypothesised that chymotrypsins may be responsible for the spread to cutaneous tissues [3]. Chymotrypsins secrete serine protease, which causes intercellular degradation to adhesive structures of the cornified skin layer, allowing for cutaneous tissue invasion [3,14]. There is a possibility that other receptors, such as androgen receptors, may be part of the metastatic process, however, further studies are required.

Metastatic cutaneous lesions can result in diagnostic dilemmas for clinicians due to the rarity of presentations. Most cases will present with a known history of metastatic prostate cancer. Therefore, if prostate cancer is revealed in the past medical history, it should raise suspicions and aid prompt diagnosis. Interestingly, the literature reports that 15% of undiagnosed prostate cancer present as cutaneous lesions [3]. Differential diagnoses for cutaneous lesions include angiosarcoma, cellulitis, mammary Paget's disease, sebaceous cyst, Sister Joseph nodule, basal cell carcinoma, pyoderma, morphea, and trichoepithelioma [3,7,8,19-21].

A definitive diagnosis is achieved with skin biopsy sent for histopathology and staining. The histopathology is often similar to the primary tumour, with undifferentiated cells diffusely infiltrating the dermis and gland-like structures in the case of adenocarcinoma [3]. Typically, immunohistochemistry staining is positive for PSA and/or prostatic acid phosphatase (PAP) [3]. Another key investigation is a raised serum PSA level, which in this case was markedly elevated at 174 ug/L. Other investigations may include a restaging scan, such as a computer tomography (CT) chest, abdomen, and pelvis and/or PSMA-PET scan, to check for distant metastases. In this case, the patient decided against biopsy. Therefore, the team made the likely diagnosis of cutaneous metastatic castration-resistant prostate cancer based on the PSMA PET avidity within cutaneous lesions and the patient's clinical history. Given the uncommon features of this presentation, a biopsy would have been useful for definitive diagnosis and could have guided treatment of variant histology which may only respond to certain treatments.

Cutaneous metastasis is associated with a poor prognosis as there is often overt systemic disease present [3,7,8,22]. The mean survival time after diagnosis of cutaneous metastasis has been calculated to be between six to seven months [3,7,8,22,23]. Treatments are mostly palliative, including local excision, chemotherapy, or radiotherapy [3,7,8]. As most patients have advanced disease, the efficacy of management options has not yet been evaluated. Most patients are treated with a conservative approach, including palliative care and local radiation therapy, in an attempt to treat symptoms and improve the patient's quality of life [3]. In patients receiving more aggressive treatment for cutaneous metastases, chemotherapeutic agents have been utilized without much improvement [17,26]. Other systemic therapies, such as androgen deprivation therapy, have shown encouraging results with resolution of lesions [17,22].

There is PSMA targeted radionuclide therapy (TRT), which binds and emits radiation to PSMA-expressing tissues, destroying the prostate cancer cells [27]. Prostate specific membrane antigen TRT may also be offered as treatment for metastatic prostate cancer and is predominantly used when other treatments fail [27]. Targeted radionuclide therapy is an advancing area of oncology treatment and has shown some promising outcomes in metastatic prostate cancer; however, there is limited research available regarding the efficacy of TRT in cutaneous metastatic prostate cancer [28].

Conclusion

This report presents the case of an 83-year-old man with cutaneous metastases of prostate carcinoma. Although prostate cutaneous metastasis is an uncommon presentation, it remains an important diagnostic consideration in patients with unrecognised and advanced disease. Treating clinicians, including radiation oncologists, medical oncologists, dermatologists, urologists, and general practitioners, should consider the diagnosis of cutaneous metastasis in the case of skin lesions in prostate cancer patients. The presence of cutaneous metastatic lesions should prompt further assessment as they are associated with dedifferentiated pathology, high burden of the disease, and poor prognosis.

References

[1] [1] Australian Institute of Health and Welfare. Prostate cancer in Australia [Internet]. Canberra; 2013 [updated 2013 Nov; cited 2020 Dec 10]. Available from: https://www.aihw.gov.au/getmedia/79bf7508-9ef2-41a1-8014-6ac11610ab72/14374.pdf.aspx?inline=true

[2] [2] Amling CL, Blute ML, Bergstralh EJ, Seay TM, Slezak J, Zincke H. Long-term hazard of progression after radical prostatectomy for clinically localised prostate cancer: continued risk of biochemical failure after 5 years. J Urol. 2000;164(1):101-5.

[3] Esquivel-Pinto IA, Torres-Alvarez B, Gómez-Villa RJ, Castanedo-Cázares JP. A case of prostatic carcinoma manifesting as cutaneous facial nodule. Case Rep Urol. 2018;2018:e1-6.

[4] Moreno Perez MP, Sanchez Iznaola M, Garcia A, Muñoz del Toro J, Casariego J, Robinson P, et al. Neuropsychiatric adverse events of enzalutamide and abiraterone acetate: Meta-analysis of randomized clinical trials with real world reporting patterns from EudraVigilance. J Clin Oncol. 2018;36(6):217.

[5] Rathee VS, Patnaik P, Shaw D, Khan SW, Trivedi S, Dwivedi US. Cutaneous metastasis from prostatic adenocarcinoma - a rare presentation. Urol Nephrol Open Access J. 2018;6(1):00196.

[6] Sharma R, Chandra M. Cutaneous metastases from carcinoma of the prostate: a case report. Dermatol Online J. 2005;11(1):24.

[7] Brown G, Kurtzman F, Lian M, Sligh J. Review of the literature regarding metastatic prostate carcinoma to the skin, "beyond the abstract". Beyond the Abstract Urotoday. 2015;1(1):1-5.

[8] Kataria P, Kendre P, Patel A, Dalsaniya S. Cutaneous metastasis leading to the diagnosis of carcinoma of the prostate: a rare case report and review of literature. Indian J Dermatol. 2018;63(2):182-5.

[9] Kavak A, Yılmaz M, Çam H, Tuğcu V, Albayrak H, Sakız D, et al. Cutaneous metastasis in prostate cancer: two cases with similar clinical findings. J Cancer Res Ther. 2018;14(7):1213.

[10] Wang S, Mecca P, Myskowski P, Slovin S. Scrotal and penile papules and plaques as the initial manifestation of a cutaneous metastasis of adenocarcinoma of the prostate: case report and review of the literature. J Cutan Pathol. 2008;35(1):681-4.

[11] Arita K, Kawashima T, Shimizu H. Cutaneous metastasis of prostate carcinoma. Clin Exp Dermatol. 2002;27:64-5.

[12] Bailey C, Broadbent A. Cutaneous metastases of prostate cancer. J Palliat Med. 2007;10:980-2.

[13] Mueller TJ, Wu H, Greenberg RE, Hudes G, Topham N, Lessin SR, et al. Cutaneous metastases from genitourinary malignancies. Urology. 2004;63:1021-6.

[14] Mo L, Zhang J, Shi J, Xuan Q, Yang X, Qin M, et al. Human kallikrein 7 induces epithelial-mesenchymal transition-like changes in prostate carcinoma cells: a role in prostate cancer invasion and progression. Anticancer Res. 2010;30:3413–20.

[15] Kraft Rovere R, Silva de Lima A, Casemiro KP. A case of small-cell prostate cancer with a metastasis to the scalp. Jpn J Clin Oncol. 2013;43(11):1156.

[16] Lopez-Navarro N, Lopez-Sanchez JC, Perez-Enriquez JE, Bosch RJ, Herrera E. Atypical skin metastases of mucinous adenocarcinoma of the prostate with signet ring cells. Actas Dermosifiliogr. 2009;100(4):338-41.

[17] Njiaju UO, Truica CI. Metastatic prostatic adenocarcinoma mimicking inflammatory breast carcinoma: a case report. Clin Breast Cancer. 2010;10(1):e3-5.

[18] Ogunmola AO, Shittu OB, Olapade-Olaopa EO. Cutaneous metastasis from prostate cancer in a Nigerian: a case report and literature review. Afr J Med Med Sci. 2013;42(3):283-6.

[19] Fukuda H, Saito R. A case of Sister Mary Joseph's nodule from prostatic cancer. J Dermatol. 2006;33:46-51.

[20] Boswell JS, Davis MD. Violaceous plaque on the forehead clinically resembling angiosarcoma: cutaneous metastasis in a patient with prostatic adenocarcinoma. J Am Acad Dermatol. 2005;53:744-5.

[21] Reddy S, Bang RH, Contreras ME. Telangiectatic cutaneous metastasis from carcinoma of the prostate. Br J Dermatol. 2007;156:598–600.

[22] Rattanasirivilai A, Kurban A, Lenzy YM, Yaar R. Cutaneous metastasis of prostatic adenocarcinoma: a cautionary tale. J Cutan Pathol. 2011;38(6):521-4.

[23] Rodríguez-Lojo R, Castiñeiras I, Rey-Sanjurjo J, Fernández-Díaz M. Distant cutaneous metastases of prostate cancer: a report of 2 cases. Actas Dermo-Sifiliográficas (English Edition). 2016;107(7):e52-6.

[24] Mak G, Chin M, Nahar N, De Souza P. Cutaneous metastasis of prostate carcinoma treated with radiotherapy: a case presentation. BMC Res Notes. 2014;7:505

[25] Brown G, Kurtzman D, Lian F, Sligh J. Eruptive nodules of the head and neck: a case report of metastatic prostate cancer. Dermatol Online J. 2014;20:18

[26] Yildirim Y, Akcay Y, Ozyilkan O, Celasun B. Prostate small cell carcinoma and skin metastases: a rare entity. Medical Principles and Practice. 2008;17(3):250-2.

[27] Emmett L, Willowson K, Violet J, Shin J, Blanksby A, Lee J. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. J Med Radiat Sci. 2017;64(1):52-60.

[28] Malcolm J, Falzone N, Lee BQ, Vallis KA. Targeted radionuclide therapy: new advances for improvement of patient management and response. Cancers (Basel). 2019;11(2):268-80.

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Case Report

A case of abdominal pain with a diagnosis of epiploic appendagitis

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Malini was a final year medical student at Monash University when the piece was written and is currently an intern at Eastern Health. She is the recipient of the Australasian College of Dermatology prize in dermatology. **Dr On Bon Chan** was a GP in East Doncaster at the time the piece was written and is currently in his first year as a dermatology registrar.

Key learning points

- Abdominal pain is a common presentation in general practice and a systematic approach is important to exclude serious pathology and achieve an accurate diagnosis.
- Murtagh's diagnostic framework and safety netting are effective strategies in managing diagnostic uncertainties.
- Epiploic appendagitis is a benign condition and an early diagnosis can prevent unnecessary investigations and treatment.

Abstract

Introduction: Abdominal pain is a common presentation in general practice and a systematic approach is required to exclude serious pathology and achieve an accurate diagnosis. **Case overview**: We present a case of a 76-year-old male who complained of left lower quadrant abdominal pain to illustrate a systematic approach to managing diagnostic uncertainty. The patient was subsequently diagnosed with epiploic appendagitis (EA). **Discussion overview:** Epiploic appendagitis can mimic other acute abdominal conditions including diverticulitis, omental infarction, and appendicitis. The recognition and early diagnosis of epiploic appendagitis helps to avoid unnecessary investigations and treatment.

Keywords: epiploic appendagitis; left lower quadrant pain; appendicitis; diverticulitis

Introduction

Acute abdominal pain is a common presentation to general practitioners, representing 2.1 per 100 consultations [1]. It is often a diagnostic dilemma with several causes ranging from benign to life threatening. This report presents a case of epiploic appendagitis (EA), a cause of abdominal pain that affects 8.8 per 1 million people per year [2]. It presents with sharp pain localised to either the right or left lower quadrant that self-resolves with simple analgesia [2]. In order to reach a diagnosis of EA, a strategy is required. The "restricted rule-outs", otherwise known as Murtagh's diagnostic framework, allows for this by asking clinicians to consider the most common causes of the presenting problem alongside serious diagnoses that must be ruled out [3]. The differential diagnoses for this patient were formulated using Murtagh's diagnostic framework (Table 1) [4]. The framework categorises differential diagnoses into probability diagnoses, serious disorders not to be missed, pitfalls, and rare conditions. Another strategy, "safety netting", is also useful when managing diagnostic uncertainty during consultations. It comprises of transparent communication with the patient regarding the diagnostic uncertainty and natural progression of the condition, “red flag” signs to be aware of, and avenues to seek further help [5]. In patients who present with acute abdominal pain, laboratory investigations and imaging are guided by the clinical presentation and published guidelines [6,7]. As a minimum, full blood examination and urinalysis should be performed on all patients with acute abdominal pain, with women of reproductive age also requiring a pregnancy test.

The Case

A 76-year-old male presented to a general practitioner with a three-day history of gradual onset, intermittent and stabbing left lower quadrant (LLQ) non-migratory abdominal pain. The pain was moderate to severe in intensity with no aggravating or relieving factors. He denied fever, night sweats, gastrointestinal and genitourinary symptoms. His significant medical history included obesity, hypertension, type 2 diabetes, and paroxysmal atrial fibrillation. His medications included amlodipine, apixaban, metformin, prazosin, ramipril, simvastatin, and allopurinol.

On examination, his vital signs were within normal limits. Cardiovascular examination was normal. Abdominal examination revealed no visible scars, striae, protrusions, or vascular changes. Superficial palpation of the abdomen revealed left lower quadrant tenderness with guarding but no rebound tenderness. Percussion of the abdomen was tympanic over the stomach and intestine and muffled over the spleen and liver. Bowels sounds were present. Rectal examination and urinalysis were normal.

Based on the clinical presentations, such as the gender and the age of the patient, the sudden onset of LLQ pain, and the abdominal guarding on palpation, the differential diagnoses that were considered include acute diverticulitis, omental infarction, and appendicitis. The clinical features of the above conditions are listed in Table 2 [8,9,10]. Urgent laboratory investigations and abdominal computerised tomography (CT) were requested to confirm the diagnosis and evaluate for complications. The investigations revealed normal white cell count and urinalysis (Table 3). The CT image showed three fatty epiploic appendages associated with the distal descending colon and proximal sigmoid colon. The epiploic appendages located at the distal descending colon measuring 45 x 14 mm had mild surrounding inflammation indicative of EA (Figure 1). Simple analgesics were prescribed and a follow-up appointment in two days was organised. The patient was instructed to present to the emergency department if his condition deteriorated. The abdominal pain improved significantly at the follow up appointment and resolved completely after two weeks.

Table 1: The differential diagnoses considered using Murtagh's diagnostic model [3]

Probability diagnosis
Diverticulitis
Renal colic
Colitis/ Gastroenteritis
Mesenteric artery occlusion
Serious disorders not to be missed
Cardiovascular
Ruptured AAA
Dissecting aneurysm aorta
Malignancy
Infective causes
Prostatitis
Seminal vesiculitis
Intra-abdominal abscess
Psoas abscess
Small bowel obstruction/strangulated hernia
Sigmoid volvulus
Perforated viscus
Appendicitis
Pitfalls (commonly missed)
Faecal impaction
Herpes Zoster
Rare conditions
Epiploic appendagitis
Porphyria
Lead poisoning
Haemochromatosis
Haemoglobinuria
Addison's disease

Figure 1: The axial view of the patient's CT abdomen image showing inflamed epiploic appendages in the descending colon (Green circle)

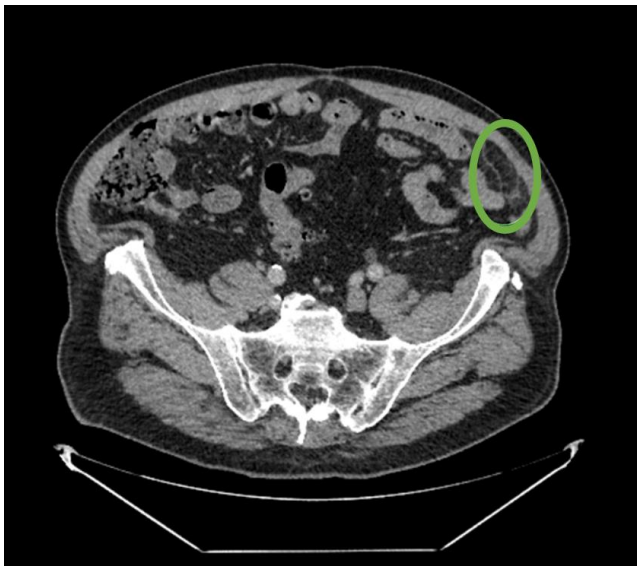


Table 2: The clinical features of diverticulitis, omental infarction and appendicitis [8,9,10]

Conditions	**Clinical Features**
Diverticulitis	• The most common cause of left lower quadrant abdominal pain in adults. It often presents in older patients (> 50) and is associated with nausea, vomiting, and change in bowel habits. • The triad of fever, left lower quadrant abdominal pain and leucocytosis are highly suggestive of diverticulitis.
Omental infarction	• The patient often presents with sudden onset abdominal pain associated with tenderness and gastrointestinal symptoms in the absence of a fever. It is encountered in healthy patients, such as marathon runners due to reduced omental blood flow.
Appendicitis	• The classic presentation consists of periumbilical pain (referred) which within a day or so localises to McBurney's point with associated fever, nausea and vomiting. It can also present with left iliac fossa pain in patients with a long appendix.

Table 3: Laboratory investigations

Test	Result

Urinalysis	no abnormality detected
Haemoglobin	183 g/L
White cells	6.3 x 10*9 /L
Neutrophils	3.3 x 10*9/L
Sodium	142mmol/L
Potassium	5.4mmol/L
Urea	5.1mmol/L
Creatinine	98umol/L
eGFR	64
Alkaline phosphatase test (ALP)	50U/L
Gamma-glutamyl transferase (GGT)	29U/L
Alanine transaminase (ALT)	21U/L
Aspartate aminotransferase (AST)	20U/L

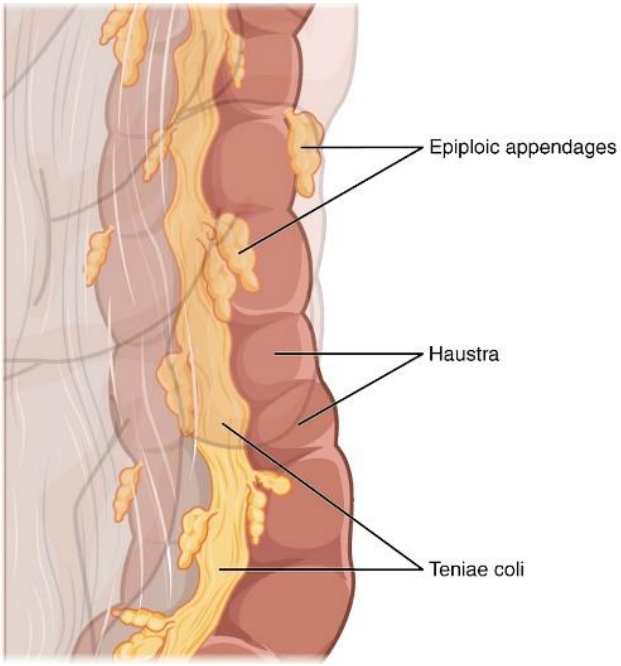
Table 4: Red flag symptoms and signs [16,17,18]

History	Signs
Age > 65 or Age < 5	Unstable vital signs (fever, hypotension
Female of reproductive age group	Rebound tenderness and guarding
History of malignancy	Decrease urine output
Cardiac disease (AF, IHD)	Abdominal mass / distension on palpation
Severe abdominal pain	
Pregnancy	
Intractable vomiting	

Discussion

In this case, the patient was diagnosed with EA, a benign and self-limiting condition. EA is the inflammation of the adipose tissue projection from the serosal surface of the colon along the free taenia and taenia omentalis. The most common sites of acute EA are the rectosigmoid junction (57%), ileocaecal region (26%), and ascending colon (9%) [11]. The causes of EA can be divided into primary and secondary. In the primary form, torsion of the epiploic appendages combined with spontaneous venous thrombosis causes ischaemia, localised inflammation, and infarction. Secondary EA is due to inflammation of the surrounding structures, such as the appendix and diverticula [12]. EA primarily affects those between the ages of 20 and 50. The risk factors include being obesity, strenuous exercise, and being male [13]. EA often presents as acute localised abdominal pain with variable location, intensity, and duration. Examination of the area may elicit localised and rebound tenderness Patients are usually afebrile and do not have other gastrointestinal symptoms or leukocytosis [11]. EA has been diagnosed in around seven percent of patients who were suspected of having acute diverticulitis and around one percent of patients suspected of having acute appendicitis [14,15]. Hence, it is important to treat it as a diagnosis of exclusion. Unnecessary admissions, medical and surgical interventions can be a result of misdiagnosing EA. The diagnosis of EA is usually made by CT scan, which is the gold standard technique of evaluating patients presenting with acute abdominal pain [16]. The condition resolves spontaneously within 3-14 days with simple analgesia, such as paracetamol and anti-inflammatories [11].

Figure 2: Epiploic appendages on the large intestine [8]



Abdominal pain has a wide range of causes, ranging from benign to life threatening. One of the main tasks of a general practitioner is to minimise the risk of missing a serious illness. "Red flags" are symptoms or signs found in the patient's history and clinical examination which could indicate the possibility of a serious underlying condition (Table 4) [17-19]. The presence of such signs and symptoms should prompt clinicians to consider further investigations or assessment at the emergency department. Unstable vital signs, signs of peritonitis on abdominal examination, leukocytosis, and elevated inflammatory markers have been associated with a higher incidence of hospitalisation [20].

This case emphasises the diagnostic and management strategies which can be used to manage acute abdominal pain in an outpatient setting. The early adaptation and practice of the above strategies may help medical students transition from medical school to clinical practice. The published guidelines can also be a valuable resource for junior doctors when choosing investigations and imaging modalities.

References

[1] BEACH Program, AIHW General Practice Statistics and Classification Unit. Presentations of abdominal pain in Australian general practice. Aust Fam Physician.2004; 33(12):968–9.

[2] P. de Brito, M. A. Gomez, and M. Bessson, "Frequency and epidemiology of primary epiploic appendagitis on CT in adults with abdominal pain," Journal de Radiologie. 2008; 89(2): 235–43.

[3] Morgan S, Chan M,Starling C. Starting off in general practice – consultation skill tips for new GP registrars. Aust Fam Physician. 2014; 43(9): 645-8.

[4] Murtagh J. Murtagh's Diagnostic Strategies. 1st edition. North Ryde NSW: McGraw-Hill Education; 2013.

[5] Jones D, Jones D, Dunn L, Dunn L, Macleod U, Watt I, et al. Safety netting for primary care: evidence from a literature review. Br Jr Gen Pract. 2019;69(678):e70–e79.

[6] Department of Health Western Australia. Imaging Pathway [Internet]. 2016 [updated 2021; cited 2020 Dec 13]. Available from: http://www.imagingpathways.health.wa.gov.au/index.php/initiatives

[7] The Royal College of Pathologists of Australasia. Abdominal pain [Internet]. 2019 [updated 2019; cited 2020 Dec 13]. Available from: https://www.rcpa.edu.au/Manuals/RCPA-Manual/Clinical-Problems/A/Abdominal-pain

[8] Chan E, El-Banna A. A case report of epiploic appendagitis as a mimic of acute cholecystitis. Int J Surg Case Rep. 2018; 53:327–9.

[9] You H, Sweeny A, Cooper M, Von Pape M, Innes J. The management of diverticulitis: a review of the guidelines. Med J Aust. 2019;211 (9): n/a. doi:10.5694/mja2.50276.

[10] Liu CC, Lu CI, Yen DH, Chern Ch, Wang LM et al. Diagnosis of appendicitis in the ED: comparison of surgical and non surgical residents. Am J Emerg Med. 2001; 19(2):109

[11] Subramaniam R. Acute appendagitis: emergency presentation and computed tomographic appearances. Emerg Med J EMJ. 2006;23(10):e53].

[12] Giannis, D., Matenoglou, E., Sidiropoulou, M. S., Papalampros, A., Schmitz, R., Felekouras, E., & Moris, D. (2019). Epiploic appendagitis: pathogenesis, clinical findings and imaging clues of a misdiagnosed mimicker. Annals of Translational Medicine, 7 (24), 814-814. Doi: 10.21037/atm.2019.12.74

[13] Nadida D, Amal A, Ines M, Makram M, Amira M, Leila BF, et al. Acute epiploic appendagitis: Radiologic and clinical features of 12 patients. Int J Surg Case Rep. 2016;28:219–22

[14] Mollà E, Ripollés T, Martínez M J, Morote V, & Roselló-Sastre E. Primary epiploic appendagitis: US and CT findings. Eur Radiol.1998; 8(3), 435–8.

[15] Rao PM, Rhea JT, Wittenberg J, Warshaw A L. Misdiagnosis of primary epiploic appendagitis. American J Surg.1998;176(1), 81–5.

[16] de Burlet KJ, MacKay M, Larsen P, Dennett ER. Appropriateness of CT scans for patients with non-traumatic acute abdominal pain. Brit J Radiol. 2018;91(1088):20180158–20180158.

[17] Leong, KF. Pitfalls and red flags in common clinical syndromes. SFP. Vol 39 No. 3. 2013.

[18] Soh, SB. Revisiting red flags in family practice. SFP. July-September 2005. Available at: https://www.cfps.org.sg/publications/the-singapore-family-physician/article/513_pdf

[19] Murtagh J. General Practice. 5th Edition. 308-309. 2011. McGraw-Hill Australia Pty Ltd.

[20] Velissaris D, Karanikolas M, Pantzaris N, Kipourgos G, Bampalis V, Karanikola K et al. Acute Abdominal Pain Assessment in the Emergency Department: The Experience of a Greek University Hospital. J Clin Med Res. 2017; 9(12):987-93

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Case Report

Asherman's syndrome – an important clinical update

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Dr Emma Keen graduated from Bond University in 2015 as a postgraduate having done a Bachelor of Nursing as an undergraduate degree. Her field of interest is obstetrics and gynaecology with special interests in reproductive medicine and gynaecology oncology.

Abstract

Asherman's syndrome is a gynaecological condition that can present with a myriad of symptoms, making it diagnostically challenging. Patient outcomes can be significantly altered with targeted and timely investigation and intervention. It is hoped that increased awareness surrounding this condition will contribute to better patient outcomes.

Keywords: Asherman's, Infertility, Pelvic pain, Gynaecology

Introduction

The patient is a 36-year-old G2P2 female with a complex gynaecological history, including a previous diagnosis of Asherman's syndrome. She presented to an outpatient clinic with complaints of increasing pelvic pain, intermenstrual bleeding and subfertility. The patient detailed a 12-month history of increasing pelvic pain. She also reported intermenstrual bleeding, lasting up to one week. The patient reported that her menstrual flow had significantly decreased over the last 12 months. The patient and her husband had a strong desire to have a third child and the ongoing implications of Asherman's syndrome could be seen to have a significant emotional impact on the couple.

Background

- P1: Spontaneous vaginal delivery at K37, third degree tear repaired, retained products with hysteroscopy dilation and curettage, post partum haemorrhage 1.5L with transfusion.
- P2: Threatened preterm labour at K32, elective LUSCS at K35 due to preterm labour
- Hysteroscopy dilation and curettage 2011 for complaints of pelvic pain and amenorrhea – diagnosed with Asherman's syndrome
- Pap smears up to date, never abnormal
- Hx chlamydia 1999- treated

Physical examination

A limited physical examination was performed in the outpatient clinic as the treating consultant deemed it unnecessary to subject the patient to an intimate examination given the need for further invasive testing.

Abdominal examination was unremarkable. Vaginal examination findings from a recent GP consultation were noted; they included generalised tenderness in both adnexa; no masses were felt and no cervical motion tenderness elicited. The results initial investigations are presented in Table 1.

Table 1. Results of Mrs. P's initial investigations

Investigations	
b-HCG	<5
Pelvic USS (TA and TV)	Diffuse slightly increased vascularity throughout myometrium. Endometrial stripe 1mm. Calcification in endometrial cavity – may reflect prior inflammation or Asherman's.
TFTs	Normal
Iron studies	Normal

Diagnosis

A provisional diagnosis of recurrence of Asherman's syndrome was made. Differential diagnoses included endometriosis, dysfunctional uterine bleeding which encompasses a multitude of causes, easily remembered using the FIGO pneumonic "PALMCOEIN" (see Figure 1), and infection.

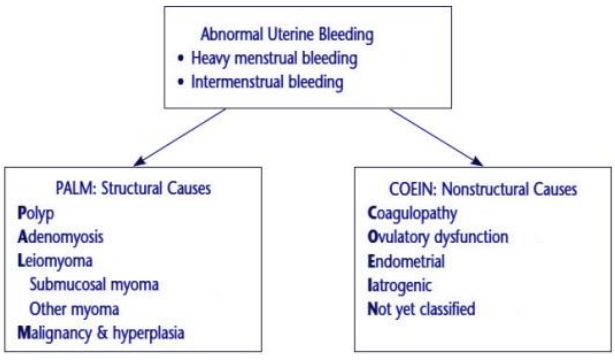

Figure 1. FIGO mnemonic for abnormal uterine bleeding. [10]

Management

The three issues of priority in this case were: pain, bleeding and fertility.

With these issues in mind, it was necessary to proceed with targeted investigations in attempt to confirm the diagnosis of Asherman's syndrome as a cause for subfertility and menstrual changes.

The patient was sent for the following investigations:

- Hysterosalpingogram (HSG) to assess the uterine cavity, fallopian tubes and endometrium [3]. The patient was advised that this investigation is best performed in the early proliferative phase of her menstrual cycle. The procedure carries 75% sensitivity and a positive predictive value of 42.9% for Asherman's syndrome [3].
- Day 21 progesterone level: to assess whether ovulation is occurring. The test is done at the expected time of ovulation [9]. A level above 20-25 nmol/L confirms ovulation [9]. A low level can indicate anovulatory cycles or incorrect timing of the test [9]. If a low result is received, the patient is advised to re-test in the next cycle with two separate measurements one week apart [9].
- Hysteroscopy dilation and curettage: direct visualisation of the uterine cavity is the most appropriate way to diagnose Asherman's syndrome and is used as an adjunct to a HSG [8]. The procedure is both diagnostic and therapeutic as division of adhesions can be performed concurrently. Postoperative high dose oestradiol is recommended for 6 weeks to encourage endometrial growth over the areas of deficient endometrium followed by progesterone during the 6th week with a withdrawal bleed to follow [8]. Simultaneous laparoscopy was also discussed with the added benefit of investigating for other causes of infertility.
- A high vaginal swab, FBC and CRP were ordered to rule out infection as a cause for the patients' symptoms9.
- The patient was encouraged to continue with simple analgesia – non steroidal anti-inflammatories are advised for pelvic pain of reproductive origin given that the pain associated with menstruation is prostaglandin mediated [9].
- The patient was scheduled for a review in outpatient clinic for 6-8 weeks postoperatively to check for resolution of symptoms and withdrawal bleed from progesterone.

Outcome

The patient underwent investigations as outlined in the management plan above. The results of her hysterosalpingogram showed irregularity of the endometrial cavity with a filling defect at the corneal part of the uterus. Findings were consistent with a diagnosis of Asherman's syndrome. Day 21 progesterone levels were 58nmol/L indicating that her cycles were ovulatory and that subfertility was not a result of anovulatory cycles. Hysteroscopy with division of adhesions was performed and the prescribed course of oral oestrogen and progesterone completed. The patient reported a withdrawal bleed and improvement of her pelvic pain. She was subsequently given conception counselling and scheduled for a further check up in outpatient clinic.

Discussion

Incidence

The true incidence of Asherman's syndrome is unclear, however, estimates suggest figures range between 6-40% post dilation and curettage and up to 7% as a cause in cases of secondary amenorrhea [1, 5]. Many cases of Asherman's syndrome are undiagnosed and therefore it is difficult to assess the true incidence of the condition. The reported incidence varies greatly depending on the classification system used, and the suggested aetiology. An example of a classification system developed by the American Fertility Society is given below in Table 2.

Table 2. American Fertility Society classification of intrauterine adhesions. [11]

Extent of cavity involved	**<1/3 (1 point)**	**1/3-2/3 (2 points)**	**>2/3 (4 points)**
Type of adhesions	Filmy (1 point)	Filmy and dense (2 points)	Dense (4 points)
Menstrual pattern	Normal (0 points)	Hypomenorrhoea (2 points)	Amenorrhoea (4 points)
Stage 1 – mild	1-4 points		
Stage 2- moderate	5-8 points		
Stage 3- severe	9-12 points		

*The scores from each category are added together to give a total score indicative of the severity of intrauterine adhesions***.**

Risk factors

Table 3 shows the risks factors for the development of Asherman's syndrome or intrauterine adhesions. Interestingly, the development of Asherman's syndrome is most commonly related to iatrogenic trauma to the endometrium [2]. A study published in 1982 showed that women who underwent uterine curettage were at high risk of developing intrauterine adhesions, particularly those who underwent curettage between the second and fourth post partum weeks [1-2]. Curettage after miscarriage was shown to have the highest association with the development of Asherman's syndrome2. One suggested way to group the risk factors for Asherman's syndrome is to place the possible causes under the following headings: mechanical and iatrogenic complications, pathophysiological disturbance and idiopathic causes [11].

Table 3. Risk factors for Asherman's syndrome.

Miscarriage curettage
Post partum curettage
Caesarean section
Trophoblastic disease evacuation
Infection (genital tuberculosis)
Diagnostic curettage
Abdominal myomectomy
Uterine artery embolization
Hysteroscopic surgery
Insertion of IUD
Uterine compressive sutures for post partum haemorrhage

Mullerian duct malformation

Clinical features

The clinical presentation of Asherman's syndrome varies greatly. Women may present to gynaecology clinics with manifestations ranging from menstrual irregularity, dysmenorrhea and subfertility to pregnancy complications [5].

History should be aimed at identifying risk factors for the condition including previous infections such as pelvic inflammatory disease, iatrogenic complications, obstetric complications and a history of genital tuberculosis [1].

Clinical examination in patients with Asherman's syndrome is most often unremarkable [2]. A thorough history and examination should be performed on all patients presenting with similar complaints. Basic investigations should include haematological testing (including full blood count, beta HCG), and pelvic ultrasound9. A suggested physical examination would include detailed general examination including assessing for lymphadenopathy, an abdominal examination palpating for masses, ascites or organomegaly, a vaginal speculum exam and a bimanual exam9. A rectal examination should be considered if clinically indicated, as the pouch of douglas for example, best felt on the anterior rectal wall, is implicated in endometriosis9. A detailed history and examination should provide assistance in narrowing down differential diagnoses. Key points that suggest Asherman's syndrome are those outlined in the clinical features above, particularly; a change in menstrual pattern, specifically reducing flow or absent menses, cyclical pelvic pain and fertility concerns [2].

Treatment

There is currently a lack of evidence to support any one treatment method being superior to another in the management of Asherman's syndrome. In general, the management principles involve lysis of the intrauterine adhesions followed by promoting regrowth of the endometrium [11]. Due to the lack of consensus on treatment regimes, the management is currently purely clinician dependent.

The lysis of intrauterine adhesions is performed during hysteroscopy with caution taken not to cause further trauma to the endometrial basal layer [8]. Lysis is primarily undertaken in symptomatic patients presenting with infertility, recurrent pregnancy loss, and pelvic pain [8]. In those patients who do not desire fertility or who are asymptomatic with intrauterine adhesions, there is no clinical indication to perform lysis [8].

One of the main concerns with Asherman's syndrome is the recurrence of adhesion formation after treatment. The case example given above exemplifies this complication. Up to 50% of patients will suffer from reformation of adhesions after hysteroscopic lysis [4]. There are several methods available to prevent reformation of adhesions, however none have been proven to be more superior [4].

As demonstrated in this case, oestrogen can be used to promote regrowth of the endometrium [11]. Oestrogen is given for between 30 to 60 days depending on the severity of adhesions, followed by progesterone to induce a withdrawal bleed and recommence the menstrual cycle [11]. It is thought that oestrogen helps to restore growth of normal uterine lining and subsequently prevent further scar tissue forming [11].

Other methods used to prevent recurrence of adhesions include barrier devices such as intrauterine devices (IUD), paediatric foley catheters and intrauterine balloons6. More recently, studies have been conducted into the use of anti-adhesion barriers including spray gels and sheets such as those used during laparoscopy [8]. There are several different compounds available including hyaluronic acid gel and sodium hyaluronate (Seprafilm™) [8]. Studies have demonstrated increased pregnancy rates and decreased adhesion formation in the context of adhesion barrier use and Asherman's syndrome [8]. These studies are promising, but there is a lack of significant confirmatory data to support the proposed advantage of their use as treatment for Asherman's syndrome.

Conclusion

Asherman's syndrome can be a very distressing condition in the setting of desired fertility and is known to have a significant impact on female reproduction. Hence, it is extremely important to ensure continuing awareness of the causes, clinical presentation and treatment. Increased awareness will ensure early recognition and management of the condition and provide support and advice to those patients who wish to conceive despite this diagnosis.

References

[1] Asherman JG. Traumatic intra-uterine adhesions. BJOG 1950; 57:892-96.

[2] Conforti A, Alviggi C, Mollo A, De Placido G, Magos A. The management of Asherman syndrome: a review of literature. Reprod Biol Endocrinol 2013; 11: 118.

[3] Tan I, Robertson M. The role of imaging in the investigation of Asherman's syndrome. AJUM 2011; 14 (3): 15-18.

[4] Oluwasseun F. Reproductive outcome following hysteroscopic adhesiolysis in patients with Asherman's syndrome. World J Lap Surg 2011; 4(1): 31-39.

[5] March CM. Intrauterine adhesions. Obstet Gynecol Clin North Am 1995; 22: 491-525.

[6] Amer MI, El Nadim A, Hassanein K. The role of intrauterine balloon after operative hysteroscopy in the prevention of intrauterine adhesions. Acta Eur Fertil 1976; 7: 215-18.

[7] Katz Z, Ben-Arie A, Lurie S, Manol M, Insler V. Reproductive outcome following hysteroscopic adhesiolysis in Asherman's syndrome. Int J Fertil Menopausal Stud 1996; 41: 462-65.

[8] Bellingham FR. Intrauterine adhesions: hysteroscopic lysis and adjunctive methods. Aust NZ J Obstet Gynaecol 1996; 36: 171-174.

[9] Practice Committee of the American Society for Reproductive Medicine. Current evaluation of amenorrhea. Fertil Steril 2006; 86: 5148-155.

[10] Munro M, Critchley H, Fraser I. FIGO systems for nomenclature and classification of causes of abnormal uterine bleeding in the reproductive years: who needs them? Am J Obstet Gynecol 2002; 207: 259-265.

[11] AAGL Practice Report. Practice guidelines for management of intrauterine synechiae. J Minim Invasive Gynecol 2010; 17(1).

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Case Report

Post-Operative Wound Infection in the Context of Immunosuppression

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Sarah Noonan is a 4th year medical student, at University of Wollongong, NSW. I aspired to a career in medicine because it is the highest pursuit for someone who loves problem solving and continual learning. I have a strong commitment to rural communities, and I look forward to a long career in rural medicine. I am from a rural background and chose to undertake my studies at UOW for their strong rural connection. I further undertook many clinical placements in rural and remote communities and consider myself a rural health advocate. I would eventually like to further my career into rural paediatric medicine. I have always held an interest in this field as seen by my previous research in paediatric immobilisation in medical imaging as well as rural induction of labour.

Key learning points

- It would be appropriate to consider ceasing biologic DMARDs including TNF-alpha inhibitors perioperatively to decrease the risk of surgical site infections in patients taking these agents. The time course of this should be carefully correlated to the pharmacokinetics and half-life of the agent under consideration.
- Glucocorticoids increase the risk of surgical site infections in a dose dependent manner and professionals should consider weaning patients to a dose of <10mg per day.
- Conventional DMARDs have not demonstrated an increase in risk of surgical site infections, and these can be safely continued peri-operatively.
- There is a fine balance between the risk of surgical site infections versus benefit of preventing disease flares in ceasing medications perioperatively which often requires the expertise of more than one medial team.

Abstract

Introduction: Surgical site infections remain one of the most common complications associated with surgery in Australia and the world. Many factors contribute to infection risk, however, immunosuppressive and immunomodulatory drugs such as DMARDs, biological DMARDs and glucocorticoids pose a unique risk. **Case Overview:** A 70-year-old female developed a surgical site infection post-repair of a ruptured Achilles tendon. She had a background of psoriatic arthritis treated with immunosuppressive agents which were not ceased prior to the surgical treatment. **Discussion Overview:** The current literature suggests that biologic DMARDs and glucocorticoids increase the risk of surgical site infections in patients undergoing a procedure. It is therefore imperative to emphasize the importance of careful medication histories and recognition of medication side effects with a risk versus benefit balance.

Keywords: Post-operative, Infection, Immunosuppression, Surgical, DMARDs.

Introduction

Surgical site infections are healthcare-associated infections that occur after a surgical incision. They are one of the most common complications associated with surgery and in Australia, occurring in approximately 3% of surgical patients [1]. Surgical site infections contribute significantly to adverse clinical outcomes, increased morbidity and mortality as well as increased healthcare costs [1].

Many factors contribute to infection risk, including perioperative antibiotic use, surgical experience and technique, post-operative care and patient characteristics [2]. The single most important risk factor for surgical site infections remains a history of prior surgical site infection or skin infection. However, immunosuppressive and immunomodulatory drugs used in the treatment of inflammatory conditions pose a unique risk for some patients [2].

Immunosuppressive and immunomodulatory drugs such as conventional disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs including tumour necrosis factor (TNF) alpha antagonists and glucocorticoids are indicated for the treatment of inflammatory arthritic conditions and inflammatory bowel disease to name a few [3]. Commonly used conventional DMARDs include methotrexate and leflunomide. Biologic DMARDs are usually only prescribed after the failure of treatment with a conventional DMARD therapy [3].

The theory that immunosuppressant medications may predispose to postoperative complications and surgical site infections is rooted in their role in inhibiting the inflammatory cascade, a key component of the wound healing process. Via this mechanism of action, it is important to understand that stopping these medications before surgery can lead to a higher chance of flares of the inflammatory condition. A higher dose of glucocorticoid may be required post-surgery to control the inflammation and it may take up to three months for DMARDs and biological DMARDs to become fully effective again. Medication management requires a risk-benefit discussion between patients, surgeons, and physicians [4].

Case

JM, a 70-year-old female, presented to a rural hospital with a one-week history of worsening pain and swelling in the right

ankle with general malaise. JM described isolated 7/10 deep, throbbing pain to the achilles tendon. This was on a background of achilles tendonitis after an injury 19 months earlier for which she received physiotherapy. JM then suffered an achilles tendon rupture 11 months ago and surgical repair two months ago receiving five days roxithromycin 150mg orally for infection prophylaxis. The wound was healing well immediately post-operatively.

Past medical history was significant for right total knee replacement nine months prior to achilles tendon rupture which required significant immobilisation and precipitated a right groin DVT. This was being treated with rivaroxaban 20mg daily as treatment. There was a medical history of obesity, hypothyroidism, hypertension, and hypercholesterolaemia for which she was taking levothyroxine 125mcg daily, candesartan/hydrochlorothiazide 32/25mg daily and rosuvastatin 20mg daily. There was an important history of moderate psoriatic arthritis diagnosed at 36 years of age. JM has been taking prednisone 3mg daily, adalimumab 40mg subcutaneously fortnightly and leflunomide 20mg orally daily for many years, although the time-course was unknown. Family history was significant for rheumatoid arthritis in JM's mother and sister. She lived at home with her husband in a rural town three hours from the nearest regional centre. JM was completely independent with activities of daily living and mobilised unaided.

JM was admitted to the rural hospital and treated with intravenous 2g cephazolin. The following day, the wound spontaneously erupted with purulent and bloody discharge from a one centimetre opening over the old excision site. JM experienced continual pain despite analgesia and progressive wound discharge, oedema, and erythema despite intravenous cephazolin and was transferred to a larger referral hospital the following day. She was then taken to theatre for a surgical washout of the Achilles wound.

Investigations undertaken on admission to the referral hospital included full blood count demonstrating lymphocytosis with neutrophilia, C-reactive protein raised to 331, and erythrocyte sedimentation rate 99 which were down-trending. A wound swab demonstrated methicillin sensitive Staphylococcus aureus. Radiographic imaging revealed no abnormalities.

On examination post-washout at the referral hospital, JM appeared systemically well. Routine observations were within normal range. A VAC dressing was in situ on the posteromedial right lower leg set to 125mmHg with suction well applied. The VAC foam sat deep to surrounding tissue, suggestive of a deep wound, although difficult to visualise. Erythema and tenderness were noted at the wound borders with a smooth mass felt in the posterior calf, suggestive of an old haematoma. Pitting oedema was evident to the right knee and the right groin was tender to palpation over the femoral triangle. The left leg was normal on examination and peripheries were neurovascularly intact bilaterally. The remainder of the cardiovascular and respiratory exam was normal.

JM continued to deteriorate the following day with much increased pain in the right ankle. The orthopaedic team performed a subsequent wound washout in theatre where the wound was described as clean with granulating tissue at the base. JM continued to improve over the next two days before developing new pain and erythema in the midfoot and distal calf. An MRI of the right ankle demonstrated two infectious collections with draining sinus. Rupture and retraction of calcaneal tendon and fatty replacement of both heads of the gastrocnemius and soleus were also noted. This led to increased patient dissatisfaction and revealed a lack of understanding surrounding biologic DMARDs and their use in immunosuppression. A subsequent wound swab later demonstrated pseudomonas and the collections were drained under ultrasound guidance. JM was started on oral clindamycin 450mg three times per day while continuing on IV cephazolin 2g four times per day.

JM continued to improve and was discharged home 15 days after transfer to the referral hospital with a plan to follow up in the rural emergency department for VAC dressing changes. Cephazolin was changed to oral cephalexin 500mg four times per day and JM was continued on oral azithromycin 450mg three times per day. JM was to withhold prednisone 3mg daily, adalimumab 40mg fortnightly and leflunomide 20mg daily until a review in two weeks with both the orthopaedics specialist and infectious diseases specialist as an outpatient.

Figure 1. Wound one week prior to hospital presentation.

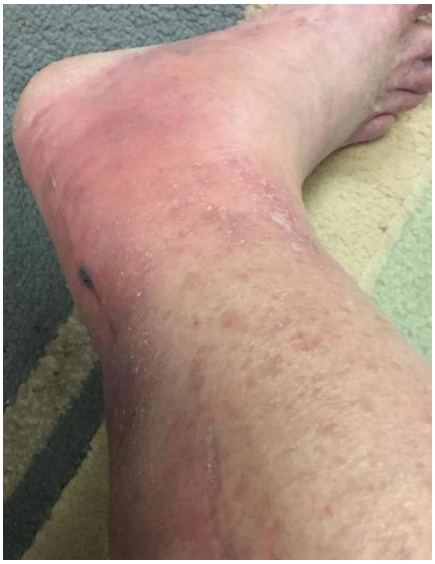

Figure 2. Vac dressing treatment.

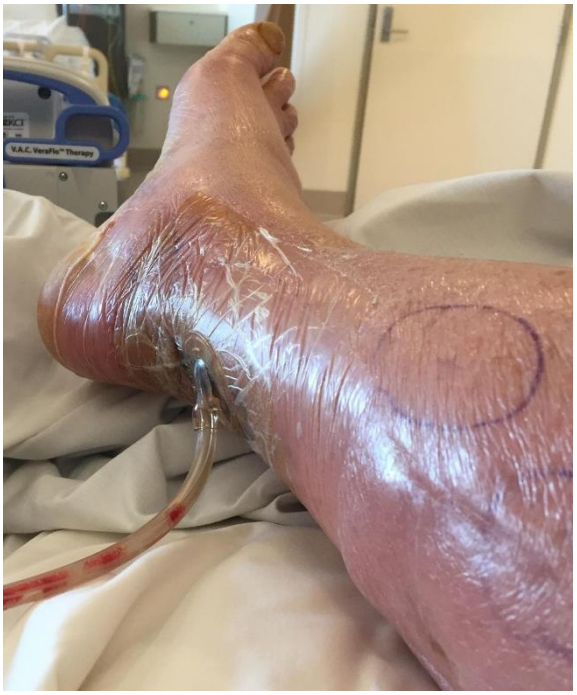

Table 1: Risks and Benefits of Continuing Medications Peri-operatively

Drug class	Risks of continuing perioperatively	Benefits of continuing perioperatively
DMARDs	No or very low risk of post-operative surgical site infection or delayed wound healing.	Decreased risk of flares which delay wound healing and overall patient recovery.
Biologic DMARDs	High risk of post-operative surgical site infection	
Glucocorticoids	Dose dependent increase in risk of post-operative surgical site infection. Added risk of delayed wound healing.	

DMARDs = disease modifying anti-rheumatic drugs

Discussion

Recommendations are outlined by the American College of Rheumatology and the Canadian Rheumatology Association for the perioperative management of immunosuppressed patients. This included continuing DMARDs such as leflunomide and methotrexate without interruption as there is low or no infection risk demonstrated in a systematic review of three clinical practice guidelines and one consensus statement [5, 6]. Stopping therapy, however, may result in a flare of disease and impede recovery from surgery [5, 7].

Recommendations for withholding biologic DMARD before surgery varied from one week to two months for TNF-alpha inhibitors. A systematic review of 12 clinical guidelines and one consensus statement recommended withholding these agents prior to surgery with the exception of the British Society of Rheumatology which suggested that they could be continued. The timeline for withholding therapy should take into account the clinical scenario, type of surgery (e.g. sterile, septic), and patient comorbidities [5]. Six guidelines suggested that the timing for withholding therapy should be based on the pharmacokinetic properties of the agent used while one recommended withholding biologic DMARDs for 3–5 half-lives and TNF-alpha inhibitors' for one dose cycle [8, 9]. Eight guidelines recommended that biologics may be restarted postoperatively if there is no evidence of infection and wound healing is satisfactory. A Spanish guideline suggested waiting 10–14 days [10] and a Japanese guideline recommended with-holding agents for at least two weeks [11].

Biologic DMARDs increased the risk of serious infection compared to conventional synthetic DMARDs [12, 13]. Side effect profiles including infection risk may differ between medications because of different mechanisms of actions or dosing and most research focuses on the use of TNF-alpha inhibitors [2]. A study of 47, 887 cases demonstrated the rate of surgical site infections was 5.7% in patients using TNF-alpha inhibitors and decreased significantly to 2.8% in patients using conventional DMARDs. This was more than the 1.6% rate of surgical site infections in patients with inflammatory disease not using any agents and 0.8% in other surgical patients without any history of inflammatory disease [14]. This study also significantly demonstrated that the risk of post-operative infection was 10 times higher in patients where agents were stopped less than one administration interval before surgery to compared to those stopped more than one administration interval before surgery [14]. Therefore, it should be recommended to cease biologic DMARDs perioperatively in order to decrease risk of surgical site infections as outlined in table 1.

Glucocorticoids including prednisone, methylprednisolone and dexamethasone demonstrate an increased risk of surgical site infection in a dose dependent manner as outlined in table 1 [6]. For patients taking >10mg/day of glucocorticoid, 13.25% experienced post-operative infection compared to 8.76% of patients taking 5-10mg/day and 6.78% of those not taking glucocorticoids in a statistically significant study [2]. Wound healing is also delayed in patients taking glucocorticoids and it is suggested to wean doses to at least <10mg/day [2]. It is suggested to maintain a small dose of glucocorticoid rather than administering perioperative supraphysiologic dose or "stress-dosing" [15].

Surgical site infections remain one of the most common complications associated with surgery in Australia and throughout the world. Immunosuppressive and immunomodulatory drugs such as DMARDs, biological DMARDs, and glucocorticoids pose a unique risk to surgical patients and highlight the importance of a careful medication history. In addition to this, it is also important to be aware of medications side effects and contra-indications. Once this is considered, there remains a decision to cease or continue medications peri-operatively. The risk must always be weighed against the benefit of continuing medications and as for many inflammatory conditions, the risk of disease flares is often large and debilitating. This is a complex process and often requires the expertise of more than one medical team.

References

[1] Australian Commission on Safety and Quality in Health Care. Approach to Surgical Site Infection Surveillance. Sydney: Australian Commission on Safety and Quality in Health Care; 2017. Available from: https://www.safetyandquality.gov.au/sites/default/files/migrated/Approaches-to-Surgical-Site-Infection-Surveillance.pdf.

[2] George MD, Baker JF, Winthrop K, Alemao E, Chen L, Connolly S, et al. Risk of Biologics and Glucocorticoids in Patients With Rheumatoid Arthritis Undergoing Arthroplasty. Annals of internal medicine. 2019; 170(12):825-36. Available from: https://www.acpjournals.org/doi/abs/10.7326/M18-2217. DOI: 10.7326/m18-2217.

[3] Benjamin O, Bansal P, Goyal A, Lappin SL. Disease modifying anti-rheumatic drugs. StatPearls [Internet]: StatPearls Publishing; 2020. Available from: https://pubmed.ncbi.nlm.nih.gov/29939640/

[4] Krause ML, Matteson EL. Perioperative management of the patient with rheumatoid arthritis. World Journal Orthopedics. 2014; 5(3):283-91. Available from: https://pubmed.ncbi.nlm.nih.gov/25035831. DOI: 10.5312/wjo.v5.i3.283

[5] 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. Available from: https://pubmed.ncbi.nlm.nih.gov/22707613/. DOI: 10.3899/jrheum.120165

[6] Baker JF, George MD. Prevention of infection in the perioperative setting in patients with rheumatic disease treated with immunosuppression. Current rheumatology reports. 2019; 21(5):17. Available from: https://pubmed.ncbi.nlm.nih.gov/30847768/. DOI: 10.1007/s11926-019-0812-2

[7] 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 (Oxford, England). 2016; 55(3):573-82. Available from: https://pubmed.ncbi.nlm.nih.gov/26447162/. DOI: 10.1093/rheumatology/kev364

[8] Royal College of Nursing: Rheumatology Biologics Working Party. Assessing, managing and monitoring biologic therapies for inflammatory arthritis Guidance for rheumatology practitioners. London: The Royal College of Nursing; 2003.

[9] Rezaieyazdi Z, Sahebari M, Khodashahi M. Preoperative Evaluation and Management of Patients Receiving Biologic Therapies. The archives of bone and joint surgery. 2019; 7(3):220-8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6578481/.

[10] Tornero Molina J, Sanmartí Sala R, Rodríguez Valverde V, Martín Mola E, Marenco de la Fuente JL, González Álvaro I, et al. [Update of the Consensus Statement of the Spanish Society of Rheumatology on the management of biologic therapies in rheumatoid arthritis]. Reumatologia clinica. 2010; 6(1):23-36.

[11] Koike R, Harigai M, Atsumi T, Amano K, Kawai S, Saito K, et al. Japan College of Rheumatology 2009 guidelines for the use of tocilizumab, a humanized anti-interleukin-6 receptor monoclonal antibody, in rheumatoid arthritis. Modern rheumatology. 2009; 19(4):351-7. Available from: https://pubmed.ncbi.nlm.nih.gov/19590933/. DOI: 10.1007/s10165-009-0197-6

[12] Ito H, Kojima M, Nishida K, Matsushita I, Kojima T, Nakayama T, et al. Postoperative complications in patients with rheumatoid arthritis using a biological agent – A systematic review and meta-analysis. Modern rheumatology. 2015; 25(5):672-8. Available from: https://pubmed.ncbi.nlm.nih.gov/25671400/. DOI: 10.3109/14397595.2015.1014302

[13] Franco AS, Iuamoto LR, Pereira RMR. Perioperative management of drugs commonly used in patients with rheumatic diseases: a review. Clinics (Sao Paulo). 2017; 72(6):386-90. Available from: https://pubmed.ncbi.nlm.nih.gov/28658439/. DOI: 10.6061/clinics/2017(06)09

[14] Scherrer CB, Mannion AF, Kyburz D, Vogt M, Kramers-de Quervain IA. Infection Risk After Orthopedic Surgery in Patients With Inflammatory Rheumatic Diseases Treated With Immunosuppressive Drugs. Arthritis Care & Research. 2013; 65(12):2032-40. Available from: https://pubmed.ncbi.nlm.nih.gov/23861140/. DOI: 10.1002/acr.22077

[15] 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. Arthritis & Rheumatology. 2017; 69(8):1538-51. Available from: https://pubmed.ncbi.nlm.nih.gov/28620948/. DOI: 10.1002/art.40149

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Literature Review

Pharmacotherapies for muscle wasting in older ICU patients: A narrative review of the current literature

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Dr. Finn Dolan Caogswell was born and raised in Canada, completing a Bachelor of Science in exercise science and, while an undergraduate, serving as a medic in the Canadian Army Reserves. He moved to Melbourne for medical school, and having graduated with an MD from the University of Melbourne in 2021, he now works at the Royal Melbourne Hospital as a junior doctor. Finn's evolving medical interests lay in critical care medicine, emergency medicine, psychiatry, and space/aerospace medicine.

Key learning points

- At present, there is no easy fix for muscle wasting in critical illness. The need for an effective and safe therapy targeting this important issue remains unmet.
- Mitigating the amount of muscle we lose with age, via appropriate physical activity and nutrition throughout life, is perhaps one of the few physiological defences we have for periods of critical illness in older age.
- For the future of therapies targeted at reducing muscle loss in critical illness, the most promising research currently lies in biologic therapies.

Abstract

Background: The predominantly geriatric syndrome of frailty can result from the gradual reduction of function in multiple physiologic systems that occurs with increasing age. Critical illness accelerates the age-related loss of muscle that often accompanies frailty, and the combination of these two conditions creates a distinctly morbid state of vulnerability. Muscle wasting while in the intensive care unit (ICU) results in greater patient morbidity, making the preservation of muscle mass an important therapeutic target. This article narratively reviews the drug therapies that have been trailed for mitigating muscle wasting in older critically ill patients.

Materials and Methods: MEDLINE, PubMed, Web of Science and EMBASE were searched. Inclusion criteria were drug trials with muscle-related outcome measures in critically ill populations aged 50 or older. Exclusion criteria were non-pharmacological interventions, a lack of muscle related outcomes, review articles, case studies, case series and non-English articles.

Results: From 4586 identified articles, 27 articles were included in the final review. While burn populations benefitted from oxandrolone, the only pharmacotherapy that demonstrated an improvement of muscle outcomes in older general ICU patients was intensive insulin therapy. However, due to the risk of hypoglycaemia, the use of intensive insulin therapy remains largely unfavourable.

Discussion: The requirement for an effective drug therapy targeting the preservation of muscle mass in older ICU populations remains unfulfilled. Several novel drug therapies targeting myostatin and activin receptors have recently been studied in frail, non-critically ill populations. Future research should focus on studying novel pharmacotherapies in the frail and critically ill.

Keywords: Critical illness, ICU, Frailty, Sarcopenia, Muscle Wasting

Introduction

Muscle loss is a core feature of both critical illness and frailty. Patients with a combination of these two catabolic states have a heightened risk of morbidity and mortality, proportional to the amount of lean body mass that is lost [1, 2]. Frailty, which increases with age, is defined as a state where the generalised impairment of multiple organ systems results in an increased vulnerability to stressors. A condition related and often comorbid to frailty is sarcopenia, which is the progressive age-related loss of skeletal muscle mass and strength [3-5]. The chronic catabolic state of frailty is partly due to inflammatory mediators that are also elevated in critical illness [3]. Previous studies have demonstrated that approximately one in three patients admitted to ICUs are frail, and frailty is associated with an increased incidence of critical illness [3, 6, 7]. When the frail with pre-existing sarcopenic muscle loss are afflicted by critical illness, the combination of these two conditions leads to an amplification of lean mass loss and a rise in morbidity [1].

Critical illness encompasses life-threatening disorders of the respiratory, cardiovascular or neurological systems, often in combination. Regardless of the primary cause of disease, critical illness is accompanied by muscle loss, including loss of respiratory muscle, beginning in the acute phase of severe disease [8, 9]. This is due to a dramatic hypermetabolic response that results in profound proteolysis, as metabolic derangement results in protein being used more for energy rather than for protein synthesis [1, 10-12]. With muscle being the largest protein reservoir in the body, muscle is broken down for fuel. This catabolic response is a prolonged process which has severe implications for long-term prognosis and recovery. The loss of muscle mass leads to decreased strength, causing a markedly impaired capacity for rehabilitation [8, 11, 13]. More than half of ICU survivors have been shown to experience a substantially

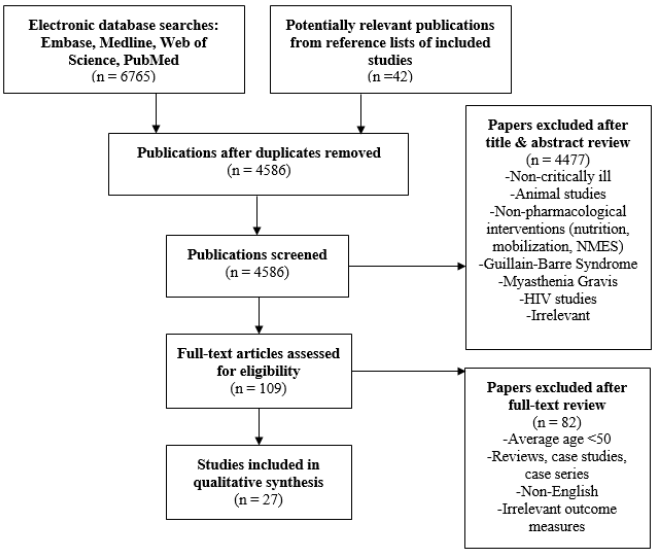
reduced quality of life, financial hardship and significant loss of function enduring long after their ICU admission [14, 15].

In the critically ill, the preservation of lean body mass and skeletal muscle function is vital not only for reducing the acute risk of morbidity and mortality, but also in achieving satisfactory post-ICU outcomes. Neither nutritional nor physical therapies in isolation adequately address the loss of muscle in ICU, and, thus, alternative interventions are required [7, 14, 16-20]. Pharmacological therapies are an attractive option. The purpose of this review was to identify and evaluate all of the pharmacological therapies that have been used to mitigate muscle wasting in older ICU patients.

Materials and Methods

On the 04/09/2020, a search was conducted on MEDLINE, PubMed, Web of Science and EMBASE, using the following search strategy: ("Intensive Care" OR "Critical Care" OR "Critical Illness") AND (Frail* OR Sarcopeni* OR "Weakness") AND (therap* OR "Pharmacotherapy"). No restrictions were placed on the search. Reference lists of each included study were screened for relevant articles which had not been included in the initial search. Included studies had populations of critically ill adults with an average age of 50 or older. This minimum average age was set to capture a frailer cohort, as older adult populations would be more likely to have a higher prevalence of frailty, and literature specific to frail populations was limited. Study interventions must have included a pharmacotherapy and reported outcomes on a muscle-related measure, including measures of protein balance and metabolism and measures of muscle function, such as the duration of ventilatory support. Exclusion criteria included non-pharmacological interventions or studies without muscle-relevant outcomes. In addition, non-critically ill surgical populations, review articles, case studies, case series and studies not available in English were excluded.

Figure 1. PRISMA diagram of the search strategy.



Results

Following the removal of duplicate publications, the initial search identified 4586 articles, including 42 from the reference lists of included studies (Figure 1). 4477 articles were excluded after title and abstract screening, and 82 were excluded following full-text review, leaving 27 articles meeting inclusion criteria. No studies utilising novel biologic therapies were identified. There were eight publications on recombinant human growth hormone (Table 1) (8-11, 21-24), fourteen on insulin therapy (Table 2) (25-38), two on oxandrolone, (Table 3) [39, 40], one on intravenous immunoglobulin (Table 4) [41], and two investigated theophylline for the diaphragm (Table 5) [42, 43].

Growth hormone

Each of the eight studies investigating the impact of recombinant human growth hormone (rHGH) injections in older critically ill patients measured markers of protein metabolism [8-11, 21-24]. In the first of these, patients lost significantly less protein following four days of rHGH, but, nonetheless, remained catabolic overall [21]. Similarly, a subsequent study showed increased protein synthesis with rHGH, but apart from a transient anabolic period in a small population subset, patients were largely catabolic [23]. However, two trials of rHGH induced enough protein synthesis to attain a positive protein balance, which was a marked improvement relative to controls in both settings [9, 11]. A further three studies that measured nitrogen balance, a surrogate for protein metabolism as nitrogen retention corresponds with protein retention, demonstrated significant but transient improvements with rHGH [10, 22, 24, 44].

Two of the rHGH studies measured muscle function [22, 24]. The first, a trial of 20 patients on prolonged mechanical ventilation, reported a significant improvement in lean body mass, accompanied by a marked improvement in nitrogen balance, with rHGH [22]. However, these improvements did not influence mechanical ventilation duration, nor did they affect muscle strength. The second study, a large multicentered trial in frail ICU patients requiring prolonged admission, also could not demonstrate a benefit [24]. In fact, rHGH significantly increased

the duration of mechanical ventilation and impaired exercise tolerance [24].

Intensive insulin therapy

Trials of intensive insulin therapy (IIT) commonly included the duration of mechanical ventilation as an outcome measure, and several large studies reported that IIT could expedite weaning. In the first major study of IIT in 1548 patients, Van den Berghe and colleagues [25] initially did not demonstrate an effect on the duration of ventilatory support. However, this overall population had a two-day median requirement of ventilatory support, and subgroup analyses in those with ICU admissions longer than five and 14 days showed that IIT did, in fact, reduce their duration of ventilatory support significantly. Similar results were found in a later study by the same group, and while the IIT population overall had reduced weaning time (Hazard Ratio 1.21, 95% CI 1.02-1.44), those requiring admission for longer than three days had a greater benefit from tight glycaemic control (Hazard Ratio 1.43, 95% CI 1.16-1.75) [27]. In those admitted to ICU for a week or more, IIT was later found to be independently protective against prolonged mechanical ventilation (Odds Ratio 0.56, 95% CI 0.36-0.87) [28]. A separate research group also demonstrated that IIT reduced ventilation time by nearly two days (Median 4.2 days vs. 6.1 days) in 483 postoperative brain surgery patients requiring three or more days of admission [35].

Overall, however, more studies found evidence that IIT did not improve the duration of mechanical ventilation. The largest IIT trial was conducted by the NICE-SUGAR Study investigators in 6104 patients expected to have ICU admissions of at least three days. With IIT, maintaining euglycaemia between 4.5-6.0 mmol/L provided no weaning benefit [33]. Both the IIT and control populations required an average of 6.6 days of mechanical ventilation. These results were in concordance with three large, earlier studies which showed no weaning benefit from tight glucose control below 6.1 mmol/L [30-32]. Three later trials also failed to show any improvement of mechanical ventilation with IIT [34, 36, 37].

Three studies explored the impact of IIT on critical illness polyneuropathy (CIP). Compared to conventional glycaemic control, IIT-treated patients in the first Van den Berghe trial [25] were less likely to have CIP when screened. Conventional insulin therapy was found to be an independent predictor of CIP (OR 2.6, 95% CI 1.6-4.2). In their later trial, critical illness neuromyopathy (CINM) incidence was significantly lower in patients receiving IIT, and IIT was an independent protective factor for CINM (OR 0.61, 95% CI 0.43-0.92) [28]. The most recent study of insulin therapy in frail ICU patients reproduced these results with a less restrictive blood glucose range of 4.4-7.8 mmol/L [38].

Oxandrolone

Demling et al. conducted two studies investigating the effect of oxandrolone on muscle in older patients with major burns, and both studies demonstrated significant benefit [39, 40]. The first administered oxandrolone during rehabilitation and resulted in a higher weekly weight gain than controls. Further, 76% of this weight gain was lean mass, which was significantly higher than the 51% gained in the control patients. This translated into an improved Functional Independence Measurement score at discharge from rehabilitation [39]. A subsequent study by the same group administered oxandrolone prior to rehabilitation in 50 acute post-burn patients and demonstrated a significant protein-sparing effect, as well as a significant preservation of body weight and a reduced time to discharge.

Intravenous immunoglobulin

Brunner et al. [41] are the only research group that investigated intravenous immunoglobulin (IVIG) in older critically ill patients. IVIG was trialed in 38 septic patients but failed to improve either CIP or critical illness myopathy (CIM), and the apparent futile effect of IVIG led to the early termination of the study [41].

Theophylline

Two recent studies investigated theophylline for assisting older ICU patients to wean from mechanical ventilation. The first study demonstrated that theophylline exerted a marked improvement in diaphragm movement by increasing diaphragmatic excursion in mechanically ventilated patients. However, these patients did not wean faster than controls, and had no significant reduction in ventilator time [42]. The results were similar in a subsequent study conducted in 160 comparable patients. Theophylline provided a significant improvement in global tests of respiratory muscle strength, however, did not significantly improve weaning success or reduce mechanical ventilation time [43].

Table 1: Articles investigating growth hormone

GROWTH HORMONE										
Study (n=8)	Population	Age – Intervention	Age – Control	N – Intervention (Control)	Intervention	Duration of treatment	Outcome		P Value	Effect
Douglas et al, 1990 (1)	Critically ill surgical patients requiring Parenteral Nutrition	61.3 years (Mean; SD ± 9.3)	-	8 (-)	Daily subcutaneous injection of 20 units of rHGH	3 days	Day 0 (Pre-rHGH) Protein Loss: 0.82g/kg/day (Mean; SD ± 0.17)	Day 4 (Post-rHGH) Protein Loss: 0.43g/kg/day (Mean; SD ± 0.2)	.02	+
	Critically ill surgical patients, Enteral Nutrition	56.4 years (Mean; SD ± 17.2)	-	13(-)		3 days	Day 0 (Pre-rHGH) Protein Loss: 1.92g/kg/day (Mean; SD ± 0.27)	Day 4 (Post-rHGH) Protein Loss: 1.66g/kg/day (Mean; SD ± 0.23)	.05	+
Voerman et al, 1992 (2)	Septic Shock requiring Parenteral Nutrition	59.0 years (Mean; SD ± 13.1)	59.0 years (Mean; SD ± 20.2)	10 (10)	Daily continuous IV infusion of rHGH at 0.1mg/kg	3 days	INTERVENTION	CONTROL		
							Nitrogen balance, treatment day 1:			
							-6.9g (Mean; SD ± 4.5)	-6.7g (Mean; SD ± 6.0)	>.05	0
							Nitrogen balance, treatment day 2			
							+1.2g (Mean; SD ± 4.0)	-3.7 (Mean; SD ± 3.8)	.05	+
							Nitrogen balance, treatment day 3			
							Positive	Negative	>.05	0
							Nitrogen balance, post-treatment; days 5-7			
							Negative	Negative	>.05	0
							Nitrogen production, during treatment			
							Low	High	.05	+
							Nitrogen production, post-treatment			
							High	High	>.05	0
							3-methylhistidine excretion (marker of skeletal muscle breakdown)			
							Decreased	Decreased	>.05	0
Pichard et al, 1996 (3)	Acute respiratory failure requiring ≥7 days of mechanical ventilation	54.6 years (Mean; SEM ± 7.0)	62.5 years (Mean; SEM ± 5.1)	10 (10)	Daily subcutaneous injection of rHGH at 0.14mg/kg	12 days	INTERVENTION	CONTROL		
							Cumulative nitrogen balance			
							+44.9g/12 days (Mean; SEM ± 17.3)	-65.8g/12 days (Mean; SEM ± 11.8)	.0001	+

							Change in maximal adductor pollicis muscle force at 10Hz, day 0 to day 12		>.05	0
							-2.51 (Mean; SEM ± 1.32)	-0.01 (Mean; SEM ± 1.74)		
							Change in maximal adductor pollicis muscle force at 20Hz, day 0 to day 12		>.05	0
							-5.33 (Mean; SEM ± 3.18)	-4.37 (Mean; SEM ± 4.04)		
							Change in maximal adductor pollicis muscle force at 30 Hz, day 0 to day 12		>.05	0
							-5.28 (Mean; SEM ± 3.22)	-4.89 (Mean; SEM ± 4.83)		
							Change in maximal adductor pollicis muscle force at 50Hz, day 0 to day 12		>.05	0
							-5.52 (Mean; SEM ± 3.64)	-4.29 (Mean; SEM ± 5.61)		
							Cumulative duration of mechanical ventilation		>.05	0
							235.6 hours/12 days (Mean; SEM ± 17.6)	245.4 hours/12 days (Mean: SEM ± 14.7)		
							Change in fat-free mass, day 0 minus day 12		.0001	+
							2.6kg/12 days (Mean; SEM ± 1.4)	-6.0kg/12 days (Mean; SEM ± 0.9)		
Koea et al, 1996 (4)	Septic surgical patients requiring Parenteral Nutrition	64.3 years (Mean; SD ± 10.7)	61.7 years (Mean; SD ± 15.9)	10 (10)	Twice daily subcutaneous injections of rHGH at 0.3 units/kg	7 days	Percentage decrease in net protein catabolism, after 7 days		.05	+
							INTERVENTION	CONTROL		
							92.8% (Mean; SEM ± 16.8)	45.4 % (Mean; SEM ± 7.5)		
Takala et al, 1999 (5) (data from two parallel trials)	Patients requiring ICU admission for ≥10	Finnish Study: 60 years (Mean;	Finnish Study: 57 years (Mean; SD ± 15)	Finnish Study: 119 (123)	Daily subcutaneous injections of rHGH. Patients <60kg	Duration of ICU admission, up to 21 days	Finnish Study			

	days, with one of cardiac surgery, abdominal surgery, multiple trauma, or acute respiratory failure	SD ± 13)			received 5.3mg. Patients ≥60kg received 8.0mg.		INTERVENTION Duration of Mechanical Ventilation: 14 days (Median; IQR 4-22) Grip Strength: 14kg (Median; IQR 8-21) Exercise tolerance at discharge (walk upstairs, walk without limitation, walk without aid, walk with aid, stand without aid, stand with aid) 52 patients able to complete any one of the above Nitrogen Balance (day 7): Better Nitrogen Balance (day 14): Better Nitrogen Balance (day 21): Better	CONTROL 9 days (Median; IQR 4-19) 13kg (Median; IQR 6-24) 69 patients able to complete any one of the above Worse Worse Worse	0.18 0.92 0.49 .002 .003 .21	0 0 0 + + 0
		Multinational Study: 61 (Mean; ± 15)	Multinational Study: 61 years (Mean; SD ± 15)	Multinational Study: 139 (141)			Multinational Study INTERVENTION Duration of Mechanical Ventilation 12 days (Median; IQR 7-21) Grip Strength 10kg (Median; IQR 6-19) Exercise tolerance at discharge (walk upstairs, walk without limitation, walk without aid, walk with aid, stand without aid, stand with aid) 54 patients able to complete any one of the above	CONTROL 8 days (Median; IQR 4-14) 13kg (Median; IQR 7-22) 79 patients able to complete any one of the above	.001 .27 .008	+ 0 +
Gamrin et al, 2000 (6)	ICU patients with multiple organ failure requiring ≥5 days admission	53.1 years (Mean; SD ± 14.1)	57.2 years (Mean; SD ± 14.2)	10 (10)	Daily subcutaneous injection of rHGH at 0.3U/kg	5 days	INTERVENTION Skeletal muscle protein content, pre-treatment vs post treatment No change Skeletal muscle protein fractional synthesis rate:	CONTROL 8% decrease (Mean; SD ± 11%)	>.05	0

							33% increase (Mean; SD ± 48)	4% increase (Mean; SD ± 36)	.01	+
							Skeletal muscle free glutamine concentration:			
							207% increase (Mean; SD ± 327)	No change	.05	+
Umpleby et al, 2002 (7)	ICU patients requiring Parenteral Nutrition	62 years (Mean; SD ± 5)	68 years (Mean; SD ± 2)	5 (6)	Daily intravenous rHGH at 0.2IU/kg, with recombinant human IGF-1 at 160µg/kg	3 days	Protein balance, pre-treatment vs. post-treatment			
							Intervention: Shift from negative to positive	Control: Negative	.05	+
Carroll et al, 2003 (8)	Mechanically ventilated ICU patients	62 years (Mean; SEM ± 5)	TPN Group: 69 years (Mean; SEM ± 3) TPN and Glutamine Group: 60 (Mean; SEM ± 6)	5 (14)	Daily subcutaneous rHGH injection at 0.2IU/kg, and recombinant human IGF-1 at 160 µg/kg	3 days	Net protein balance, after treatment			
							Intervention: Positive	Both Control Groups: Negative	.05	+

(rHGH = Recombinant Human Growth Hormone; USS = Ultrasound Sonography; VIDD = Ventilator-Induced Diaphragm Dysfunction; PImax = Maximum Inspiratory Pressure; RSBI = Rapid Shallow Breathing Index; TPN = Total Parenteral Nutrition; ICU = Intensive Care Unit; EMG = Electromyography; ENMG = Electroneuromyography; CIP = Critical Illness Polyneuropathy; CIM = Critical Illness Myopathy; CIPNM = Critical Illness Polyneuropathy and/or Myopathy; IQR = Inter-quartile Range; SD = Standard Deviation; SEM = Standard Error of the Mean; CI = Confidence Interval; ITT = Intention to Treat)

Table 2: Articles investigating insulin therapy

INSULIN THERAPY									
Study (n=14)	Population	Age - Intervention	Age - Control	N – Intervention (Control)	Intervention	Duration of treatment	Outcome	P Value	Effect
Van den Berghe et al, 2001 (9)	ICU patients requiring mechanical ventilation	63.4 years (Mean; SD ± 13.6)	62.2 years (Mean; SD ± 13.9	765 (783)	Insulin maintenance of blood glucose between 4.4-6.1mmol/L. (Control blood glucose was maintained between 10.0-11.1mmol/L)	Until ICU Discharge (Median 3 days; IQR 2-6)	INTERVENTION / CONTROL Duration of ventilatory support 2 days (Median; IQR 1-4) / 2 days (Median; IQR 1-6) Duration of ventilatory support in patients staying in ICU for >5 days 10 days (Median; IQR 6-16) / 12 days (Median; IQR 7-23) Patients requiring >14 days of ventilatory support 7.5% / 11.9% EMG evidence of CIP, at any time 28.7% / 51.9% EMG evidence of CIP, 2 or more times 7.0% / 18.9%	>.05 .006 .003 .001 .001	0 + + + +
Hoedemaekers et al, 2005 (10)	Post-operative elective coronary artery bypass graft surgery	65.2 years (Mean; SD ± 8.7)	63.2 years (Mean; SD ± 6.6)	10 (10)	Insulin maintenance of blood glucose between 4.4-6.1mmol/L. (Control blood glucose was kept below 11.1mmol/L)	24 hours	Duration of ventilatory support Intervention: 11.2 hours (Mean; SD ± 6.6) Control: 9.8 hours (Mean; SD ± 4.6)	0.65	0
Van den Berghe et al, 2006 (11)	ICU patients	ITT Group: 63 years (Mean; SD ± 16) ≥3-days Group; 62 years (Mean; SD ± 16)	ITT Group: 64 years (Mean; SD ± 16) ≥3-days Group: 64 years (Mean; SD ± 16)	ITT Group: 595 (605) ≥3-days Group; 386 (381)	Insulin maintenance of blood glucose between 4.4-6.1mmol/L. (Control blood glucose was kept below 12mmol/L)	Until ICU Discharge	ITT Group: Earlier weaning from mechanical ventilation: Hazard Ratio 1.21 (95% CI 1.02-1.44) ≥3-days Group: Earlier weaning from mechanical ventilation: Hazard Ratio 1.43 (95% CI 1.16-1.75)	.03 .001	+ +

Hermans et al, 2007 (12)		≥7-days Group: 61 years (Mean; SD ± 15)	≥7-days Group: 64 years (Mean; SD ± 16)	≥7-days Group: 208 (212)			INTERVENTION / CONTROL ENMG diagnosis of CIP/CIM 38.9% / 50.5% Days of mechanical ventilation 12 (Median; IQR 8-20) / 14 (Medan; IQR 9-22) Requiring prolonged (≥14 days) of mechanical ventilation 34.6% / 46.7% Intensive Insulin Therapy as an independent protective factor for ENMG diagnosis of CIP/CIM: Odds Ratio 0.61 (95% CI 0.43-0.92) Intensive Insulin Therapy as an independent protective factor against prolonged mechanical ventilation: Odds Ratio 0.56 (95% CI 0.36-0.87)	.02 .04 .01 .02 .01	+
Biolo et al, 2008 (13)	Post-surgical female cancer patients	54 years (Mean; SD ± 4)	54 years (Mean; SD ± 4)	8 (8)	Insulin maintenance of blood glucose at 5.8mmol/L (Mean; SD ± 0.4) before or after a 24-hour control period of hyperglycaemia (Mean 9.6mmol/L, SD ± 0.6)	24 hours	Muscle protein synthesis Intervention: -3 nmol phenylalanine/100mL/min (Mean; SEM ± 3) Control: -11 nmol phenylalanine/100mL/min (Mean; SEM ±3)	.05	+
Brunkhorst et al, 2008 (14)	Severely septic patients	64.0 years (Mean; SD ± 14.3)	65.2 years (Mean; SD ±13.2)	247 (290)	Insulin maintenance of blood glucose between 4.4-6.1mmol/L. (Control blood glucose was maintained between 10.0-11.1mmol/L)	Up to 21 days	Ventilator-free days Intervention: 3 (Median; IQR 1-7) Control: 3 (Median; IQR 1-6)	.83	0
Arabi et al, 2008 (15)	ICU patients with admission blood glucose >6.1mmol/L	50.6 years (Mean; SD ± 22.6)	54.3 years (Mean; SD ± 20.5	266 (257)	Insulin maintenance of blood glucose between 4.4-6.1mmol/L. (Control blood glucose was maintained between 10.0-11.1mmol/L)	Until discharge from ICU	Duration of mechanical ventilation Intervention: 8.3 days (Mean; SD ± 7.9) Control: 9.7 days (Mean; SD ± 11.0)	.11	0
Mackenzie et al, 2008 (16)	ICU patients	66 years (Median; IQR 53-75)	63 years (Median; IQR 52-74)	121 (119)	Insulin maintenance of blood glucose between 4.0-6.0mmol/L. (Control blood glucose was maintained below 11.0mmol/L)	Until discharge from ICU	Duration of respiratory support Intervention: 111 hours (Median; IQR 24-341) Control: 120 hours (Median; IQR 35-330)	.58	0

Finfer et al, 2009 (17)	ICU patients expected to be admitted for ≥3 days	60.4 years (Mean; SD ± 17.2)	59.9 years (Mean; SD ± 17.1)	3054 (3050)	Insulin maintenance of blood glucose between 4.5-6.0mmol/L. (Control blood glucose was maintained below 10.0 mmol/L)	Until discharge from ICU, up to 90 days	Duration of mechanical ventilation Intervention: 6.6 days (Mean; SD ± 6.6) Control: 6.6 days (Mean; SD ± 6.5)	.56	0
Preiser et al, 2009 (18)	ICU patients	64.8 years (Median; IQR 50.8-74.0)	64.5 years (Median; IQR 51.1-74.1)	536 (542)	Insulin maintenance of blood glucose between 4.4-6.1mmol/L. (Control blood glucose was maintained between 7.8-10.0mmol/L)	Until discharge from ICU	Duration of mechanical ventilation Intervention: 1155 patient days Control: 1179 patient days	.56	0
Bilotta et al, 2009 (19)	Postoperative brain surgery requiring ICU admission for ≥3 days	57.34 years (Mean; SD ± 11.94)	56.9 years (Mean; SD ± 12.65)	241 (242)	Insulin maintenance of blood glucose between 4.44-6.11 mmol/L. (Control blood glucose was maintained below 11.94 mmol/L)	Until discharge from ICU, up to 14 days	Duration of mechanical ventilation Intervention: 4.2 days (Median) Control: 6.1 days (Median)	.0001	+
Annane et al, 2010 (20)	Patients with septic shock treated with hydrocortisone	63.7 years (Mean; 95% Confidence Interval 61.9-65.4)	64.3 years (Mean; 95% Confidence Interval 62.4-66.1)	255 (254)	Insulin maintenance of blood glucose between 4.4-6.1mmol/L. (Control blood glucose was maintained between 10.0-11.1mmol/L)	Until discharge from ICU	Days free of mechanical ventilation, up to 28 days Intervention: 10 (Median; IQR 2-22) Control: 13 (Median; 2-23)	.51	0
Hsu et al, 2012 (21)	ICU patients expected to be admitted for ≥4 days	68.1 years (Mean; SD ± 16.3)	70.4 years (Mean; SD ±12.1)	55 (57)	Insulin maintenance of blood glucose between 6.7-7.8mmol/L. (Control blood glucose was maintained between 10.0-11.1mmol/L)	Until discharge from ICU	INTERVENTION / CONTROL Ventilator days 20 (Median; IQR 11-30) / 23 (Median; IQR 11-43.5) Nitrogen balance, days 3 to 14 Less negative / More negative	.19 .07	0 0
Mikaeili et al, 2012 (22)	ICU patients	52.65 years (Mean; SD ± 18.63)	52.35 years (Mean; SD ± 18.46)	20 (20)	Insulin maintenance of blood glucose between 4.4-7.8mmol/L. (Control blood glucose was maintained between 10.0-	Until discharge from ICU	INTERVENTION / CONTROL Duration of mechanical ventilation 9.72 days (Mean; SD ± 3.84) / 14.05 days (Mean; SD ± 8.14) Electrophysiological diagnosis of CIP	.04	+

(rHGH = Recombinant Human Growth Hormone; USS = Ultrasound Sonography; VIDD = Ventilator-Induced Diaphragm Dysfunction; PImax = Maximum Inspiratory Pressure; RSBI = Rapid Shallow Breathing Index; TPN = Total Parenteral Nutrition; ICU = Intensive Care Unit; EMG = Electromyography; ENMG = Electroneuromyography; CIP = Critical Illness Polyneuropathy; CIM = Critical Illness Myopathy; CIPNM = Critical Illness Polyneuropathy and/or Myopathy; IQR = Inter-quartile Range; SD = Standard Deviation; SEM = Standard Error of the Mean; CI = Confidence Interval; ITT = Intention to Treat)

Table 3: Articles investigating Oxandrolone

OXANDROLONE										
Study (n=2)	Population	Age - Intervention	Age - Control	N – Intervention (Control)	Setting	Intervention	Duration of treatment	Outcome	P Value	Effect
Demling et al, 2001 (23)	Patients recovering from deep burns of 30-55% total body surface	Intervention + Control Mean: 60 years (SD ± 5)		8 (7)	Acute Rehabilitation Unit	Twice daily oral Oxandrolone 10mg	4 weeks	INTERVENTION: Weight gain per week: 1.6kg (Mean; SD 0.3) / CONTROL: 0.5kg (Mean; SD ± 0.2)	.05	+
								Lean mass gained at 4 weeks, as percent of total weight gained: 76% (Mean; SD ± 5) / 51% (Mean; SD ± 6)	.05	+
								Functional Independence Measurement Score at 4 weeks: 96 (Mean; SD ± 6) / 86 (Mean; SD ±7)	.05	+
Demling et al, 2003 (24)	Patients with burns of 10-30% total body surface	Intervention + Control Mean: 70 years		25 (25)	Burn Center inpatients	Twice daily Oxandrolone 10mg	Until discharge to rehabilitation	INTERVENTION / CONTROL — Loss in body weight: Decreased / No change	.05	+
								Loss of body protein: Decreased / No change	.05	+

Table 4: Article investigating intravenous immunoglobulin

INTRAVENOUS IMMUNOGLOBULIN									
Study (n=1)	Population	Age - Intervention	Age – Control	N – Intervention (Control)	Intervention	Duration	Outcome	P Value	Effect
Brunner et al, 2013 (25)	Septic patients with multiple organ failure and early signs of CIPNM	61 years (Mean; SD ± 11)	66 years (Mean; SD ± 12)	19 (19)	Continuous intravenous infusion of IgM-enriched immunoglobulin at a dose of 0.25g/kg/day, infused at 2g/hour	3 days	INTERVENTION / CONTROL — Electrophysiological CIP Score, days 4, 7, and 14: No difference / No difference	>.05	0
							Biopsy CIM Score, day 14: No difference / No difference	>.05	0
							CIPNM severity sum score, day 14: No difference / No difference	>.05	0

(rHGH = Recombinant Human Growth Hormone; USS = Ultrasound Sonography; VIDD = Ventilator-Induced Diaphragm Dysfunction; PImax = Maximum Inspiratory Pressure; RSBI = Rapid Shallow Breathing Index; TPN = Total Parenteral Nutrition; ICU = Intensive Care Unit; EMG = Electromyography; ENMG = Electroneuromyography; CIP = Critical Illness Polyneuropathy; CIM = Critical Illness Myopathy; CIPNM = Critical Illness Polyneuropathy and/or Myopathy; IQR = Inter-quartile Range; SD = Standard Deviation; SEM = Standard Error of the Mean; CI = Confidence Interval; ITT = Intention to Treat)

Table 5: Articles investigating Theophylline

THEOPHYLLINE										
Study (n=2)	Population	Age – Intervention	Age - Control	N – Intervention (Control)	Setting	Intervention	Duration of treatment	Outcome	P Value	Effect
Kim et al, 2016 (26)	Mechanically ventilated for ≥ 72 hours with USS-diagnosed VIDD	65 years (Median; IQR 48-72)	64 years (Median; IQR 56-75)	21 (19)	ICU	200mg (Median; IQR 200-400mg) daily oral Theophylline	12 days (Median; IQR 7-25)	INTERVENTION: Change in diaphragm excursion at 72 hours: 6.9mm (Mean; SD ± 9.1) / CONTROL: 0.5mm (Mean; SD ± 5.7) Weaning time: 8 days (Median; IQR 3-22) / 9 days (Median; IQR 4-14) Total ventilation time: Time = 18 (Median; IQR 9-35) / Time = 28 (Median; IQR 14-45)	.02 .84 .41	+ 0 0
Yu et al, 2019 (27)	Mechanically ventilated for ≥ 21 days	72.0 years (Mean; ± 15.1)	73.8 years (Mean; ± 14.4)	84 (76)	Respiratory Care Center	Twice daily 200mg oral Aminophylline (which contains 85.7% anhydrous Theophylline) = 343mg of Theophylline per day	23 days (Mean; Range 9-34)	INTERVENTION / CONTROL PImax: 30.1cmH2O (Mean; ± 9.7) / 26.9cmH2O (Mean; ± 9.1) RSBI: 107.0 (Mean; ±68.4) / 131.7 (Mean; ±77.7) Weaning Success: 78.6% / 65.8% Mechanical ventilation time: 20.1 days (Mean; ± 14.2) / 23.1 days (Mean; ± 13.5)	.034 .036 .071 .192	+ + 0 0

(rHGH = Recombinant Human Growth Hormone; USS = Ultrasound Sonography; VIDD = Ventilator-Induced Diaphragm Dysfunction; PImax = Maximum Inspiratory Pressure; RSBI = Rapid Shallow Breathing Index; TPN = Total Parenteral Nutrition; ICU = Intensive Care Unit; EMG = Electromyography; ENMG = Electroneuromyography; CIP = Critical Illness Polyneuropathy; CIM = Critical Illness Myopathy; CIPNM = Critical Illness Polyneuropathy and/or Myopathy; IQR = Inter-quartile Range; SD = Standard Deviation; SEM = Standard Error of the Mean; CI = Confidence Interval; ITT = Intention to Treat)

Discussion

For the older general ICU population, IIT was the only therapy that demonstrated an improvement in muscle outcomes. However, due to the risk of hypoglycaemia with IIT its use remains controversial. No clinical benefit could be demonstrated by rHGH, IVIG or theophylline. While oxandrolone was beneficial for older patients with burns, it was not studied in a general ICU cohort. Muscle wasting derived from increased protein breakdown and decreased protein synthesis are core features of both frailty and critical illness, making protein metabolism a major therapeutic target [2]. Studies have largely focused their efforts on countering this net catabolism with the anabolic hormone's insulin and growth hormone, which are depleted in illness and advancing age, and share similar anabolic mechanisms [1].

1. *Growth Hormone*

Growth hormone (GH) exerts a potently anabolic effect by increasing the cellular influx of amino acids, while also decreasing amino acid efflux, which enhances cellular proliferation and protein synthesis [60, 61]. Moreover, GH increases fat oxidation, which reduces the amount of protein being used for energy and, thus, further increases the amount of protein substrate available for protein synthesis [1]. GH production declines rapidly following young adulthood and is released in even smaller quantities during prolonged ICU admission [7]. Thus, replenishing its levels in the old and critically ill seems a plausible strategy for countering catabolism [1].

Despite rHGH consistently producing an anabolic effect by improving protein balance, even leading to an increased muscle mass, it failed to have an impact on clinical outcomes. Indeed, two studies which enhanced nitrogen balance, yet failed to achieve functional improvement, cast doubt on the utility of using protein metabolism markers to make inferences on muscle function [22, 24]. Apart from most studies not reporting on functional outcomes, a notable limitation is that all but one study had small sample sizes of between 11 to 21 patients. The single large, multicentered growth hormone study produced concerning results, with rHGH causing a significantly increased duration of mechanical ventilation, and a marked impairment of exercise tolerance [24]. Furthermore, rHGH administration also increased mortality (42% versus 18% in controls). These results were unexpected, and it was later suggested that excessive doses of rHGH may have been the cause [45]. The high doses used led to a subsequent increase in IGF-1 levels which likely caused several unintended effects, including hypercalcaemia, fluid retention and insulin resistance with accompanying

hyperglycaemia [45]. The harm caused by over-supplementation of GH suggests that the suppression of its release in response to critical illness may be appropriate in some capacity [7].

The clinical utility of GH, as used in these older studies, appears limited, and in recent years, there has been minimal research of growth hormone supplementation in frail critically ill populations. However, if GH were to be further investigated, it has been suggested that studies attempt to attain lower, more pulsatile GH concentrations that better represent physiologic activity [7, 45]. This may be attainable with GH secretagogues, including GH releasing peptide-2 and thyrotropin releasing hormone [45].

2. *Insulin*

Insulin has critical anabolic actions [1]. Following protein and carbohydrate ingestion, it is the most important hormone in mediating an anabolic response [2]. Insulin enhances amino acid uptake in cells, increases the synthesis of fatty acids and decreases protein catabolism [46, 47]. However, in critical illness, the anabolic effect of insulin is dampened by the hypermetabolic response induced by catabolic factors, including cortisol, inflammatory cytokines and catecholamines [12, 48]. Furthermore, this hypermetabolic response also induces insulin resistance, and the resulting hyperglycaemia is a risk factor for ICU-acquired weakness [12, 49]. Thus, the two-pronged impairment of the functions of insulin impacting muscle during critical illness have made insulin therapy the most popular as per the literature.

Several studies are ultimately divided on the impact of IIT for weaning from mechanical ventilation in older ICU patients, with three large trials suggesting a benefit particularly for those with longer admissions [25, 27, 28, 35], while seven other trials failed to demonstrate any benefit [30-34, 36, 37]. This discordance of results is likely partly accounted for by marked differences in the studies. These include differing study protocols, populations, differing times of glucose control initiation and differences in the realized levels of glucose control [50] Schultz et al [50] provide a comprehensive discussion surrounding the discrepancies of these trials.

CIP was reduced by IIT in three trials [25, 28, 38]. Intensive care unit acquired weakness (ICUAW) is the main clinical manifestation of CIP, CIM, or the combination of CIP and CIM known as CINM [51, 52]. ICUAW presents as a generalised muscular weakness and occurs in up to 50% of ICU patients, frequently resulting in a prolonging of mechanical ventilation, and is associated with increased mortality and long-term disability [51-54]. The positive results of these trials indicate that avoiding hyperglycaemia with insulin therapy is likely beneficial for patients at risk of developing CINM, and, thus, ICUAW [51].

Ultimately, glucose control remains a significant therapeutic target in older ICU patients, but due to discordant results from studies, the ideal range and method of control continue to be elusive [50]. Additionally, it is important to consider the higher incidence of hypoglycaemic episodes with intensive glucose control, and while not leading to morbidity in most cases, it was associated with increased mortality in the NICE-SUGAR Study [33]. Due to the divided results from many large trials, it is clear that more evidence is needed before a recommendation can be made regarding appropriate glycaemic control in older critically ill populations.

3. *Oxandrolone*

Oxandrolone acts through the same mechanisms as testosterone to maximize its anabolic action, but with fewer masculinizing effects [1]. By stimulating androgen receptors, it acts similarly to growth hormone and insulin by increasing the amount of amino acids in cells. Indeed, protein synthesis is induced, new tissue is generated and fat becomes the preferred source of energy [1]. Burns are a particularly catabolic subset of critical illness with marked muscle breakdown and are thus an especially troublesome complication for older patients with pre-existing muscle loss [39, 55].

Both studies of oxandrolone in older burn patients produced positive results. The first study was limited by a small sample size of 15, but the same research group's later study in a larger population of 50 patients reproduced its positive results. In the later study, as patients' discharge relied on functional ability, the authors concluded that the reduced discharge time likely reflected preservation of muscle mass [40]. Thus, both studies successfully demonstrated that oxandrolone's body weight-preserving effect could be translated into palpable clinical benefits.

The promising results of oxandrolone in burn patients have resulted in its regular use in this population [14]. A meta-analysis of oxandrolone in patients with severe burns shows findings in other burn populations consistent with those of Demling's trials [56]. Unfortunately, there has been no research on oxandrolone in older non-burn ICU populations, which limits the external validity of the effectiveness of oxandrolone.

4. *Intravenous immunoglobulin*

Due to the strong association of CINM with sepsis and systemic inflammation, it was thought that the administration of IgM-enriched intravenous immunoglobulin (IVIG) could mitigate the effects of CIP and CIM. In a single study, IVIG was theorized to modulate pro-inflammatory cytokines, thereby reducing cytokine-mediated neuron and muscle protein damage [41]. However, the results of the study [41] were ultimately disappointing as IVIG showed no improvement of either CIP or CIM, and the trial concluded early as a result. The effect of IVIG on muscle in the frail and critically ill is limited to the results of this single small trial, which suggest a lack of benefit.

5. *Theophylline*

Prolonged mechanical ventilation results in respiratory muscle weakness, due to diaphragmatic atrophy and contractile dysfunction. This contractile dysfunction is linked to an increase in reactive oxygen species, causing proteolysis in the diaphragm [57]. Theophylline is a methylxanthine that has demonstrated beneficial effects in various patient populations by strengthening respiratory muscles and improving diaphragm function [42]. It was hypothesized that theophylline could inhibit xanthine oxidase, a source of reactive oxygen species that increased activity in the diaphragm after prolonged mechanical ventilation in animal models [43, 57].

Neither of the theophylline studies [42, 43] could improve weaning outcomes for older critically ill patients, despite

improvements to respiratory muscle function. Due to its large sample size, the later study, in particular, provides convincing data on the lack of utility for theophylline in weaning [43]. Thus, theophylline's use in this capacity cannot be currently recommended.

6. *Novel therapeutics*

The therapies outlined in this review have largely produced unsatisfactory results and new biologic drugs are currently under investigation. Particular interest has been garnered in the inhibition of activin receptors and myostatin. Bimagrumab, a monoclonal antibody against activin receptor type II, significantly improved muscle mass, strength and gait speed in sarcopenic adults [58], but a more recent trial could not reproduce functional benefit (NCT02333331). Anti-myostatin antibodies Landogrozumab (NCT01369511) and Trevogrumab (NCT01963598) have both increased lean mass in the frail, but with no functional improvements. Similarly, targeting the androgen receptor with selective androgen receptor modulators has produced lean mass gains in frail women, again without functional benefits [59]. These therapies are yet to be trailed in the critically ill.

Limitations

Limitations of Included Articles

The included studies also have limitations. Many of the included trials had small samples and, in some instances, investigators were not blinded which likely introduced bias. Several studies were not randomised controlled trials. Additionally, most of the included trials are over 10 years old, further emphasising the need for future research on novel drug therapies in this field. Moreover, their frequent reporting of surrogate measures of muscle rather than clinical outcomes is a limitation, as these do not always reliably translate into clinical effects. Notably, the literature investigating muscle-related outcomes in frail critically ill populations was minimal.

Limitation of this Review

This review has some important limitations. These include there being a single reviewer, exclusion of non-English articles and no formal quality assessment of the literature. Due to the higher prevalence of frailty in older populations, any trial with an average age less than 50 was excluded to better capture a frailer cohort. As a result, frail populations younger than 50 may have been excluded, and non-frail populations 50 or older were possibly included.

Conclusion

Muscle loss in critical illness contributes to a variety of detrimental patient outcomes, with a particularly high risk conferred to those with pre-existing loss of muscle mass. Strict glucose control with insulin is the only drug therapy to have improved muscle outcomes of older patients with critical illness, but its risk of hypoglycaemia creates implications for its use. Oxandrolone has proven beneficial for older burn patients but has not been adequately studied outside of this population. The results of this review emphasise the necessity for further research of novel experimental therapies, aimed at generating functional benefit for the frail critically ill populations who need it most.

References

[1] Demling, RH. The role of anabolic hormones for wound healing in catabolic states. J Burns Wounds. 2005 Jan 17;4:e2.

[2] Sakurai Y, Aarsland A, Herndon DN, Chinkes DL, Pierre E, Nguyen TT, et al. Stimulation of muscle protein synthesis by long-term insulin infusion in severely burned patients. Ann Surg. 1995 Sep;222(3):283-97.

[3] Hanna JS. Sarcopenia and critical illness: a deadly combination in the elderly. J Parenter Enteral Nutr. 2015 Mar;39(3):273-81.

[4] Nascimento CM, Ingles M, Salvador-Pascual A, Cominetti MR, Gomez-Cabrera MC, Viña J. Sarcopenia, frailty and their prevention by exercise. Free Radic Biol Med. 2019 Feb 20;132:42-9.

[5] Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013 Mar 2;381(9868):752-762.

[6] Reddy M, Gill SS, Rochon PA. Preventing pressure ulcers: a systematic review. JAMA. 2006;296(8):974-84.

[7] Paul JA, Whittington RA, Baldwin MR. Critical illness and the frailty syndrome: mechanisms and potential therapeutic targets. Anesth Analg. 2020 Jun;130(6):1545-55.

[8] Gamrin L, Essén P, Hultman E, McNurlan MA, Garlick PJ, Wernerman, J. Protein-sparing effect in skeletal muscle of growth hormone treatment in critically ill patients. Ann Surg. 2000; 231(4):577–86.

[9] Umpleby AM, Carroll PV, Russell-Jones DL, Treacher DF, Jackson NC. Glutamine supplementation and GH/IGF-I treatment in critically ill patients: effects on glutamine metabolism and protein balance. Nutrition. 2002 Feb;18(2):127-9.

[10] Voerman BJ, Strack Van Schijndel RJ, Groeneveld AB, De Boer H, Nauta JP, Van der Veen EA, et al. Effects of recombinant human growth hormone in patients with severe sepsis. Ann Surg. 1992 Dec;216(6):648-55.

[11] Carroll PV, Jackson NC, Russell-Jones DL, Treacher DF, Sonksen PH, Umpleby AM. Combined growth hormone/insulin-like growth factor I in addition to glutamine-supplemented TPN results in net protein anabolism in critical illness. Am J Physiol Endocrinol Metab. 2004;286:151–7.

[12] Stanojcic M, Finnerty CC, Jeschke MG. Anabolic and anticatabolic agents in critical care. Curr Opin Crit Care. 2016 Aug;22(4):325-31.

[13] Hart DW, Wolf SE, Mlcak R, Chinkes DL, Ramzy PI, Obeng MK, et al. Persistence of muscle catabolism after severe burn. Surgery. 2000 Aug;128(2):312-9.

[14] Wischmeyer PE, Suman OE, Kozar R, Wolf SE, Molinger J, Pastva AM. Role of anabolic testosterone agents and

structured exercise to promote recovery in ICU survivors. Curr Opin Crit Care. 2020 Oct;26(5):151-508.
[15] Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med. 2014 Apr;370(17):1626–35.
[16] Heyland DK, Stapleton RD, Mourtzakis M, Hough CL, Morris P, Deutz NE, et al. Combining nutrition and exercise to optimize survival and recovery from critical illness: conceptual and methodological issues. Clin Nutr. 2016 Oct;35(5):1196-206.
[17] Miranda Rocha AR, Martinez BP, Maldaner da Silva VZ, Forgiarini Junior LA. Early mobilization: why, what for and how? Med Intensiva. 2017 Oct;41(7):429-36.
[18] Wandrag L, Brett SJ, Frost G, Hickson M. Impact of supplementation with amino acids or their metabolites on muscle wasting in patients with critical illness or other muscle wasting illness: a systematic review. J Hum Nutr Diet. 2015 Aug;28(4):313-30.
[19] McKendry J, Thomas ACQ, Phillips SM. Muscle mass loss in the older critically ill population: potential therapeutic strategies. Nutr Clin Prac. 2020 Jun;35(4):607-16.
[20] Demling RH, DeSanti L. Oxandrolone induced lean mass gain during recovery from severe burns is maintained after discontinuation of the anabolic steroid. Burns. 2003 Dec;29(8):793–7.
[21] Douglas RG, Humberstone DA, Haystead A, Shaw JHF. Metabolic effects of recombinant human growth hormone: isotopic studies in the postabsorptive state and during total parenteral nutrition. Br J Surg. 1990 July;77(7):785-90.
[22] Pichard C, Kyle U, Chevrolet JC, Jolliet P, Slosman D, Mensi N, et al. Lack of effects of recombinant growth hormone on muscle function in patients requiring prolonged mechanical ventilation: a prospective, randomised, controlled study. Crit Care Med. 1996 Mar;24:403-13.
[23] Koea JB, Breier BH, Douglas RG, Gluckman PD, Shaw JH. Anabolic and cardiovascular effects of recombinant human growth hormone in surgical patients with sepsis. Br J Surg. 1996 Feb;83(2):196-202.
[24] Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, et al. Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med. 1999 Sep 9;341:785–92.
[25] Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001 Nov 8;345(19):1359-67.
[26] Hoedemaekers CW, Pickkers P, Netea MG, van Deuren M, Van der Hoeven JG. Intensive insulin therapy does not alter the inflammatory response in patients undergoing coronary artery bypass grafting: a randomized controlled trial. Crit Care. 2005 Nov 16;9(6):R790-97.
[27] Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449-61.
[28] Hermans G, Wilmer A, Meersseman W, Milants I, Wouters PJ, Bobbaers H, et al. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. Am J Respir Crit Care Med. 2007;175(5):480-89.
[29] Biolo G, De Cicco M, Lorenzon S, Dal Mas V, Fantin D, Paroni R, et al. Treating hyperglycemia improves skeletal muscle protein metabolism in cancer patients after major surgery. Crit Care Med. 2008;36(6):1768-75.
[30] Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358(2):125-39.
[31] Arabi YM, Dabbagh OC, Tamim HM, Al-Shimermeri AA, Memish ZA, Haddad SH, et al. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. Crit Care Med. 2008;36(12):3190-97.
[32] Mackenzie IM, Ercole A, Blunt M, Ingle S, Palmer CR. Glycaemic control and outcome in general intensive care: the East Anglian GLYCOGENIC study. Br J Intensive Care. 2008 Dec;18:121-26.
[33] Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009 Mar 26;360(13):1283-97.
[34] Preiser J, Devos P, Ruiz-Santana S, Melot C, Annane D, Groeneveld J, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Med. 2009 Oct;35(10):1738-48.
[35] Bilotta F, Caramia R, Paoloni FP, Delfini R, Rosa G. Safety and efficacy of intensive insulin therapy in critical neurosurgical patients. Anesthesiology. 2009 Mar;110(3):611–9.
[36] Annane D, Cariou A, Maxime V, Azoulay E, D'honneur G, Timsit JF, et al. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. JAMA. 2010;303(4):341–8.
[37] Hsu CW, Sun SF, Lin SL, Huang HH, Wong KF. Moderate glucose control results in less negative nitrogen balances in medical intensive care unit patients: a randomized, controlled study. Crit Care. 2012 Dec 12;16(2):R56.
[38] Mikaeili H, Yazdchi M, Barazandeh F, Ansarin K. Euglycemic state reduces the incidence of critical illness polyneuropathy and duration of ventilator dependency in medical intensive care unit. Bratisl Lek Listy. 2012;113(10):616–9.
[39] Demling RH, DeSanti L. The rate of restoration of body weight after burn injury, using the anabolic agent oxandrolone, is not age dependent. Burns. 2001;27(1):46-51.
[40] Demling RH, Desanti L. The beneficial effects of the anabolic steroid oxandrolone in the geriatric burn population. Wounds. 2003;15:54–8.
[41] Brunner R, Rinner W, Haberler C, Kitzberger R, Sycha T, Herkner H, et al. Early treatment with IgM-enriched intravenous immunoglobulin does not mitigate critical illness polyneuropathy and/or myopathy in patients with multiple organ failure and SIRS/sepsis: a prospective, randomized, placebo-controlled, double-blinded trial. Crit Care. 2013 Oct 2;17(5):R213.

[42] Kim WY, Park SH, Kim WY, Huh JW, Hong SB, Koh Y, et al. Effect of theophylline on ventilator-induced diaphragmatic dysfunction. J Crit Care. 2016 Jun;33:145-50.
[43] Yu TJ, Liu YC, Chu CM, Hu HC, Kao KC. Effects of theophylline therapy on respiratory muscle strength in patients with prolonged mechanical ventilation: A retrospective cohort study. Medicine. 2019;98(2):e13982.
[44] Dickerson RN. Nitrogen balance and protein requirements for critically ill older patients. Nutrients. 2016 Apr 18;8(4):226.
[45] Téblick A, Langouche L, Van den Berghe G. Anterior pituitary function in critical illness. Endocr Connect. 2019;8(8):R131-43.
[46] Dimitriadis G, Mitrou P, Lambadiari V, Maratou E, Raptis SA. Insulin effects in muscle and adipose tissue. Diabetes Res Clin Pract. 2011 Aug;93 Suppl 1:S52–9.
[47] Ferrando AA, Chinkes DL, Wolf SE, Matin S, Herndon DN, Wolfe RR. A submaximal dose of insulin promotes net skeletal muscle protein synthesis in patients with severe burns. Ann Surg. 1999 Jan;229(1):11-8.
[48] Gauglitz GG, Herndon DN, Kulp GA, Meyer III WJ, Jeschke MG. Abnormal insulin sensitivity persists up to three years in pediatric patients post-burn. J Clin Endocrinol Metab. 2009 May; 94(5):1656-64.
[49] Hermans G, Van den Berghe G. Clinical review: intensive care unit acquired weakness. Crit Care. 2015 Aug 5;19(1):274.
[50] Schultz MJ, Harmsen RE, Spronk PE. Clinical review: strict or loose glycemic control in critically ill patients--implementing best available evidence from randomized controlled trials. Crit Care. 2010;14(3):223.
[51] Wieske L, Harmsen RE, Schultz MJ, Horn J. Is critical illness neuromyopathy and duration of mechanical ventilation decreased by strict glucose control? Neurocrit Care. 2011 Jun;14(3):475-81.
[52] Apostolakis E, Papakonstantinou NA, Baikoussis NG, Papadopoulos G. Intensive care unit-related generalized neuromuscular weakness due to critical illness polyneuropathy/myopathy in critically ill patients. J Anesthesia. 2015;29(1):112-21.
[53] Chawla J, Gruener G. Management of critical illness polyneuropathy and myopathy. Neurologic Clinics. 2010;28(4):961-77.
[54] Dres M, Goligher EC, Heunks LMA, Brochard LJ. Critical illness-associated diaphragm weakness. Intensive Care Medicine. 2017;43(10):1441-52.
[55] Jahoor F, Desai M, Herndon DN, Wolfe RR. Dynamics of the protein metabolism response to burn injury. Metabolism. 1988 Apr;37(4):330-7.
[56] Li H, Guo Y, Yang Z, Roy M, Guo Q. The efficacy and safety of oxandrolone treatment for patients with severe burns: a systematic review and meta-analysis. Burns. 2016 Jun;42(4):717–27.
[57] Whidden MA, McClung JM, Falk DJ, Hudson MB, Smuder AJ, Nelson WB, et al. Xanthine oxidase contributes to mechanical ventilation-induced diaphragmatic oxidative stress and contractile dysfunction. J Appl Physiol. 2009 Feb;106(2):385-94.
[58] Rooks D, Praestgaard J, Hariry S, Laurent D, Petricoul O, Perry RG, et al. Treatment of sarcopenia with bimagrumab: results from a phase II, randomized, controlled, proof-of-concept study. J Am Geriatr Soc. 2017 Sep;65(9):1988-95.
[59] Papanicolaou DA, Ather SN, Zhu H, Zhou Y, Lutkiewicz J, Scott BB, et al. A phase IIA randomized, placebo-controlled clinical trial to study the efficacy and safety of the selective androgen receptor modulator (SARM), MK-0773 in female participants with sarcopenia. J Nutr Health Aging. 2013;17(6):533–43.
[60] Bonert VS, Melmed S. Growth hormone. In: The pituitary. 4th ed. Massachusetts: Academic Press; 2017:85-127.
[61] Kostyo JL. Rapid effects of growth hormone on amino acid transport and protein synthesis. Ann N Y Acad Sci. 1968 Feb 5;148(2):389-407.

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Review Article

Optimising Anti-TNF Therapy for Management of Crohn's Disease

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Eric is a third year undergraduate medical student studying at James Cook University with a special interest in Inflammatory Bowel Disease. He was a speaker at a 2019 Crohn's and Colitis Australia speaker night at Sydney Children's Hospital. He has since become an advocate for advancing IBD understanding and awareness as its prevalence continues to increase in the developed world.

Key learning points

- The use of anti-TNF therapy for managing Crohn's Disease is rising globally, yet there is significant variation amongst global guidelines as to how to best optimise this therapy for patients.
- In patients where it is already indicated, emerging research suggests that anti-TNF therapy should be initiated as early in the disease course as possible, at therapeutic levels established by drug level monitoring regimes, and consideration should be given to the use of a concurrent immunomodulator, especially for those taking infliximab.
- Further high powered, long-term trials ought to be conducted comparing different types of anti-TNF therapies with different immunomodulator types, the benefits of a top-down vs step-up approach to treatment, other environmental factors implicated in treatment failure aside from smoking as well as ascertaining the aetiology of other non-immunogenic causes of PNR and SLR.

Abstract

Introduction: This article reviews, using a systematic approach, the role of anti-TNF therapies in CD and the incidence and predictors of primary nonresponse (PNR) and secondary loss of response (SLR) to these drugs to optimise anti-TNF management of Crohn's disease (CD). A search with the following key words was conducted using MEDLINE and the Cochrane IBD Group Specialised Trials Register: 'Crohn's disease', 'primary nonresponse', 'secondary loss of response', 'infliximab', 'adalimumab', 'certolizumab', 'anti-TNF', 'biologics', 'endoscopy', 'immunomodulators', 'immunogenicity', 'combination therapy'. **Summary**: Regularly timed anti-TNF drug regimens at patient-specific therapeutic levels at induction and throughout maintenance therapy remains the clearest predictor of both PNR and SLR respectively. The addition of the immunomodulator azathioprine with infliximab was found to be moderately effective at minimising the risk of SLR and increasing remission rates. No studies were found which compared the efficacy of individual immunomodulators with anti-TNFs in direct reference to SLR and PNR. Smoking was found to be the only environmental factor increasing risk of both PNR and SLR. PNR and SLR can be minimised by early initiation of treatment, ideally within two years, although some studies concluded that the focus should be on the number of diseases flares/relapses rather than duration post-diagnosis. As a predictor of both PNR and SLR, proactive therapeutic drug monitoring (TDM) has been shown to optimise response to anti-TNF agents and should be implemented to ensure drug concentrations are maintained at appropriate levels to prevent formation of anti-drug antibodies. Pre-treatment corticosteroid use was also found to enhance response to anti-TNF drugs in some small-scale studies.

Keywords: Crohn's disease, anti-TNF therapy, primary nonresponse, secondary loss of response.

Introduction

Monoclonal anti-Tumour Necrosis Factor-alpha (anti-TNF) antibodies, namely - infliximab, adalimumab, and certolizumab, have become a mainstay of Inflammatory Bowel Disease (IBD) therapy since their introduction into clinical practice in 1998 [1]. This is due to their unique ability to target and modulate the pro-inflammatory cytokine TNF-alpha which is thought to be at the centre of CD's dysregulated host immune response to tissue injury and dysbiosis [1].

These medications are efficient for the induction and maintenance of remission in patients with Crohn's disease (CD), with extensive evidence showing that they can induce mucosal healing, reduce the need for surgery, decrease hospitalisation rates, and improve quality of life for CD patients [1,2]. However, anti-TNF agents are not effective for a subset of patients with IBD who also experience primary nonresponse (PNR); defined as a lack of improvement in clinical symptoms after the induction phase [3]. The incidence of PNR has been found to occur in 10-40% of patients. ,In patients who initially respond to anti-TNF therapy, secondary loss of response (SLR) may prompt intensification or discontinuation of treatment in up to 50% of patients after 12 months [3,4]. SLR is defined as worsening symptoms linked to active CD during maintenance therapy in a patient with previously stable disease following induction treatment [3]. Treatment plan optimisation is a key priority for clinicians as clinical guidelines can vary widely across

jurisdictions and often are reactive to failed treatment rather than proactive [5,6]. In addition, emerging research suggesting combination therapy and predicting nonresponse through mechanisms such as proactive therapeutic drug monitoring (TDM) may have roles in achieving this [6,7].

As a result, the aim of this review is to provide those interested in gastroenterology (students and practicing clinicians alike) with a brief overview of the therapeutic role of anti-TNF in CD. This includes examining the aetiopathogenesis of CD, the main predictors of PNR and SLR and how they inform various treatment regimens to effectively optimise anti-TNF therapy.

Role of TNF blockers in the treatment of CD

While the underlying cause of CD is not yet fully understood, the aetiopathogenesis is thought to involve an interplay between environmental triggers, dysbiosis, aberrant immune responses and genetic susceptibility [1,8]. CD results in transmural mucosal injury and inflammation, whereby a breach to the epithelial barrier triggers the microflora to stimulate a proinflammatory immune response [8,9]. Tumour necrosis factor-alpha (TNF-α or TNF) was identified in 1975 by Carswell et al. who established that the serum of endotoxin-treated rabbits and mice infected with Bacillus Calmette-Guerin caused haemorrhagic necrosis of various tumours [10]. Cerami et al. later found that TNF secreted by macrophages was responsible for the severe cachexia observed in parasite-infested animals [11]. By the mid-1980s, TNF-α was identified to be the body's sentinel cytokine central to initiating a defence response following T-cell coordinated response to tissue injury [1]. TNF-α comes in both a transmembrane and soluble form, the latter which binds to TNF receptor 1 and TNF receptor 2, which triggers the production of interleukins (IL-1β, IL-6), expression of adhesion molecules, activation of T cells, and inhibition of apoptosis [1]. It was Murch et al. who first established that IBD patients have increased basal levels of TNF in serum as well as in the lamina propria in the bowel; a homeostatic imbalance that has been repeatedly linked to severe systemic health problems in mice, such as severe chronic polyarthritis, and widespread inflammation [12,13]. Further, it has been demonstrated, in vivo, to be involved in increased neutrophil accumulation and granuloma formation seen in CD [14,15].

The mechanism behind how TNF-α inhibitors work is somewhat understood [1,9]. Despite targeting and subsequently inhibiting or neutralising TNF-α (thus preventing it from exerting its pro-inflammatory downstream effects), simple neutralisation of TNF-α is not the only mechanism by which they work [9]. This was established by Zinsmeister et al. who found that some anti-TNF drugs including etanercept (soluble TNF receptor fusion protein) has been shown to have little to no efficacy in CD [16]. This suggests that anti-TNF drugs block other proinflammatory signals that are upregulated by TNF [1,2].

Optimised dosing regimes

Various studies have shown that appropriate dosing of anti-TNF agents can minimise the risk of both PNR and SLR, which are key determinants of treatment failure [2,3]. Even though both adalimumab and certolizumab are fully human antibodies (and infliximab is a chimeric humanised hybrid of both human and mouse antibodies), their structure as large antibodies or antibody fragments render them vulnerable to phagocytosis and subsequent antibody formation, which can interfere with their activity [17]. In a prospective study by Echarri et al., after induction of 32 patients (15 treated with infliximab, 7 with adalimumab), those who were in clinical remission had higher anti-TNF trough levels compared with those with active disease [18]. Notably, 26% of the infliximab-treated patients developed sustained antibodies which was associated with low trough drug levels and a greater chance of infliximab PNR [18]. For adalimumab, in the CLASSIC I dose-finding induction study, remission at 4 weeks was achieved in more patients receiving the higher dose adalimumab than those on lower doses (36% vs 24%, p=0.01), a finding also appreciated in the CHARM trial, which evaluated the maintenance of response and remission to adalimumab 40mg fortnightly and weekly vs placebo [19,20]. However it should be noted that in the CHARM trial there was no significant difference in clinical efficacy observed between the weekly and fortnightly dosing intervals [19,20]. Similarly, in the PRECISE-II (certolizumab) and the ACCENT-I trials (infliximab), higher doses of anti-TNF during the induction phase resulted in lower PNR and SLR rates [21,22].

In an earlier study by Rutgeerts et al, episodic therapy on relapse had less efficacy and was frequently associated with issues resulting from the formation of antibodies to infliximab [23]. The paper found that patients who received scheduled infliximab treatment instead of episodic treatment had fewer hospitalisations, higher rates of mucosal healing, and a reduction in the formation of anti-drug antibodies compared to patients who received episodic treatment based on flare occurrences [23]. Similar conclusions were made by Maser et al., who compared the efficacy of episodic and scheduled dosing in a prospective cohort with an average of 88 weeks of follow up. In this study, when adjusted by dosing schedule, the incidence of antibodies to infliximab was higher in those receiving episodic therapy compared to those who had regularly scheduled dosing (39% vs 16%, p=0.036) [24].

It is thus clear that regularly scheduled dosing is optimal for preventing PNR and SLR to anti-TNF therapies, in conjunction with sufficient dosing both at induction and for maintenance,

the latter being 40mg every other week for adalimumab, 5mg/kg 6-weekly for infliximab and 400mg 4-weekly for certolizumab according to current clinical guidelines [7,19,21,22].

Smoking

Smoking is the only environmental factor that has been directly associated with PNR and SLR [3,7,25]. To optimise anti-TNF therapy, smoking cessation advice should be given to those patients with a history of smoking. Smokers have been found to be 30% less likely to respond to infliximab at week 4 compared to controls [25]. Kiss et al. further established smoking as a predictor of SLR at twelve months in adalimumab-treated patients in a study of 221 patients of whom 21.2% were smoking at induction [26]. The proposed mechanisms behind this link are still widely debated, and while limited research has been conducted in this area, two separate human studies found that nicotine leads to a reduction in TNF-alpha levels in peripheral blood mononuclear cells and macrophage cultures, suggesting that this smoking-induced cytokine suppression may explain the PNR to anti-TNF therapies [27,28]. More research is needed to remove confounders and assess other environmental and patient factors such as obesity which are likely to also affect response to anti-TNF therapy.

Disease duration

Shorter disease duration has been repeatedly described to predict higher responsiveness to anti-TNF drugs and better clinical outcomes [29,30,31]. In a post-hoc analysis of phase 3 clinical trials, patients with disease duration less than 2 years had significantly better primary response rates to adalimumab and certolizumab than those with long standing disease [20,32]. In addition, the CHARM trial found that the week-26 rate of maintenance of remission was 46% in patients with disease duration less than 2 years, 35% in those with disease duration of 2-5 years and 37% in those diseases longer than 5 years [20]. Similar findings were demonstrated in the PRECISE II study with certolizumab [21]. This data suggests that using biologics as a first line 'top down' therapy over existing immunomodulators may be favourable to a 'step up' approach in terms of patient outcomes, a finding supported by a two-year randomised European trial using a top-down approach, combining early immunosuppression with infliximab and azathioprine [33]. It showed that the top-down group had significantly fewer flares than the step-up group which started with just azathioprine or corticosteroids (7% vs 19%, p=0.01), despite negligible differences in remission rates [33]. A recent 2020 population-based study by Jung et al. further concluded that early anti-TNF therapy amongst Korean CD patients within 1 year of diagnosis was associated with lower surgery and decreased Emergency Room presentations [34]. Despite this evidence, there is ongoing debate within the academic community as to the benefits of a top-down approach, with some studies suggesting that optimising anti-TNF therapy timing is dependent on disease relapses rather than duration [35].

Combination therapy

Given the aforementioned problems of non-response in certain patients, it has been suggested that using an immunomodulator, such as azathioprine, 6-MP, or methotrexate in combination with an anti-TNF agent may decrease the risk of both PNR and SLR [4,6,7]. The influential SONIC trial, randomised 508 steroid-exposed CD patients to either azathioprine alone, infliximab alone, or azathioprine alongside infliximab combination therapy.It was found that steroid-free clinical remission and endoscopic mucosal healing at 6 months was greater among patients in combination therapy, followed by monotherapy infliximab, and monotherapy azathioprine (43.9% vs 30.1% vs 16.5%, respectively) [6]. Somewhat conflictingly, in the COMMIT trial, infliximab in combination with methotrexate was not more effective than infliximab monotherapy at achieving prednisone-free remission at week 14, however many researchers have criticised the study design, including the use of prednisolone at induction, making its findings questionable [36,37]. Despite this, a study by Ben-Horin et al. demonstrated that the addition of an immunomodulator to five patients who developed antibodies to infliximab restored response to the drug via elimination of the antibodies and increase in anti-TNF trough levels [38]. In a separate clinical trial by Farrell et al, prophylaxis with hydrocortisone before each infusion of infliximab was shown to decrease the formation of antibodies to infliximab, suggesting that another aspect of anti-TNF optimisation involves a short course of corticosteroids pre-treatment [39].

To date, there have been few similar robust randomised controlled trials directly comparing adalimumab or certolizumab combination therapy with monotherapy. A small meta-analysis by Kopylov et al. found that combination therapy with adalimumab adjunct to an immunomodulator was mildly superior to adalimumab monotherapy to induction of remission, but there was no difference in remission rates at 1 year [40]. Furthermore, the 2016 DIAMOND study found that there was no statistical difference of a combination of adalimumab and azathioprine at week 6 vs monotherapy in terms of remission rate (71.8% vs 68.1%, p=0.63) [41].

The main hesitation to using combination therapy is the small, albeit statistically significant increased risk of non-Hodgkin's lymphoma, although when compared with the general population, the absolute risk remains small (6.1 per 10,000 patient years) [42]. Hence, the management decision should be tailored to individual patients after a careful risk/benefit

assessment in conjunction with consideration of the most up-to-date European Crohn's and Colitis (ECCO) guidelines on Therapeutics in CD.

Role of Therapeutic Drug Monitoring (TDM) in predicting PNR and SLR

Optimal clinical response requires the maintenance of clinically effective drug concentrations, something made difficult by the variability of actual drug levels among patients due to the unique pharmacokinetics of anti-TNF drugs [3,7]. Karmiris et al. demonstrated in a study of 168 CD patients on adalimumab that there is a trough level which correlates with mucosal healing which may be used to predict clinical response [43]. Then, in 2017, the American Gastroenterological Association (AGA) Institute published guidelines recommending reactive TDM in patients with partial response or loss of response to anti-TNF and subsequently optimising or switching therapy based on TDM results, but stopped short of making recommendations for proactive TDM [44]. Clinically, it is ideal to optimise therapy before loss of response develops, hence the role of proactive TDM in keeping medications within a narrow therapeutic window, to prevent both toxicity in excess levels but also sub-optimal concentrations and the subsequent development of anti-drug antibodies typical of immunogenicity-related treatment failure (SLR) [3,7,45]. TDM can also provide guidance in cases where there are no anti-drug antibodies despite high drug levels (pharmacodynamic treatment failure) by switching to an alternate drug class [45].

Despite limited research, a recently reported prospective trial showed that proactive adalimumab TDM may lead to improved outcomes. In this study, 78 paediatric patients with CD and no prior exposure to anti-TNF agents, who had responded to adalimumab induction therapy, were randomised to receive proactive TDM after SLR [46]. Rates of sustained corticosteroid-free clinical remission were significantly higher with proactive TDM than with reactive monitoring (82% vs 48% respectively). The TAXIT study also showed that increasing the infliximab dose in CD patients with suboptimal drug levels via proactive TDM lead to better disease control [47]. More recently, Papamichael et al. demonstrated that proactive TDM in patients in remission after induction with infliximab was associated with less antidrug antibodies formation and infusion reactions, increased drug durability, and decreased IBD-related hospitalisation and surgeries [48].

Despite the clinical utility described, several questions remain unanswered – it is not clear how often drug levels need to be checked after the initial optimisation and what target trough levels are needed during maintenance beyond a year in patients with sustained clinical remission [49].

Conclusion

The use of anti-TNF medications has revolutionised Crohn's disease management, with the ability to induce long-term steroid-free endoscopic remission in patients and greatly improve their quality of life. Being able to predict which patients are vulnerable to PNR or SLR may allow clinicians to optimise therapy to improve clinical outcomes. Numerous studies have shown that sub-optimal drug concentrations are predictive of PNR and SLR, but more assessment behind the mechanisms for PNR in patients that do not have high anti-drug antibodies is needed (non-immunogenic treatment failure). This review has found that the best response to TNF therapy can be achieved by starting as early in the disease course (ideally less than 2 years) with sufficient and regularly timed dosage and using concomitant immunomodulators with infliximab (but more research is needed for its use with adalimumab and certolizumab). Some limited evidence suggests that a short course of corticosteroids before anti-TNF treatment also enhances anti-TNF response. Smoking is also linked to a decreased anti-TNF response, but more studies are required to assess other environmental factors possibly affecting response. The role of TDM is essential to ensuring optimal management guidance in patients who have failed to respond or subsequently lose response to anti-TNF therapy, however more research is needed to clarify the contexts of where it should best be used proactively. Perhaps the greatest potential for research into the future is more comprehensively examining the clinical outcomes between the newer 'top down' biologics approach vs the prevalent 'step up' approach.

With their potential to induce sustained remission in CD, finding ways to enhance the effectiveness of anti-TNF therapies will service not only patients but health services as biologics continue to disseminate further into mainstream clinical practice.

References

[1] Adegbola SO, Sahnan K, Warusavitarne J, et al. Anti-TNF Therapy in Crohn's Disease. *Int J Mol Sci*. 2018;19(8):2244. doi:10.3390/ijms19082244.

[2] Altwegg R, Vincent T. TNF Blocking Therapies and Immunomonitoring in Patients with Inflammatory Bowel Disease. *Mediators of Inflammation*. 2014;52(1)1-7. doi:10.1155/2014/172821.

[3] Fine S, Papamichael K, Cheifetz AS. Etiology and Management of Lack or Loss of Response to Anti-Tumor Necrosis Factor Therapy in Patients With Inflammatory

Bowel Disease. *Gastroenterol Hepatol.* 2019;15(12):656-665. PMID:31892912.

[4] Allez M, Karmiris K, Louis E, et al. Report of the ECCO pathogenesis workshop on anti-TNF therapy failures in inflammatory bowel diseases: definitions, frequency and pharmacological aspects. *J Crohns Colitis*. 2010;4(4):355-66. doi:10.1016/j.crohns.2010.04.004.

[5] Nguyen DL, Solaimani P, Nguyen ET, et al. Antitumor necrosis factor α is more effective than conventional medical therapy for the prevention of postoperative recurrence of Crohn's disease: a meta-analysis. *Eur J Gastroenterol Hepatol*. 2014;26(10):1152-9. doi:10.1056/NEJMoa0904492.

[6] Colombel JF, Sandborn WJ, Reinisch W et al. Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease (SONIC trial). *N Engl J Med*. 2010;362(1):1383-1395. doi:10.1056/NEJMoa0904492.

[7] Kopylov U, Seidman E. Predicting durable response or resistance to antitumor necrosis factor therapy in inflammatory bowel disease. *Therap Adv Gastroenterol*. 2016;9(4):513-526. doi:10.1177/1756283X16638833.

[8] Boyapati R, Satsangi J, Ho GT. Pathogenesis of Crohn's disease. *F1000Prime Rep*. 2015;7(1):44. doi:10.12703/P7-44.

[9] Petagna, L., Antonelli, A., Ganini, C. et al. Pathophysiology of Crohn's disease inflammation and recurrence. *Biol Direct*. 2020;15(1):23. doi:10.1186/s13062-020-00280-5.

[10] Carswell EA, Old LJ, Kassel RL, et al. An endotoxin-induced serum factor that causes necrosis of tumors. *Proc Natl Acad Sci USA*. 1975;72(9):3666-3670. doi:10.1073/pnas.72.9.3666.

[11] Cerami A, Ikeda Y, Trang N et al. Weight loss associated with an endotoxin-induced mediator from peritoneal macrophages: The role of cachectin (tumor necrosis factor). *Immunol Lett*. 1985;11(3-4):173-177. doi:10.1016/0165-2478(85)90165-8.

[12] Murch SH, Braegger CP, Walker-Smith JA, et al. Location of tumour necrosis factor alpha by immunohistochemistry in chronic inflammatory bowel disease. *Gut*. 1993;34(12):1705-1709. doi:10.1136/gut.34.12.1705.

[13] Perse M, Unkovic A. The Role of TNF in the Pathogenesis of Inflammatory Bowel Disease. InTechOpen publications website. Updated January 14, 2019. Accessed March 22, 2021. https://www.intechopen.com/books/biological-therapy-for-inflammatory-bowel-disease/the-role-of-tnf-in-the-pathogenesis-of-inflammatory-bowel-disease.

[14] Rampart M, De Smet W, Fiers W, et al. Inflammatory properties of recombinant tumor necrosis factor in rabbit skin in vivo. *J Exp Med*. 1989;169(6):2227-2232. doi:10.1084/jem.169.6.2227

[15] Amiri P, Locksley RM, Parslow TG, et al. Tumour necrosis factor alpha restores granulomas and induces parasite egg-laying in schistosome-infected SCID mice. *JH Nature*. 1992;356(6370):604-607. doi:10.1038/356604a0.

[16] Johnson T, Diehl NN, Zinsmeister AR, et al. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Gastroenterology*. 2001;121(5):1088-1094. doi:10.1053/gast.2001.28674.

[17] Cassinotti A, Travis S. Incidence and clinical significance of immunogenicity to infliximab in Crohn's disease: a critical systematic review. *Inflamm Bowel Dis*. 2009;15(8):1264-1275. doi:10.1002/ibd.20899.

[18] Echarri A, Ferreiro R, Fraga-Iriso R, et al. Sa1264 Drug Trough Levels and Primary Nonresponse to antiTNF Therapy in Moderate-Severe Crohn Disease. Results of the Optimiza Study. *Gastroenterology*. 2014;146(5):S-247. doi:10.1016/S0016-5085(14)60868-4.

[19] Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology*. 2006;130(2):323-333. doi:10.1053/j.gastro.2005.11.030.

[20] Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132(1):52-65. doi:10.1053/j.gastro.2006.11.041.

[21] Sandborn WK, Feagan BG, Stoinov S, et al. Certolizumab Pegol for the Treatment of Crohn's Disease (PRECISE II trial). *N Engl J Med*. 2007;357(1):226-238. doi:10.1056/NEJMoa067594.

[22] Colombel JF, Rachmilewitz D, Wolf DC, et al. ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359(9317):1541-1549. doi:10.1016/S0140-6736(02)08512-4.

[23] Rugeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology*. 2004;126(1)402-413. doi:10.1053/j.gastro.2003.11.014.

[24] Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol*. 2006;4(10):1248-1254. doi:10.1016/j.cgh.2006.06.025.

[25] Arnott IDR, McNeill G, Satsangi J. An analysis of factors influencing short-term and sustained response to infliximab treatment for Crohn's disease. *Aliment Pharmacol Ther*. 2003;17(1):1451–1457. doi:10.1046/j.1365-2036.2003.01574.x.

[26] Kiss LS, Szamosi T, Molnár T, et al. Early clinical remission and normalisation of CRP are the strongest predictors of efficacy, mucosal healing and dose escalation during the first year of adalimumab therapy in Crohn's disease. *Aliment Pharmacol Ther*. 2011;34(8):911–922. doi:10.1111/j.1365-2036.2011.04827.x.

[27] Borovikova LV, Ivanova S, Zhang M, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature*. 2000 May 25;405(6785):458-62. doi:10.1038/35013070.

[28] Madretsma GS, Donze GJ, et al. Nicotine inhibits the in vitro production of interleukin 2 and tumour necrosis factor-

alpha by human mononuclear cells. *Immunopharmacology*. 1996;35(1):47-51. doi:10.1016/0162-3109(96)00122-1.

[29] Khanna R, Bressler B, Levesque BG, Zou G, Stitt LW, Greenberg GR, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. *Lancet*. 2015;386(10006):1825–34. doi:10.1016/S0140-6736(15)00068-9.

[30] Danese S, Fiorino G, Peyrin-Biroulet L. Early intervention in Crohn's disease: towards disease modification trials. *Gut*. 2017;66(12):2179–87. doi:10.1136/gutjnl-2017-314519.

[31] D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet*. 2008;371(9613):660–7. doi:10.1016/S0140-6736(08)60304-9.

[32] Schreiber S, Colombel JF, Bloomfield R, et al. Increased response and remission rates in short-duration Crohn's disease with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data. *Am J Gastroenterol*. 2010;105:1574–82. doi:10.1038/ajg.2010.78.

[33] Rutgeerts P, Feagan BG, Hommes D. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet*. 2008; 23;371(9613):660-667. doi:10.1016/S01406736(08)60304-9.

[34] Jung YS, Han M, Park S, et al. Impact of early anti-TNF use on clinical outcomes in Crohn's disease: a nationwide population-based study. *Korean J Intern Med*. 2020;35(5):1104-1113. doi:10.3904/kjim.2020.001.

[35] Tsui JJ, Huynh HQ. Is top-down therapy a more effective alternative to conventional step-up therapy for Crohn's disease? *Ann Gastroenterol*. 2018;31(4):413-424. doi:10.20524/aog.2018.0253.

[36] Feagan BG, McDonald JWD, Panaccione R, et al. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. *Gastroenterology*. 2014;146(3):161-688. doi:10.1053/j.gastro.2013.11.024.

[37] Narula N, Peyrin-Biroulet L, Colombel JF. Combination Therapy With Methotrexate in Inflammatory Bowel Disease: Time to COMMIT? *Gastroenterology*. 2014;146(3)608-611. doi:10.1053/j.gastro.2014.01.040.

[38] Ben-Horin S, Waterman M, Kopylov U, et al. Addition of an immunomodulator to infliximab therapy eliminates antidrug antibodies in serum and restores clinical response of patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2013;11(4):44-447. doi:10.1016/j.cgh.2012.10.020.

[39] Farrell R.J. Alsahli M. Jeen Y.T. Falchuk K.R. Peppercorn M.A. Michetti P. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. *Gastroenterology*. 124(4):917-924. doi:10.1053/gast.2003.50145.

[40] Kopylov U, Al-Taweel T, Yaghoobi M, et al. Adalimumab monotherapy versus combination therapy with immunomodulators in patients with Crohn's disease: a systematic review and meta-analysis. *J Crohns Colitis*. 2014;8(12):1632-1641. doi:10.1016/j.crohns.2014.07.003.

[41] Matsumoto T, Motoya S, Watanabe K, et al. Adalimumab Monotherapy and a Combination with Azathioprine for Crohn's Disease: A Prospective, Randomized Trial (DIAMOND study). *J Crohns Colitis*. 2016;10(11):1259-1266. doi:10.1093/ecco-jcc/jjw152.

[42] Dahmus J, Roasrio M, Clarke K. Risk of Lymphoma Associated with Anti-TNF Therapy in Patients with Inflammatory Bowel Disease: Implications for Therapy. *Clin Exp Gastroenterol*. 2020;13(1):339-350. doi:10.2147/CEG.S237646Fg.

[43] Karmiris K, Paintaud G, Noman M, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology*. 2009;137(1):1628–40.

[44] Feuerstein JD, Nguyen GC, Kupfer SS, et al. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. *Gastroenterology*. 2017;153(3):827-834. doi:10.1053/j.gastro.2017.07.032

[45] Strik AS, Berends SE, Lowenberg M. Therapeutic drug monitoring-based dosing of TNF inhibitors in inflammatory bowel disease: the way forward? *Expert Rev. Clin. Pharmacol*. 2019;12(9):885-891. doi:10.1080/17512433.2019.1642745.

[46] Assa A, Matar M, Turner D, et al. Proactive Monitoring of Adalimumab Trough Concentration Associated With Increased Clinical Remission in Children With Crohn's Disease Compared With Reactive Monitoring. *Gastroenterology*. 2019;157(4):985-996. doi:10.1053/j.gastro.2019.06.003.

[47] Casteele NV, Ferrante M, Assche GV, et al. Trough Concentrations of Infliximab Guide Dosing for Patients With Inflammatory Bowel Disease. *Gastroenterology*. 2015;148(7):1320-1329. doi:10.1053/j.gastro.2015.02.031.

[48] Papamichael K, Chachu KA, Vajravelu RK, et al. Improved long-term outcomes of patients with inflammatory bowel disease receiving proactive compared with reactive monitoring of serum concentrations of infliximab. *Clin Gastroenterol Hepatol*. 2017;15(1):1580-1588. doi:10.1016/j.cgh.2017.03.031.

[49] Mitrev N, Vasteele NV, Seow CH, et al. Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases. *Ailment Pharmacol Ther*. 2017;46(1):1037-1053. doi:10.1111/apt.14368.

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Original Research

Australian medical students' desire to become a general practitioner: has it changed between 2009 and 2019?

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Key learning points

- Medical student awareness of the benefits and rewards of a career in general practice is important to encourage increased uptake of general practice training positions.
- Medical students value holistic patient-centred care and a healthy work-life balance, both of which are offered by a career in general practice.
- General practice training organisations should be aware of the perceptions of medical students to ensure effective marketing strategies to maintain, and increase, positive perceptions of general practice amongst medical students.

Abstract

Introduction: There is major concern given the reduction in junior doctors applying for general practice training positions, which has considerably dropped in recent years. It is possible that medical student perceptions of a career in general practice influence the later decision to choose general practice as their first-choice specialty and apply for general practice training positions. **Aim:** To examine the changes in Australian medical student perceptions of a career in general practice by a cross-sectional analysis of student cohorts in 2009 and 2019. **Methods** Two identical cross-sectional studies were administered in 2009 and 2019 via an online quantitative survey to understand medical student perceptions of a career in general practice. **Results:** Almost 6% of all Australian medical students responded to the survey (1129 in 2019 and 1227 in 2009). Medical students' positive perceptions of a career in general practice increased by 6.5% from 2009 to 2019 ($p<0.0001$). Over the same period, the proportion of respondents who agreed that general practice provides the opportunity to pursue diverse special interests increased by 12% ($p<0.001$), while there was a 9.8% increase in respondents who agreed that general practitioners have a healthy work-life balance ($p<0.001$). One in five respondents reported not knowing or feeling neutral towards the ability for general practitioners to earn a sufficient income. General practice was perceived to be as challenging as other specialties in both surveys. **Conclusion:** Medical students' positive perceptions of holistic patient-centred care, ability to pursue special interests, and work-life balance are important in ensuring a sustainable primary care workforce. Further education regarding the ability of general practitioners to receive appropriate remuneration is crucial to encouraging medical students to pursue a career in general practice. Given the consistently high levels of interest from medical students, future interventions should shift to focus on promoting general practice to junior doctors.

Keywords: Academic Medicine; Career Development; Family Practice; General Practice; Health Planning; Medical Students

Introduction

Health Workforce Australia forecasts predict that due to the aging demographic of the medical workforce, an increasing number of doctors across all specialties will retire from 2025, producing an estimated shortfall of 2500 doctors by 2025 and 5000 doctors by 2030 [1]. This is particularly concerning in general practice given the vital role that general practitioners (GPs) play in providing quality, holistic, and longitudinal care to the community, significantly reducing the burden on tertiary hospitals [2]. There has been a significant decrease in the number of junior doctors applying for general practice training in Australia since 2015 [3] with a 20% drop, equivalent to 443 applicants, since 2015 [3]. In both 2018 and 2019, there has been a deficit in the number of training positions filled within the Australian General Practice Training Program, resulting in 63 fully funded general practice training places across Australia remaining unfilled.

Only 15.4% of graduating medical students in 2019 chose general practice as their first-choice specialty [4]. Medical students spend much of their clinical time in tertiary care settings. This is incongruent with teachings around primary care being the front line of healthcare, and the importance of prevention over cure. Furthermore, the failure to recognise general practice as a specialty and the misconception regarding it as a second or later career preference for medical graduates, may be perpetuating negative perceptions of general practice [5]. Therefore, it is vital that the government invest in recruiting and developing GPs of the future to ensure the ongoing health needs of the Australian population are met.

There is no clear understanding of why there has been a reduction in the number of junior doctors entering general practice training. Current evidence suggests a shift away from general practice centres around poor remuneration and misconceptions about the intellectual rigour of the work fuelled by poor clinical experiences and stereotyping of this field [6,7]. This study aims to examine the changes in medical student perceptions of a career in general practice by a cross-sectional analysis of student cohorts in 2009

Methods

Two identical cross-sectional studies were undertaken in 2009 and 2019 via an online quantitative survey to compare Australian medical students' awareness, knowledge, and attitudes towards general practice. The survey was developed collaboratively by General Practice Students Network (GPSN), General Practice Registrars Australia (GPRA), and the University of Wollongong. The novel 2009 survey, conducted as an evaluation of the GPSN, benchmarked awareness, knowledge, and attitudes towards the GPSN and general practice amongst medical students. It was intended that future iterations of the survey would provide a measure of change in students' attitudes towards general practice. The survey tool and questions were developed based on important themes within the existing literature [8].

Data

The initial survey was undertaken over an 8-week period from May to July 2009, while the second survey was undertaken over an 8-week period from September to November 2019. Both were undertaken through an online survey platform (Survey Monkey). The same recruitment strategy and participant inclusion and exclusion criteria were applied across both surveys. Information was collected on participant demographics which included gender, age (categorical), year of university, and GPSN membership status. Participant attitudes towards general practice were obtained through a self-reported questionnaire assessing the following variables: career pathway, work-life balance, holistic patient care, career satisfaction, and remuneration. The survey questionnaire is included in Appendix A.

Participants

The survey was distributed through the GPSN membership database, as well as student newsletters, social media groups, and student ambassadors to increase participation across the wider medical student body and reduce selection bias. All medical students enrolled at an Australian university at the time of survey distribution were eligible to participate. In 2019, this included a total student body of 17 460 medical students, of which 8 938 were members of GPSN, while in 2009 this included a total student body of 14 611 medical students, of which 3 638 were members of GPSN [4].

Statistical Methods

Quantitative data analysis was performed using JMP SAS software. Chi-squared analysis and Fisher's exact tests were performed to compare responses from the two survey cohorts. Statistical significance was set at $p<0.05$ and demographic data was expressed as mean +/- standard deviation (SD).

Survey questions utilised a five-point Likert scale (strongly agree – 5, agree, neutral, disagree, or strongly disagree – 1) or yes/no questions to assess participant attitudes. For Likert scale responses, strongly agree and agree responses were grouped together to represent positive attitudes towards general practice and the same was done with strongly disagree and disagree responses.

Ethics approval was received from University of Wollongong (HREC No. 2019/297) and the University of Notre Dame Australia (HREC No 2021-054F). Consent was obtained implicitly by the participant beginning the survey. Data collection ensured all participant responses were anonymous.

Table 1 Demographic Data for 2019 and 2009 Cohorts

	2009	2019
Sex Number (%)		
Male	403 (32.8%)	385 (34.15)
Female	824 (67.2%)	738 (65.4%)
Prefer not to disclose	N/A	6 (0.5)
Age Number (%)		
Under 18	25 (2%)	1 (0.1%)
18-24	871 (71%)	695 (61.6%)
25-30	231 (18.8)	334 (29.6%)
31-40	78 (6.4%)	82 (7.3%)
41-50	20 (1.6%)	15 (1.3%)
Over 50	2 (0.2%)	2 (0.2%)
Member of GPSN		
Yes	833 (67.3%)	707 (66.4%)
No*	404 (32.3%)	357 (33.6%)

*Respondents who answered maybe were deemed to not be active members of GPSN

Results

Participants

A total of 1 129 medical students completed the 2019 survey from 22 medical schools, while 1 270 medical students from 19 universities completed the 2009 survey. In 2019, the overall participation rate was 6.5% of all medical students, compared with 8.7% in 2009. Demographic data of the respondents is presented in Table 1. A similar proportion of respondents were female in 2009 (65.4%) and 2019 (67.2%). In both surveys, most participants were aged 18 to 24 years of age, however, a significantly higher proportion of older participants were present in the 2019 survey (mean age 21.3±4.7 years in 2019, 0.8 years older than the 2009 cohort [p<0.001]). Most participants in the 2019 survey were in their third or later years of study (60%), compared to the 2009 survey where most participants were in their first or second year (53%). In 2019, 7.4% of respondents were GPSN members, who were personally involved in the organisation, compared to 3.5% in 2009. In both 2009 and 2019, one in three respondents were not members of GPSN, however, respondents who answered 'maybe' to this question were deemed to not be members of GPSN.

General practice as a career choice

In 2019, 78.3% of respondents indicated they felt positive towards a career in general practice, a statistically significant increase of 6.5% from 2009 (p<0.0001), as demonstrated in Table 2 (Question 1).

Career pathway

In 2019, 98% of respondents identified general practice as "a specialty in its own right", compared to 96.6% in 2009 (p=0.032) (Question 2, Table 3). In 2019, 96.7% of respondents were aware that general practice requires further training after internship and residency, compared to 94.3% in 2009, a statistically significant increase (p=0.004) (Question 3). In 2019, 85% of respondents agreed that general practice offers the opportunity to pursue diverse special interests during training and practice, compared to 73% of respondents in 2009, a statistically significant increase (p<0.001) (Question 3, Table 4).

Table 2 Medical students' perceptions of general practice as a career choice

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	Don't know/Not
Question 1: How would you rate your overall attitude towards General Practice as a career choice?	*2019*	25.5% (274)	52.8% (568)	14.3% (154)	5.9% (63)	1.1% (12)	0.4% (4)
	2009	19.9% (247)	51.9% (645)	18.3% (227)	7.9% (98)	1.0% (12)	1.0% (13)

Table 3 Medical students understanding of the general practice career pathway.

		Yes	No	Don't know/Not sure
Question 2: Is GP a specialty in its own right?	*2019*	98% (1053)	0.7% (7)	1.4% (15)
	2009	96.6% (1200)	1.6% (20)	1.8% (22)
Question 3: Does General Practice require further training after internship/residency?	*2019*	96.7% (1039)	1.2% (12)	2.1% (23)
	2009	94.3% (1171)	2.1% (26)	3.6% (45)

Table 4 GP opportunity to practice diverse interests

		Strongly Agree	Agree	Neither Agree nor	Disagree	Strongly Disagree	Don't know/Not
Question 4: GP offers the opportunity to pursue diverse special interests during training and practice	*2019*	34% (366)	51% (548)	8.5% (91)	2.7% (29)	0.3% (3)	3.5% (38)
	2009	27.5% (342)	45.9% (570)	15.4% (191)	4.6% (57)	0.2% (3)	6.4% (79)

Factors contributing to career choice

Medical students perceived that general practice provides an ongoing, holistic approach to healthcare for the community. This view was stable over the two surveys, with 90% of respondents in 2019, and 89% of respondents in 2009 (p=0.26) agreeing that "an important part of general practice is the continuity of care, and this is something that is lacking in other specialties" (Question 5, Table 5).

In 2019, 93.2% of respondents agreed that GPs have a healthy work-life balance, representing a statistically significant increase of 9.8% compared to 2009 (p<0.001). The proportion of respondents who disagreed or strongly disagreed with this statement decreased from 3.7% to 0.7% (p=0.001) (Question 6, Table 5).

The proportion of respondents who believed they could earn a sufficient income while training and working as a GP remained stable at 75.3% in 2019, compared to 76.6% in 2009 (p=0.77) (Question 7, Table 5). In both 2019 and 2009, almost one in five respondents reported not knowing or feeling neutral towards the ability to earn a sufficient income while training and working as a general practitioner (18.1% and 19.2%, respectively).

Medical students in 2019 and 2009 indicated a similar understanding that general practice is as challenging as other specialties (79.7% and 78%, respectively, p=0.17) (Question 8, Table 5). In both 2019 and 2009, almost all participants agreed that general practice is central to delivering quality healthcare in Australia (78.8% and 71.8%, respectively. p= 0.094) (Question 9, Table 5).

Table 5: Medical students' perceptions of factors affecting general practice as a career pathway

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	Don't know/Not sure
Question 5: An important part of General Practice is the continuity of care and this is something that is lacking in other specialties	*2019*	46% (494)	44.0% (473)	7% (75)	2.3% (25)	0.5% (5)	0.3% (3)
	2009	50.4% (626)	38.6% (480)	7.2% (89)	3.1% (39)	0.3% (4)	0.3% (4)
Question 6; As a GP, you can enjoy a healthy work-life balance	*2019*	45.9% (493)	47.3% (509)	5.4% (58)	0.6% (6)	0.1% (1)	0.7% (8)
	2009	39.9% (495)	43.5% (540)	11% (137)	3.4% (42)	0.3% (4)	1.9% (24)
Question 7: You can earn a sufficient income while training and working as a GP	*2019*	28.8% (310)	46.5% (500)	13.1% (141)	5.5% (59)	1.1% (12)	4.9% (53)
	2009	27.5% (341)	49.1% (610)	12.6% (157)	3.8% (47)	0.3% (4)	6.7% (83)
Question 8: General Practice is just as challenging as other specialties	*2019*	37.2% (400)	42.5% (457)	10.8% (116)	7.3% (79)	1.5% (16)	0.7% (7)
	2009	39% (484)	39% (485)	13% (162)	6.6% (82)	1.1% (14)	1.2% (15)
Question 9: General Practice is central to delivering quality healthcare in Australia	*2019*	25.5% (274)	52.8% (568)	14.3% (154)	5.9% (63)	1.1% (12)	0.4% (4)
	2009	19.9% (247)	51.9% (645)	18.3% (227)	7.9% (98)	1.0% (12)	1.0% (13)

Discussion

In survey data from 2009 and 2019, we demonstrated a significant increase in positive perceptions towards general practice as a career choice amongst participating medical students. Furthermore, there were significantly fewer negative attitudes towards general practice. Our findings contrast the decrease in junior doctors applying for the general practice training program in Australia [3]. This may suggest that as junior doctors progress along the career pathway, there is a change in sentiment away from general practice. There is extensive existing international literature suggesting that negative perceptions regarding work-life balance and financial remuneration when working as a GP are potential factors which may have contributed to such a shift [7,9,10].

Almost all respondents in both years identified general practice as a specialty, akin to other medical specialties. This recognition is critically important in dispelling misconceptions that devalue general practice as a backup career for those who did not want to or were unable to enter other medical specialist training programs. Building awareness of general practice in medical school is critical in attracting medical students towards a career in general practice [7]. A clear understanding of the career pathway, including understanding that general practice is a speciality, is an essential step in allowing medical students to make an educated decision regarding a career in general practice.

The number of medical students reporting that general practice offers the opportunity to pursue diverse special interests during training and practice increased over the decade.
This may be due to increasing numbers of rural placements, where students observe GPs with diverse workloads, including rural generalists undertaking anaesthetics or obstetrics work [8]. Similarly, metropolitan and rural GPs often complete additional training, including but not limited to paediatrics, sexual health, palliative care, and addiction medicine. The Royal Australian College of General Practitioners (RACGP) also has special interest groups, allowing GPs to network and gain additional skills [11]. Special interest pathways and further training allow GPs the ability to gain expertise in topics relevant to their patient demographic. An increased appreciation of the opportunity to pursue special interests and gain extra skills during training and practice as a GP may lead to a more favourable opinion of general practice amongst medical students. Future marketing strategies by RACGP and The Australian College of Rural and Remote Medicine (ACRRM) should leverage the ability to pursue diverse special interests during training and practice to increase the desirability of a career in general practice.

There was a significant increase in respondents between 2009 and 2019 who agreed that a healthy work-life balance is possible as a GP. Recent marketing campaigns from a range of organisations, including GPSN, GPRA, RACGP, and ACRRM, promoting this as a beneficial aspect of a career in general practice may have contributed to this awareness [12]. Modern medical students have an increasing importance placed on work-life balance, which is a central factor in career planning [10]. Our results contrast the existing international and Australian literature demonstrating high levels of burnout and low levels of satisfaction with work-life balance amongst general practice registrars [13,14]. Therefore, a gap exists between the perceptions of medical students and the experiences of registrars regarding work-life balance within general practice training. These expectations should be managed for junior doctors considering entering training pathways and a career in general practice, while strategies to address high levels of burnout and lack of work-life balance should be pursued.

Medical students believe that general practice offers continuity and patient-focused holistic care. This sentiment was demonstrated in both years of our study and is consistent throughout general practice literature. The existing literature demonstrates that high levels of continuity of care results in positive patient experiences, greater patient satisfaction, increased treatment adherence, improved patient outcomes, and contributes to higher levels of GP satisfaction [15,16]. The holistic approach to healthcare that is offered by general practice, providing continuity of care and endearing relationships with patients, is often the focus of medical students' positive perceptions of a career general practice [17]. In seeking to attract medical students to general practice, future marketing campaigns should focus on the unique aspects of continuity of care offered by a career in general practice. Almost all respondents of both surveys agreed that general practice is central to delivering quality healthcare in Australia and were sufficiently aware of the benefits a career in general practice can bring. It is important that medical students maintain a positive impression of general practice, regardless of future career pathway, as it enables improved collaboration between hospital and community-based healthcare professionals to provide quality patient-centred care [18].

The comparatively inadequate income of GPs and trainees relative to hospital-based specialists is a key reason contributing to the negative perceptions towards general practice [19,20,21]. Consistent with the existing Australian literature [22], nearly one in four medical students in both surveyed years did not agree that GPs earnt an adequate income whilst working and training. Interestingly, it remains unclear why approximately 20% of students across both survey cohorts were unsure or did not

know if it was possible to earn a sufficient income whilst training and working as a GP. It is worth considering that the comparatively lower income of full time GPs relative to full time hospital-based specialists comes with increased ability for flexible working arrangements and work-life balance, as was recognised by respondents. Further, it is important to acknowledge that GP is still the sixth highest paid profession in Australia and promotional campaigns should leverage this as a strength of a career in general practice [23]. Clarity regarding earning potential as a GP is important to improve the perceptions of general practice and the number of students considering a career in general practice.

There is a common misconception that general practice is not intellectually challenging when compared to other specialties and this may be adversely affecting the desire of medical students' perceptions of general practice [5]. However, in both years, medical students indicated a similar agreement that general practice is as challenging as other specialties. GPs undertake numerous challenging tasks, including maintaining generalist skills and knowledge, managing multiple chronic conditions, and intimately understanding referral pathways within the Australian healthcare system. Further, the already challenging nature of general practice is often made more difficult when practitioners work in rural and remote areas. This study highlights that medical students are seeing beyond these negative commentaries and realising the importance of general practice.

Limitations

Our results must be interpreted in the context of several limitations. First, the cross-sectional nature of our study makes it difficult to demonstrate causality, as we only provided descriptive statistics at two specific points in time. Second, the survey was not validated, and therefore, the questions utilised may not have captured the breadth and depth of medical student opinions regarding general practice. This may suggest that the factors explored in this paper, although significant, are potentially not the source of the reduced interest in applications for general practice training. Other potential factors should be explored and may be better generated through a qualitative methodology. Third, the small time-frame during which our survey was administered may have limited uptake by students. Fourth, the self-selected nature of participants may have introduced important selection bias, limiting the generalisability of results to the wider medical student population. While the surveys were open to all Australian medical students, those who were members of GPSN, and so have shown interest in a career in general practice, may have been more likely to participate. Further analysis should seek to assess the potential impact of GPSN membership as a confounding factor. Finally, limited demographic data was collected, and therefore we were unable to analyse the potential confounding nature of other variables that might influence knowledge of training pathways or decisions about careers to pursue. This includes, but is not limited to, university of study, metropolitan or regional and remote background of student, socioeconomic status, and ethnic background.

Future research directions

Future studies should examine a longitudinal cohort to examine changes in perceptions of general practice after the completion of medical studies. Administering serial surveys may allow identification of the critical period in a medical student's or junior doctor's career when they are most receptive to a career in general practice. Further studies should also incorporate multivariate analyses to enable complete analysis of respondent demographics and perceptions of general practice and career choice. Further studies could use a qualitative approach allowing researchers to capture the breadth of medical student opinions regarding general practice. With a shift towards postgraduate medical education in Australia, further studies should aim to identify the relationship between age and medical students' perceptions of general practice.

Conclusion

Medical students are aware of the benefits and rewards of a career in general practice, and there has been significant increases in key areas when comparing 2009 and 2019. We demonstrated a clear opportunity to develop and maintain the positive perceptions of medical students towards holistic care and work-life balance. A coordinated approach by key stakeholders is essential to maintain the desirability of general practice and increase the number of applicants to general practice training programs. This will ensure the provision of quality, holistic, and longitudinal care to our communities, whilst supporting the long-term economic viability of providing health care to the Australian population.

References

[1] Health Workforce Australia. Australia's Future Health Workforce - Doctors [Internet]. Canberra: Department of Health; 2014 [updated 1 Aug 2014; cited 2021 30 Aug]. Available from: https://www.health.gov.au/resources/publications/doctors-australias-future-health-workforce-report.

[2] RACGP. General Practice: Health of the Nation Victoria: RACGP; 2019 [updated 1 Nov 2020; cited 2021 30 Aug]. Available from: https://www.racgp.org.au/health-of-the-nation/health-of-the-nation.

[3] Smith P. Junior doctors go cold on GP training [Internet]. 2019 [updated 13 Mar 2019; cited 2021 June 18]. Available from: www.ausdoc.com.au/news/junior-doctors-go-cold-gp-training.

[4] Medical Deans Australia. Medical Schools Outcomes Database Report 2020 [Internet]. Victoria: Medical Deans Australia; 2020 [updated 1 Aug 2020; cited 2021 June 18]. Available from: https://medicaldeans.org.au/data/medical-schools-outcomes-database-reports/.

[5] Yang J. Why are students not pursuing general practice? [Internet]. Victoria: MJA; 2019 [updated 14 Oct 2019; cited 2021 30 Aug]. Available from: https://insightplus.mja.com.au/2019/40/why-are-students-not-pursuing-general-practice/.

[6] Koehler N, McMenamin C. Flexible but boring: Medical students' perceptions of a career in general practice. Educ for Prim Care. 2016;27:1-12.doi:10.1080/14739879.2016.1194360

[7] Suresh S, Hoffman R, Liu S, Gosbell A. Australian medical student expectations of work-life balance as a doctor. MedEdPublish. 2020;9(1):256.doi:10.15694/mep.2020.000256.1

[8] Thistlethwaite J, Kidd M, Leeder S, Shaw T, Corcoran K. Enhancing the choice of general practice as a career. Aust Fam Phys. 2008;37(11):964

[9] Hoffman R, Bonney A. Junior doctors, burnout and wellbeing: Understanding the experience of burnout in general practice registrars and hospital equivalents. Aust J of Gen Pract. 2018;47(8):571-5.doi:10.31128/AJGP-01-18-4475

[10] Picton A. Work-life balance in medical students: self-care in a culture of self-sacrifice. BMC Med Educ. 2021;21(1):8.doi:10.1186/s12909-020-02434-5

[11] RACGP. Specific Interests groups [Internet]. Victoria: RACGP; 2021 [updated 30 Aug 2021; cited 2021 June 18]. Available from: https://www.racgp.org.au/the-racgp/faculties/specific-interests/interest-groups.

[12] RACGP. Become A GP [Internet]. Victoria: RACGP; 2020 [cited 2021 June 18]. Available from: https://www.racgp.org.au/education/students/a-career-in-general-practice/become-a-gp.

[13] Bugaj T, Valentini J, Miksch A, Schwill S. Work strain and burnout risk in postgraduate trainees in general practice: an overview. Postgrad Med. 2020;132(1):7-16.doi:10.1080/00325481.2019.1675361

[14] Winter R, Norman R, Patel R. A qualitative exploration of the lived experience of GP trainees failing to progress in training. Educ for Prim Care. 2021;32(1):10-8.doi: 10.1080/14739879.2020.1831970

[15] Thomas H, Best M, Mitchell G. Whole-person care in general practice: The nature of whole-person care. Aust J of Gen Pract. 2020;49(1-2):54-60.doi:10.31128/ajgp-05-19-49501

[16] Thistlethwaite J. The medical home: A need for collaborative practice. Aust Fam Phys. 2016;45(10):759-60

[17] Olid A, Zurro A, Villa J, Hijar A, Tuduri X, Puime Á, et al. Medical students' perceptions and attitudes about family practice: a qualitative research synthesis. BMC Med Educ. 2012;12(1):1-16

[18] RACGP. The role of specialist GPs [Internet]. Victoria: RACGP; 2021 [updated 1 Oct 2020; cited 2021 June 18]. Available from: https://www.racgp.org.au/advocacy/position-statements/view-all-position-statements/health-systems-and-environmental/the-role-of-specialist-gps.

[19] Le Floch B, Bastiaens H, Le Reste J, Linger H, Hoffman R, Czachowski S. Which positive factors give general practitioners job satisfaction and make general practice a rewarding career? A European multicentric qualitative research by the European general practice research network. BMC Fam Pract. 2019;20(1):96.doi:10.1186/s12875-019-0985-9

[20] [20] Australian Medical Association. Urgent action needed to ensure the future family doctor workforce [Internet]. Victoria: Australian Medical Association,; 2019 [updated 22 July 2019; cited 2021 June 18]. Available from: www.ama.com.au/media/urgent-action-needed-ensure-future-family-doctor-workforce.

[21] Cheng T, Scott A, Jeon S, Kalb G, Humphreys J, Joyce C. What factors influence the earnings of general practitioners and medical specialists? Evidence from the medicine in Australia: balancing employment and life survey. Health Econ 2012;21(11):1300-17.doi:10.1002/hec.1791

[22] Lennon M, McGrail M, O'Sullivan B, Tan A, Mok C, Suttie J, et al. Understanding the professional satisfaction of hospital trainees in Australia. Med Educ. 2020;54(5):419-26.doi:10.1111/medu.14041

[23] Australian Taxation Office. Individuals – top 10 occupations, by average taxable income [Internet]. Canberra: Australian Taxation Office; 2019 [updated 7 June 2021; cited 2021 23 June]. Available from: https://www.ato.gov.au/About-ATO/Research-and-statistics/In-detail/Taxation-statistics/Taxation-statistics-2018-19/?page=6#Chart5Individuals.

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Letter

Trends in mental health service access and recent implementation of telehealth and online services for mental health.

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Key learning points

- Mental health services and prescriptions appear to be obtained more frequently and coincide with peaking of COVID-19 cases in the community.
- There has been significant government funding and promotion of telehealth and online services, particularly for mental health consultations.
- Telehealth and online services do have some benefits when providing mental health care, however further research is needed to determine efficacy.

Dear Editor,
As we inevitably approach the third year of the SARS-CoV-2 (COVID-19) pandemic, the total extent of the impact remains partially an enigma. With increased encouragement to socially distance from one another and limit physical contact, the distribution of healthcare via telehealth has increased in popularity. This letter intends to discuss recent implementation of healthcare provided via telehealth, focussing on changes in mental health related services [1].

Before the pandemic, mental health related disorders such as depression, anxiety, and substance-use disorders accounted for the 77% of resources attributed to mental health within Australia [2], resulting in an excess spending of $12.9 billion dollars to the health care system annually in 2013-2014 [3]. During the pandemic, an increased need for mental health services brought about an increased expenditure of $2.3 billion dollars (12% increase per annum) [4]. This increased funding (3.3 times greater than previous years) was successfully allocated in part to the distribution of telehealth services [5]. In our personal experience thus far, this funding towards telehealth services has proved to be valuable in terms of limiting physical contact with multiple patients per day. Moreover, research shows that there is no statistical difference in consultation effectiveness between face-to-face and telehealth consultations in a mental health-related setting [6].

In general, access to mental health services and medical prescriptions have changed during the pandemic. From March 2019 to March 2020, there was an increase of prescriptions dispensed for a mental health-related disorder in a given week, from 744,072 to 860,307 the following year [4]. Another year later, prescriptions dispensed remained elevated [4]. The authors believe that this increased number of prescriptions dispensed in a given month is a reliable measure of worsening mental health outcomes during that period of time.

Overall, usage of online mental health-related service has increased since the start of the pandemic [4]. This can be seen, for example, by analysing the usage of the online platform named "HeadtoHealth." In 2019, 1,028 people used the online platform per day, as compared to 9,309 daily users the following year. This represents an 8.97 times increase in daily users (4). However, in 2021, the online daily users [4].normalised partially back down to 1,688. It is possible that the increasing numbers of mental health related prescriptions and online mental health services delivered may relate to peaking COVID-19 infections with worse mental health outcomes across the country [7]. The feasibility of logging onto a website with a phone or computer may also partially contribute to the increased online health service usage [8]. The authors suspect that some people may feel uncomfortable with discussing their emotions and mental health with another person due to stigma and prefer to gaining information and services anonymously online.

Other notable changes during the pandemic regard Medicare Benefits Schedule (MBS) mental health-related services accessed (seeing a GP, psychiatrist or psychologist). In March 2019, 260,680 MBS mental health-related services were delivered [4]. This number initially dropped to 238,044 (8.7%) MBS in 2020, but in 2021, the MBS related services rose to 292,339 (23%). This may be due to the fact that telehealth conferencing was added to the MBS subsidised list in March 2020 [4].

Table 1: Changes in Mental Health Service Access

	March 2019	March 2020	March 2021
MBS-Subsidised Mental Health Services per week	260,680	238,044	292,339
PBS mental health-related prescriptions dispensed per week	744,072	860,307	805,489
HeadtoHealth Usage per day	1,038	9,309	1,688

Another mental health platform "Lifeline", had 82,000 mental health related calls in April 2020, an increase of 20% compared to the previous year [4]. Differing months of data collection leading to different active cases in COVID-19 in community may be the reason for the discrepancy between "Lifeline" and "HeadtoHealth" usage. The suicide mortality rate in Australia, however, has remained unchanged at 13.2 since 2018 [7, 9]. A sense of connectedness in the community and people "pulling together" during turbulent times can act as protective factors [10].

New forms of technological advancement improving the accessibility of health care have emerged in recent years due to social distancing rules and a lack of available mental health resources [13]. People can now use telephones (via telehealth) to contact healthcare providers and can use computers and smart phones to access online health services. These types of online platforms serve as a quick way for people to access information and encourage people to seek help if needed. In fact, younger people feel more incline to access mental health care services via mobile applications and online resources than in person [11,12]. Support for these new forms of healthcare have been implemented, and the Australian government announced that $106 million dollars over four years will be dedicated for these telehealth services [13]. This was in addition to the reclassification of telehealth to be included by MBS-subsidised coverage [4]. These new changes to the healthcare system have all fostered an increased usage of telehealth services over the past two years [5,13].

As the sixth largest country in the world and with a relatively low population, many Australians live in regions where it is difficult for them to access health services. Telehealth has proven itself as an invaluable tool in providing healthcare to Australians living in rural and remote regions [14]. Access to internet and a computer screen allow Australians living in remote areas to use healthcare services when they are needed. Other findings of t elehealth consultations can be seen in the clinical management of older Australians. Studies show that there was no significant difference in usage of telehealth as compared to services in person [15]. In certain fields of medicine, difficulties can emerge in telehealth consultations due to difficulty in adequately completing physical exams, however that is not the case for mental health [15]. Regarding telepsychiatry, a wide range of psychiatric signs and symptoms have been successfully elicited online such as affect changes, changes to speech rate and tonicity and changes to cognition [17]. A further benefit includes ease of monitoring patient adherence to treatments [18]. However, it was shown that patient education was not found to be better online than in person, and a cohort of people felt unfavourably towards receiving healthcare via a screen [18].

This letter has addressed the new implementation of telehealth medicine, and highlighted recent trends in mental health services and prescriptions dispensed throughout the pandemic. Throughout the COVID-19 pandemic, there have been varying frequencies in mental health consultations, prescriptions dispensed and online platform usage. This demonstrates that the population's need for mental health services is consistently evolving, as are varying COVID-19 case numbers in the community. As large government investment indicates that telehealth and online services are likely to be used in the long term, it is important that medical students and doctors be aware of the unique challenges imposed by this new form of healthcare.

References

[1] Xiong J, Lipsitz O, Nasri F, Lui LM, Gill H, Phan L, et al. Impact of COVID-19 pandemic on mental health in the general population: a systematic review. *Journal of Affective Disorders*. 2020.;277:55-64. doi: 10.1016/j.jad.2020.08.001\

[2] Schofield D, Cunich M, Shrestha R, Tanton R, Veerman L, Kelly S, et al. Indirect costs of depression and other mental and behavioural disorders for Australia from 2015 to 2030. *BJ Psych open*. 2019:5;3. doi: 10.1192/bjo.2019.26.

[3] Lee Y-C, Chatterton ML, Magnus A, Mohebbi M, Le LK-D, Mihalopoulos C. Cost of high prevalence mental disorders: f indings from the 2007 Australian National Survey of Mental Health and Wellbeing. *Australian and New Zealand Journal of Psychiatry* . 2017;51(12):1198-211.. doi:10.1177/0004867417710730

[4] Australian Institute of Health and Welfare. Mental health services in Australia. Canberra: AIHW; 2021.

[5] Hunt G. $9.8 billion new investment in Australia's health care and COVID response. Ministers Department of Health. 2021: 1-15.

[6] Krzyzaniak N, Greenwood H, Scott AM, Peiris R, Cardona M, Clark J,et al. The effectiveness of telehealth versus face-to face interventions for anxiety disorders: a systematic review and meta-analysis. *Journal of Telemedicine and Telecare*. 2021: 1-12. doi:10.1177/1357633X211053738.

[7] Newby JM, O'Moore K, Tang S, Christensen H, Faasse K. Acute mental health responses during the COVID-19 pandemic in Australia. PloS *LOONE*. 2020:15;7. doi.org/10.1371/journal.pone.0236562

[8] Solomon GM, Bailey J, Lawlor J, Scalia P, Sawicki GS, Dowd C, et alal . Patient and family experience of telehealth care delivery as part of the CF chronic care model early in the COVID-19 pandemic. *Journal of Cystic Fibrosis*. 2021:20(3):41-46. doi: 10.1016/j.jcf.2021.09.005.

[9] Dawel A, Shou Y, Smithson M, Cherbuin N, Banfield M, Calear AL, et al. The effect of COVID-19 on mental health and wellbeing in a representative sample of Australian adults. Front. psychiatry. 2020;11:1026. doi:10.3389/fpsyt.2020.579985

[10] Joiner TE, Hollar D, Van Orden K. On buckeyes, gators, Super Bowl Sunday, and the miracle on ice: "pulling together" is associated with lower suicide rates. *Journal of Social and Clinical Psychology.* 2006;25(2): 179-195. Doi: 10.1521/JSCP.2006.25.2.179

[11] Montague A, Varcin K, Simmons M, Parker A. Putting technology into youth mental health practice: young people's perspectives. *SAGE Open.*. 2015;5:1–10.doi: 10.1177/2158244015581019

[12] Struthers A, Charett C, Bapuji S, Winters S, Ye Z, Metge C, et al. The acceptability of e-mental health services for children, adolescents, and young adults: a systematic search and review. *Canadian Journal of Community Mental Health.* 2015;34:1–2. doi: 10.7870/cjcmh-2015-006

[13] Department of Health. Permanent telehealth for all Australians. Australian Government; 2021

[14] Moffatt JJ, Eley DS. The reported benefits of telehealth for rural Australians. *Australian Health Review.* 2010;34(3):276-81. doi: 10.1071/AH09794

[15] Hullick C, Conway J, Hall A, Murdoch W, Cole J, Hewitt J, et al. Video-telehealth to support clinical assessment and management of acutely unwell older people in Residential Aged Care: a pre-post intervention study. BMC geriatrics. 2022;22:1.. doi: 10.1186/s12877-021-02703-y

[16] Montes J, Eichinger KJ, Pasternak A, Tochai C, Krosschell KJ. A post pandemic roadmap toward remote assessment for neuromuscular disorders: limitations and opportunities. *Ophanet Journal of Rare Diseases*. 2022;17:1. doi: 10.1186/s13023-021-02165-w

[17] Leonard S. The successes and challenges of developing a prison telepsychiatry service. *Journal of Telemedicine and Telecare*. 2004;10:69-71. doi: 10.1258/1357633042614375

[18] Lawes-Wickwar S, McBain H, Mulligan K. Application and effectiveness of telehealth to support severe mental illness management: systematic review. *JMIR Mental Health.* 2018;5:4. doi: 10.2196/mental.8816

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Response to the new draft document created by the Medical Deans Australia and New Zealand titled "Inclusive Medical Education: Guidance on medical program applicants and students with a disability"

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Jerusha Mather is a current neuroscience PhD candidate at Victoria University. She is investigating non-invasive brain stimulation and strength training, specifically if, and if so, how, it can improve strength gains and motor function. She is a passionate advocate for an inclusive medical profession. Jerusha is also an Instagram poet and has published her collection of poetry.

Key learning points

- This is a response to the new draft document created by the Medical Deans Australia and New Zealand titled "Inclusive Medical Education: Guidance on medical program applicants and students with a disability" urging strategic action to be taken.

Dear Editor,

I am writing regarding the draft document by the Medical Deans Australia and New Zealand, the peak body representing professional entry-level medical education, training, and research in Australia and New Zealand, titled "Inclusive medical education: Guidance on medical program applicants and students with a disability [1]". While this document provides a framework to guide medical schools when supporting current students with disabilities, it does not address the discrimination faced by prospective students with physical disabilities. If we endeavour to create an inclusive medical education, we must strive for supportive policies and initiatives for both current and prospective students with disabilities.

People with disabilities are under-represented within the medical profession. This is unacceptable if we wish for our medical workforce to represent the diversity of Australian society. In Australia, 17.7% of citizens self-reported as having a disability [2]. However, less than 2% of medical students report having a disability [3], comparing unfavourably to the 7% representation in other post-graduate university courses [2]. Further, of the few doctors who report having a disability, many first encountered their disability either during medical school or clinical practice, after their decision to pursue medicine [3]. This demonstrates the lack of representation for people with disabilities amongst those striving to and applying for medical school; a key deficiency which is not addressed in the document by the Medical Deans Australia and New Zealand.

There is no evidence that people with disabilities cannot have excellent clinical skills, provided appropriate supportive technology and/or physician assistants are available. Further, the Australian community has a positive opinion of doctors with disabilities [3]. Dr Dinesh Palipana, a prominent doctor and advocate for doctors with disabilities, who experienced a spinal cord injury resulting in quadriplegia, is leading the way for doctors with disabilities in Australia. Despite his disability, Dr Palipana has used technology, alternative methodologies, and assistance from others to become a senior resident emergency physician in a busy emergency department [4-7]. Doctors with Disabilities Australia (DWDA), a body advocating for an inclusive medical profession, has published numerous stories of people with disabilities succeeding in medicine, despite the challenges faced [8].

The document's list of questions titled "Reflective questions about studying medicine" exemplifies the significant discrimination faced by many people with disabilities even before they begin the process of applying for or studying medicine [1]. These questions outline physical requirements which an applicant should be able to meet, such as being able to complete a full physical examination [1]. However, instead of listing such requirements, the document should provide solutions and accommodations universities can implement to increase access for people with disabilities in the medical profession.

Medical schools should be breaking down barriers to participation and actively promoting success stories of students and doctors with disabilities to inspire prospective students. Medical school student societies – responsible for much of the advocacy effort within medical education – should participate in this promotion. When necessary, additional support in the form of specific services or mentorship could be offered to students considering this endeavour. A cross-discipline support team to assist students with disabilities could include occupational therapists to provide access solutions, counsellors to address wellbeing and mental health, and senior medical students to provide mentoring. We should strive for a future where success stories are commonplace and no longer surprising. This starts with medical schools encouraging people with disabilities to consider a career in medicine.

The document does not address the discrimination against people with disabilities present throughout the medical school application process. Individual medical schools are primarily responsible for the selection of students, with considerable variability in criteria between schools. As is the case for other disadvantaged populations, medical schools should make appropriate changes to the admission process to ensure consideration of the disadvantage posed by a person's disability.

The current structure and format of medical school admission exams are inherently discriminative against people with disabilities. Such exams, namely the Graduate Medical School Admissions Test (GAMSAT) for postgraduate studies, are lengthy, handwritten tests apparently measuring cognitive abilities in a rigorous manner [9]. Even with the provisions of reasonable adjustments – such as dictation of answers, performing tests on a computer, and additional time and rest breaks – considerable discrimination may still exist. For example, it may be too arduous to dictate the answers to a scribe due to the lengthy manipulation of formulas, extensive drawings, and substantial mathematical calculations required. Such components are difficult to undertake mentally and then dictate to the scribe. Additionally, the GAMSAT may be difficult to complete on a computer because of the required problem-solving, involving the manipulation of equations, diagrams, and drawings, heavily required in Sections One and Three, which assess reasoning in humanities, and reasoning in biological and physical sciences, respectively. Speed reading can be difficult for people with disabilities, further impacting the ability to achieve a competitive score.

To adjust for the discrimination present in admission tests, medical schools should assess the merit of an applicant with a disability using alternative methods. For example, more emphasis could be placed on a student's grade point average (GPA) for postgraduate studies. The GPA is a cumulative score over many years of academic performance and does not depend on a student's performance in a single examination, such as the GAMSAT. Additionally, more emphasis could be placed on a portfolio of extra-curricular activities to assess applicants with a disability more holistically. The American University of the Caribbean is currently waiving their requirement on medical entrance exams due to the COVID-19 pandemic and are instead performing "evaluation… on an individual basis and [using] a holistic approach" [9]. If concessions can be made for a pandemic, then universities can employ a similar holistic admissions approach for students with disabilities to alleviate discrimination.

Discrimination within the medical school application process also extends to the interview stage. In its current format, potential unconscious bias may be held by interviewers against applicants with a disability. A study of 630 university students, randomised to one of three disability conditions or a control condition, found that when an interview candidate was visibly wheelchair bound, they were less likely to be hired by the interviewer [11]. However, when candidates were wheelchair bound, but the chair was not visible, there was no difference in hiring rates [11]. Bias could be reduced by providing education sessions, such as imagined contact. Imagined contact involves participants being asked to positively imagine working with people with disabilities, whereby the person with the disability has all the necessary accommodations and is a competent colleague that contributes to the team [12]. This technique has been found to improve attitudes in people without disabilities towards work-related performance in people with disabilities [12]. Training interviewers in techniques such as these may help ensure applicants are not negatively pre-judged as less capable than their able-bodied counterparts.

The Medical Deans Australia and New Zealand can look to the Association of American Medical Colleges (AAMC) for a more inclusive solution to accessibility in medicine. The AAMC Accessibility, Inclusion, and Action in Medical Education report highlights a variety of evidence-based solutions for people with disabilities accessing medical school [13]. This report particularly acknowledges the efforts of Rush University, who actively recruit students with disabilities for their program and provide extensive supports to facilitate a culture and practice of inclusion [13].

Equity is not the only benefit of increased representation of people with disabilities amongst the medical workforces. Increased representation will also positively impact attitudes of healthcare professionals towards people with disabilities. People with disabilities have considerable interaction with the healthcare system, and unfortunately, often experience

significant harm from discrimination during these interactions [6, 13]. Integrating the lived experiences of people with disabilities into the medical workforce is crucial to reverse negative attitudes and provide compassionate, empathic care.

People may oppose such suggestions on the basis that they exemplify reverse discrimination, in that giving special attention to applicants with disabilities is unfair for other applicants. However, it is a necessary step to increase representation of a traditionally marginalised group. Without it, applicants with disabilities will continue to be disadvantaged and the medical workforce will fail to represent the diversity of Australian society.

Medical schools should strive to increase the representation of people with disabilities in their programs by creating inclusive policies and encouraging applications from disabled students. I call upon The Australian Medical Students' Association and medical school student societies from across Australia to add this to their priority agenda.

The Medical Deans Australia and New Zealand are currently seeking feedback on their new draft policy document for students with disability. I encourage the readership of the Australian Medical Students Journal to share their honest feedback and opinions via the email or form on their website.

References

[1] Medical Deans Australian and New Zealand. Inclusive medical education: guidance on medical program applicants and students with a disability [Internet]. 2021. [cited 2021 May 3]. Available from: https://medicaldeans.org.au/md/2021/04/Inclusive-Medical-Education-Guidance-on-medical-program-applicants-and-students-with-a-disability-Apr-2021-1.pdf

[2] Australian Bureau of Statistics. Disability, ageing and carers, Australia: summary of findings [Internet]. 2018 [cited 2021 May 3]. Available from: https://www.abs.gov.au/statistics/health/disability/disability-ageing-and-carers-australia-summary-findings/latest-release.

[3] Mogensen L, Hu W. "A doctor who really knows …": a survey of community perspectives on medical students and practitioners with disability. BMC Med Educ. 2019;19(1):288.

[4] Australian Story. 'I might be quadriplegic, but I'm your doctor' [Internet]. 2020 [cited 2021 May 31]. Available from: https://www.abc.net.au/news/2018-02-26/queenslands-quadreplegic-doctor-dinesh-palipana-australian-story/9462752?section=good-news&nw=0.

[5] Palipana D. Meet Australia's second quadriplegic medical intern. [Internet]. 2017 [cited 2021 May 3]. Available from: https://www.miga.com.au/dr-dinesh-palipana-article.

[6] Department of Social Services. Dinesh Palipana [Internet]. 2019 [cited 2021 May 3]. Available from: https://www.jobaccess.gov.au/stories/dinesh-palipana

[7] Lewin E. 'We need to show leadership': doctors with disability. [Internet]. 2019. [cited May 31]. Available from: https://www1.racgp.org.au/newsgp/professional/we-need-to-show-leadership-in-this-area-changing-v.

[8] Doctors with Disabilities Australia. Stories. [Internet]. 2021. [cited 2021 May 3]. Available from: http://dwda.org.au/category/stories/.

[9] American University of the Caribbean School of Medicine. [Internet]. 2021. [cited May 3]. Available from: https://med.aucmed.edu/.

[10] Mercer A, Crotty B, Alldridge L, Le L, Vele V. GAMSAT: A 10-year retrospective overview, with detailed analysis of candidates' performance in 2014. BMC Med Educ. 2015;15(1):31.

[11] Miceli NS, Harvey M, Buckley MR. Potential discrimination in structured employment interviews. Empl Responsib Rights J. 2001;13(1):15-38.

[12] Carvalho-Freitas MNd, Stathi S. Reducing workplace bias toward people with disabilities with the use of imagined contact. J Appl Psychol. 2017;47(5):256-66.

[13] Meeks LM, Herzer K, Jain NR. Removing barriers and facilitating access: increasing the number of physicians with disabilities. Acad Med. 2018;93(4):540-3.

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