Translational Interventions Targeting the Clinical Use of Vancomycin

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Dedication

This work is dedicated to my wonderful family. To my wife Preeti, whose love and support has been unfailing, together with our children Prithu and Anuttara, and my beloved father and mother-in-law, Anand and Latha. I am forever grateful for their unwavering support over years, their patience, and the sacrifices they have made to enable me to complete this work.

Summary

After more than sixty years, vancomycin is still the treatment of choice for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infection. However, vancomycin is a challenging antibiotic to prescribe and monitor as it requires individualisation of dosing and therapeutic drug monitoring. Although internationally accepted consensus-based guidelines for vancomycin dosing and monitoring are available, those recommendations have debatable impact on clinicians' practice, as evidence shows vancomycin prescribing and monitoring is still very poor. Inappropriate dosing and monitoring of vancomycin can lead to inferior clinical outcomes, renal toxicity and the emergence of bacteria with reduced susceptibility, or resistance to the drug.

The work in this thesis aims to identify what interventions can be employed to improve vancomycin prescribing and monitoring. A theoretical framework was used to identify the barriers to improving vancomycin dosing and monitoring in our healthcare network. Domains identified were knowledge, skills, beliefs about consequences, environmental context and resources. Undertaking a systematic review and meta-analysis of interventions targeting the prescribing and monitoring of vancomycin found that multifaceted interventions are more effective than singular interventions. However, included studies were generally of short duration and poor quality. Interventional bundles comprising implementation of guidelines, providing educational meetings and the dissemination of educational materials had the greatest effect.

I conducted an initial pilot study and subsequent larger study, evaluating the effect of implementing a multifaceted intervention on vancomycin dosing and monitoring. Interventions consisted of implementing guidelines, face-to-face education, electronic continuing

professional development (CPD) modules with assessment, provision of education material (pocket guideline) and dissemination of electronic communication and reminders. Post-implementation dosing, monitoring, nephrotoxicity and time-to-attainment of therapeutic target range significantly improved. Results were maintained at three-year follow-up.

The effect of face-to-face education, CPD modules and provision of pocket guidelines on junior doctors' preparedness to use vancomycin clinically were evaluated. Attending an educational session and being in possession of a pocket guideline were associated with preparedness, measured by higher self-reported confidence to use vancomycin. High knowledge scores were achieved by pharmacists and junior doctors upon completion of a CPD module on vancomycin. Attending an educational session or being in possession of a pocket guideline did not significantly impact knowledge scores.

The determination of vancomycin minimum inhibitory concentration (MIC) can influence the decision to use vancomycin or in some cases, unnecessarily escalate therapy to a broader spectrum antibiotic. We measured the accuracy of different MIC methodology and found limited overall agreement. We established practical guidance to interpret results obtained from multiple MIC methods compared against the gold standard of broth-microdilution to inform the decision to treat with vancomycin. Further studies of these exploratory finding are required in a larger dataset.

Collectively, the work within this thesis found that a multifaceted intervention targeting healthcare professionals had a significant effect on vancomycin dosing, monitoring and safety outcomes. The multifaceted intervention studied in this work can be recommended to translate contemporary guidance on the clinical use of vancomycin to healthcare professionals, and the

findings may also provide insight into implementing other antibiotic prescribing and monitoring guidelines

Key words

anti-infective, drug monitoring, dosing, education, intervention, guideline, implementation, minimum inhibitory concentration, prescribing, systematic review and meta-analysis, vancomycin

Declaration

"I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and to the best of my knowledge and belief, does not contain any material previously published or written by another person except where due reference is made in the text."

I declare that this thesis is composed of my original work and contains no previously published or work by another person except where due reference has been made in the text. I have stated the contribution of other coauthored publications that I have included in this thesis. This thesis does not contain any content that has been submitted to qualify for the award of degree or diploma in any other university or tertiary institution. No professional editing was used in the production of any of the included published works or in preparation of this thesis.

Signed……C J Phillips……**Dated**……2nd December 2019……

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List of Abbreviations

AMR	Antimicrobial resistance
AUC	Area under the (concentration) curve
CA-MRSA	Community acquired methicillin-resistant *Staphylococcus aureus*
CLSI	Clinical and Laboratory Standards Institute
CPD	Continuing professional development
CPOE	Computer physician order entry
EMR	Electronic medical record
g/mol	Grams per mol
HA-MRSA	Healthcare associated methicillin-resistant *Staphylococcus aureus*
hr	Hour
IOM	Institute of Medicine
MIC	Minimum inhibitory concentration
mg/L	Milligrams per litre
MSSA	Methicillin-sensitive *Staphylococcus aureus*
MRSA	Methicillin-resistant *Staphylococcus aureus*
MW	Molecular weight
NHMRC	National Health and Medical Research Council (Australia)
NICE	National Institute for Health and Care Excellence
PBP	Penicillin binding protein
S. aureus	*Staphylococcus aureus*
SIGN	Scottish Intercollegiate Guidelines Network
TDF	Theoretical domains framework
TDM	Therapeutic Drug Monitoring
TMOU	Trainee Medical Officer Unit

UK	United Kingdom
US	United States
USD	US dollars
VAN	Vancomycin
VISA	Vancomycin intermediate *Staphylococcus aureus*
VRSA	Vancomycin resistant *Staphylococcus aureus*
WHO	World Health Organization

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Chapter 1: Introduction

1.1 Antimicrobial resistance

Antimicrobial resistance (AMR) is the phenomena of microorganisms such as bacteria, fungi, viruses and parasites failing to respond to anti-infectives, such that the medicines are less effective or unable to treat infection with these pathogens. (1) AMR, of which antibiotic resistance is the major subset, is a staggering public health problem. A key UK government review on antimicrobial resistance stated that without global action to reduce AMR, an additional 10 million people will die annually from drug-resistant infections by the year 2050. (2) The financial costs to the global economy are difficult to establish, however a review of recent economic modelling has been performed which suggests losses range between estimates of $14 billion to $3 trillion dollars (2013 US dollars) to global gross domestic product by 2050. (3)

1.2 Antibiotic resistance in *Staphylococcus aureus*

An important example of antibiotic resistance can be seen with *Staphylococcus aureus* (*S. aureus*). A recent World Health Organisation (WHO) global report on AMR and surveillance notes that all WHO regions reported methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence beyond 20% of all *S. aureus* isolates as resistant, with some sources reporting in excess of 80% resistance. (4) In Australia, the most recent government sources report MRSA prevalence between 9.5% - 44%, depending on setting and location. (5) *S. aureus* is an organism that predominately resides on skin with natural reservoirs in the nares of the nose, skin folds and axilla and forms part of the human microbiome. *S. aureus* for over a century has been acknowledged as an important pathogen in the community and hospital environment. Penicillin initially discovered in 1928, and formulated into a medicine in the 1940's, was the first effective treatment against *S. aureus* infection, however resistance to penicillin quickly

developed. This resistance was mediated via *S. aureus* producing β-lactamase enzymes which hydrolyse the active molecular β-lactam ring of penicillin. Attempts to combat this resistance led to the development of antibiotics such as methicillin that were stable to β-lactamase enzymes, as well as β-lactam inhibiting agents such as clavulanic acid and sulbactam. (6) The introduction of methicillin as an anti-staphylococcal antibiotic in 1959 led to the nomenclature methicillin-sensitive *Staphylococcus aureus* (MSSA), however antibiotic resistance to MSSA was identified after only a few years. (7) The resistance to methicillin is mediated by substitution of Penicillin Binding Proteins (PBPs) on the *S. aureus* cell wall with a mutated receptor (PBP2a), which inhibits the binding of penicillins and other β-lactam antibiotics. (8) From the 1970s-1980s, MRSA was reported worldwide and was detected in most hospitals. (9) Two strains of MRSA emerged in the 1990's, community-associated (CA-MRSA) and healthcare-associated (HA-MRSA), although as patients moved between care settings, the origin of patient colonisation or infection between the strains is not always clear. Whilst strains of CA-MRSA are still treatable with non-β-lactam oral antibiotics such as clindamycin and co-trimoxazole, HA-MRSA often requires treatment with intravenous antibiotics. (10, 11) Vancomycin is considered the first-line antibiotic treatment for serious MRSA infection. (12)

1.3 Vancomycin

Vancomycin is a glycopeptide antibiotic, which has been in use for over 60 years and has been one of the most widely studied antibiotics. (13, 14) Vancomycin remains not only the mainstay of treatment for MRSA infection but many other serious infections caused by Gram-positive organisms. (15) Vancomycin features on the WHO list of essential medicines. (16) Additionally, vancomycin is one of the most extensively used antibiotics for patients with penicillin or β-lactam allergy when treated for MSSA infections. (17) Vancomycin inhibits bacterial cell wall peptidoglycan synthesis via binding to peptides containing D-alanyl-D

alanine, which results in destabilisation of bacterial cell wall causing cell lysis. (18) Vancomycin is a large hydrophilic molecule (MW 1485 g/mol), which renders it unsuitable for oral absorption, necessiting intravenous administration. (19, 20)

Antibiotics in hospital are only prescribed appropriately about half of the time. (21) Vancomycin is an inherently challenging antibiotic to prescribe. Inappropriate dosing and or monitoring can lead to therapeutic failure, drug toxicity, adverse reactions, and antibiotic resistance. (20) As such, vancomycin requires careful intravenous administration, dose individualisation and monitoring of serum drug levels to ensure effective and safe treatment. (22, 23) Insufficient dosing and low serum vancomycin levels have been associated with failure of infection to resolve, and prolonged low levels of vancomycin can lead to the emergence of *S. aureus* strains with reduced susceptibility or resistance to vancomycin. (24) Conversely, excessive dosing and high levels of vancomycin are associated with nephrotoxicity. (25-29) Audits of patients treated with vancomycin have generally found dosing and monitoring to be poor or suboptimal. (30-32)

1.3.1 Contemporary recommendations for dosing and monitoring of vancomycin

The recommendations for vancomycin have changed significantly over time. (33-36) Current recommendations advocate the use of a loading dose individualised to weight, maintenance dosing defined by renal function and subsequent dose adjustment based upon therapeutic drug monitoring (TDM). (37, 38) Key North American vancomycin guidelines published in 2009 renewed how vancomycin was to be clinically used, specifying duration of infusion times, calculation of loading dosages and maintenance dosing regimens. The guidelines also provided monitoring criteria, specifically for the timing of serum monitoring in relation to the number of consecutive doses administered (i.e. ensuring vancomycin was at steady-state

concentration), timing of phlebotomy sampling relative to previous dose and frequency of subsequent monitoring, target range trough for TDM 10-20mg/L, and 15-20mg/L for serious infections, and the definition of vancomycin-induced nephrotoxicity. (39) The extensive interest in maintaining the ongoing utility, efficacy and safety of vancomycin from many parts of the world has led to a number of professional societies from various countries in addition to USA, notably Japan and more recently China, to also develop high calibre guidelines, with remarkably similar recommendations, and to publish them in quality peer-reviewed medical journals. (40, 41) This is in addition to many unpublished institutional vancomycin guidelines and those published in the grey literature. (42) The Australian Therapeutic Guidelines also provides similar guidance on vancomycin dosing and monitoring to the USA, and specifies a target trough range of 15-20mg/L for most infections. (43) Whilst these guidelines provide invaluable content, a key question remains as to which interventions can be employed to translate contemporary vancomycin recommendations into practice to improve the prescribing, monitoring and safe use of vancomycin?

1.4 Determination of vancomycin minimum inhibitory concentration (MIC) for *S. aureus*

1.4.1 Diagnostics

The MIC is the lowest concentration of vancomycin that inhibits growth of *S. aureus* after a period of incubation (24-36 hours). (44) MIC determination is performed for diagnostic purposes to establish if the strain of *S. aureus* is susceptible to vancomycin. However, in some infections (e.g. skin and soft tissue, neurological, bone and joint infections), it may not be possible to obtain a specimen and vancomycin treatment will commence and continue on an empirical basis. (45) Where a specimen is obtained from the patient and identified in the laboratory as *S. aureus*, an MIC can usually be determined. *S. aureus* strains with an MIC of

≤2mg/L are considered susceptible to vancomycin. (46) If the MIC is >2mg/L, alternate newer anti-MRSA antibiotics of much greater costs and often considerable toxicity is required to treat the infection. (47) However, serious infections with MRSA strains that have MICs >1mg/L but ≤2mg/L have reportedly worse clinical outcomes when treated with vancomycin even though these MRSA strains are still considered susceptible. (48-50)

A number of methods can used to determine MIC. Commonly used methodology for MIC testing include automated technology such as Vitek2®, and MicroScan®, and diffusion methods such as E-test®. (51) In a research environment, these routine methods are often compared against the gold standard of broth-microdilution (BMD) to determine MIC. (52) There remains uncertainty about the correlation between MIC values obtained through these differing methodologies. (53-56) If the methodologies used to obtain MIC results are not properly considered, this may lead to an unnecessary abandonment of vancomycin and escalation to a newer antibiotic when vancomycin may have been successfully used, provided dosing and monitoring was appropriately undertaken. (57, 58) Unnecessary escalation to newer-generation antibiotics, often with broader spectrum of microbial action has the potential to contribute to antimicrobial resistance. However, debate still continues on how we can use and optimise MIC results obtained from different methodologies in the laboratory to help inform clinicians to make prudent antibiotic treatment choices at patients' bedside.

1.4.2 Pharmacokinetic/pharmacodynamic (PK/PD) monitoring of vancomycin

MIC is typically used if PK/PD modelling and monitoring is to be undertaken. The best reported predictor of *S. aureus* killing with vancomycin is the index, area under the concentration (AUC) curve (0-24hr) divided by the minimum inhibitory concentration (MIC)

of the *S. aureus* isolate[1]. A vancomycin AUC/MIC of ≥400 was shown to be effective for clinical and bacteriological response in MRSA infection. (59) Further research has advocated an AUC/MIC upper ceiling of 700 to limit toxicity. (60, 61) An AUC/MIC of 400 has been equated to a vancomycin trough level of 15mg/L. (23) Monitoring vancomycin therapy using AUC/MIC method requires access to personnel trained in PKPD modelling, suitable computational software and can require two blood samples collected within a dosing interval. (62) Conventional monitoring of vancomycin requires only one trough level. Researchers advocate the benefits of AUC/MIC monitoring of vancomycin to optimise efficacy and limit toxicity. (63-65) There are numerous obstacles (cost, specialist software, access to trained personnel) associated with widespread implementation of this method which to date have hindered its utility and adoption into routine clinical care, although ultimately it will likely hold an important place in future care. (66)

1.5 Reduced efficacy and resistance to vancomycin

The first signs that vancomycin might be in jeopardy as an effective antibiotic were seen in the mid-1990's. Reduced susceptibility of *S. aureus* to vancomycin was first reported in 1997 in Japan. (67) Intravenous vancomycin was first made available in Japan in 1991. (68) Further reports appeared from Japan highlighting detection of vancomycin intermediate *S. aureus* (VISA) or heterogeneous (h)VISA and clinical failure rates in excess of 20% for cases of MRSA pneumonia treated with vancomycin. (69) In Australia, treatment failure of MRSA infection with reduced susceptibility to vancomycin was first noted as a case report in 2001. (70) When dosing is insufficient or serum vancomycin levels are <10mg/L (subtherapeutic), vancomycin concentration at the site of infection may be inadequate to eradicate the infection. (14, 71) Treatment failure of MRSA infection despite appropriately dosed vancomycin has

[1] $AUC_{24\ mg/L.hr}$ / MIC mg/L

been well documented in the medical literature. (72, 73) Vancomycin resistant *S. aureus* (VRSA) emerged in the /united States in 2002. (74) Whilst it took decades for *S. aureus* to develop full resistance to vancomycin, this threat emerged into reality. (75) Both reduced susceptibility and the emergence of resistance were strong motivators for professional societies around the world to develop guidance for clinicians to use vancomycin judiciously and dose and monitor it appropriately.

1.6 Antimicrobial stewardship and vancomycin

Antimicrobial stewardship (AMS) was a term introduced in the1990's during the awakening to the problem of antibiotic resistance. (76) AMS highlighted antibiotics as precious non-renewable resources, and reflected the need to use them appropriately, as well as limiting unnecessary use and preserving their utility. (77) AMS is a collective of many elements to preserve antibiotics by ensuring appropriate clinical use of agents, choice of antibiotic, prescribing, dosing, monitoring effects, treatment duration and route of administration, whilst limiting unintended consequences of antibiotic therapy adverse effects, such as antibiotic resistance, drug toxicity and unnecessary and escalating health care costs. (78, 79) However, more than this, AMS often involves interventions to address these aforementioned problems; such as the development and dissemination of antibiotic and treatment guidelines, education, provision of education supportive material, audit and feedback of antibiotic prescribing practices, multidisciplinary ward rounds, understanding the forces that influence professional culture and clinician behaviour (80, 81), and optimising the use of diagnostic microbiological test results and selective reporting of local antibiograms or susceptibility tables of organisms to antibiotics. (82-84) Much of the work involving interventions targeting vancomycin prescribing and monitoring in this thesis can be considered as part of AMS.

1.7 Interventions

1.7.1 Clinical practice guidelines

Guidelines emerged in the 1970s principally as consensus documents of expert committees from organisations such as the US National Institutes of Health. (85) Since evidence-based medicine became a strong force in the 1990's, the role of guidelines to inform clinical practice has been understood by many (86), although not accepted by all. Despite the importance given to clinical practice guidelines, many clinicians fail to follow their recommendations. (87) When physicians were surveyed as to why they didn't follow guidelines, numerous barriers were identified including, failing to keep up with content of guidelines, lack of confidence in the developers of guidelines, guidelines not seen as practical, clinicians believing they could not carry out recommendations in guidelines, the characteristics of guidelines and environmental factors. (87) These perceived barriers highlight the importance of additional interventions to improve the uptake of guidelines. We developed institutional vancomycin dosing and monitoring guidelines (Appendix 1) after a review of the literature including assessing numerous vancomycin guidelines, key internationally accepted consensus guidelines, and Australian Therapeutic Guidelines. (42, 43, 88) We understood that while developing local vancomycin dosing and monitoring guidelines with expert and consensus engagement was important, it was not enough to effect meaningful change, as reported by others. (89) Guidelines require active dissemination and novel implementation strategies to translate them into practice. (90)

1.7.2 Education

The role of education in diffusion of new knowledge or practice developments in medicine has been a central tenet in medicine. (91) A large Cochrane review on the effect of continuing educational on professional practice and healthcare outcomes found that educational meetings

can have a modest favourable effect on professional practice outcomes, including treatment goals, whether these were conducted as single interventions or combined with other interventions. (92) Experts on effective implementation of guidelines in healthcare have stated that employing additional elements to core education including interactive educational sessions, content development through local consensus, and harnessing local opinion leaders in promotion or delivery of education can be helpful. (93) The UK National Institute for Health and Care Excellence (NICE) recommends educational programs tailor their content to the needs of staff of the organisation where they are to be used. Furthermore, NICE suggests using clinical case scenarios and online educational tools to complement guideline implementation. (94) We developed an educational continuing professional module which included a knowledge assessment for 1) pharmacists and 2) junior doctors (Appendix 2) after reviewing staff needs to follow contemporary recommendations for vancomycin use. We also developed and delivered face-to-face education sessions for doctors. The education sessions and online continuing professional development modules and associated knowledge assessments were developed with input and consensus between disciplines of infectious diseases, clinical pharmacology and pharmacy.

1.7.3 Provision of educational materials

Printed educational materials or summary documents have been recommended to be used to facilitate dissemination of guidance by the Institute of Medicine (95), and the Australian National Health and Medical Research Council. (96) Provision of educational materials includes the supply of any material in hardcopy or electronic form that can be used in an educational manner. The role of educational material on healthcare outcomes was assessed in a large review of 45 studies which found a small effect on professional practice outcomes when used in isolation and compared to no intervention. (97) The Scottish Intercollegiate Guidelines

Network and others highlight the impact of provision of educational materials might be larger than previously understood, noting that dissemination strategies should focus on local considerations. (98, 99) Provision of printed educational or summary materials is a low-cost intervention and as such is reasonable to include in a multifaceted intervention. These reasons were sufficient for us to include provision of a pocket guideline (Appendix 3) as part of our multifaceted intervention targeting vancomycin prescribing and monitoring.

1.7.4 Dissemination of communications and reminders

Reminders have been listed as a useful intervention when seeking to implement changes in the healthcare setting. (100) Reminders and communications may take the form of hardcopy or electronic, computer-assisted reminders or email reminders that prompt healthcare workers to perform a task. (101) Reminders have been reported as being largely effective. (98, 102) A randomised control trial demonstrated the beneficial effect of an initial and follow-up written communication to doctors from the England's Chief Medical Officer encouraging them to reduce unnecessary antibiotic prescribing. (103) This communication contained 1) a clinician focused letter about reducing unnecessary antibiotic prescribing and 2) patient-focused leaflets seeking to limit requests for antibiotics when they were not likely to be beneficial. Their study harnessed the imprimatur of the most senior health official in England. We decided to include communications in the form of email and email reminders in our multifaceted intervention targeting vancomycin prescribing and monitoring. Our intervention harnessed the imprimatur of the Director of Medical Service for our multi-site healthcare network. The email was distributed to all medical staff in our network advising of 1) the importance of adhering to the vancomycin dosing and monitoring guideline and 2) provision of information about how to access the guideline from the intranet. Follow-up reminder emails were sent to all junior

doctors (postgraduate year 1 and year 2) in our network from the Trainee Medical Officer Unit (TMOU). The follow-up emails also included the guideline.

1.8 Thesis aims

The main aim of the work presented in this thesis was to determine if a multifaceted bundle of interventions to healthcare professionals (junior doctors and pharmacists) improves the prescribing and monitoring of vancomycin, with resultant effects on safety to reduce nephrotoxicity.

1.9 Thesis hypothesis

The following hypothesis were formulated:

1) Interventions improve vancomycin prescribing as measured by; increased appropriate prescribing of loading and maintenance doses.
2) Interventions improve vancomycin monitoring; as measured by proportion of patients with bloods levels in the therapeutic range and a reduction in time to achieve therapeutic target.
3) Improvements in prescribing and monitoring outcomes will result in decreased nephrotoxicity.
4) Interventions to enhance health professionals' preparedness to use vancomycin result in increased self-reported confidence to use vancomycin.
5) Interventions improve measured knowledge scores of vancomycin amongst health professionals.
6) Guidance for interpreting vancomycin susceptibility determination can be established using widely available susceptibility tests compared to reference standard.
7) Multifaceted interventions are superior and effects are maintained over time compared

to singular interventions.

Chapter 2: Literature review

2.1 Introductory comments

To understand which interventions have been evaluated in targeting the prescribing and monitoring of vancomycin, a literature review was undertaken. The review was performed prior to the publication of a key paper in this thesis (Chapter 7). (104) Initial consideration of possible interventions include those that have been recommended by peak organisations involved in producing guidance for healthcare such as the US Institute of Medicine, UK National Institute for Health and Care Excellence, the Scottish Intercollegiate Guideline Network and the National Health and Medical Research Council of Australia. (94-96, 98) Review of the published literature for interventions that have specifically targeted vancomycin dosing and or monitoring, identified education, implementation of guidance and dissemination of education materials. (105-109) It led to the formation of the research question of the systematic review; 'Do interventions (alone or in combination) involving education, implementation of guidelines/protocols, or dissemination of educational materials (printed or electronic) improve the prescribing, monitoring, and safety of vancomycin?"

The systematic review was initially registered with Prospero (110), and a formal protocol for the systematic review was published (Chapter 2.2.1). (111) Subsequently, a full systematic review with meta-analysis was performed and published (Chapter 2.2.2). (112) The final systematic review with meta-analysis was completed with inclusion of our study (Chapter 7), assessing the effect of a multifaceted intervention over an extended period. Most of the included studies in the review were small scale, did not necessarily assess dosing and monitoring, were conducted over short durations, with very minimal details of the intervention provided, limiting reproducibility. The effect size on measured outcomes was greatly variable. Our study was larger than all but one study (109), and had the longest duration and the most

detailed description. Our systematic review provided a detailed description of interventions employed in the included studies, as recommended by evidence-based medicine experts. This has been reported as a key element to enhance the usability of systematic reviews. (113)

2.2 Publications

2.2.1 Protocol

Phillips CJ, Wisdom AJ, McKinnon RA, Woodman RJ, Gordon DL. Interventions targeting the prescribing and monitoring of vancomycin for hospitalized patients: a systematic review protocol. Infectious Diseases Therapy 2017; 6: 557-563.

Author contributions

I was principally responsible for the concept and design of the systematic review and meta-analysis protocol (70%) with design input from Professor Ross McKinnon (10%), Professor David Gordon (10%), Professor Richard Woodman (5%) and Alice Wisdom (5%). I registered the protocol with Prospero and updated the registration through various stages of the work. I developed the research question and had a major role in selecting the search terms with guidance from Ms. Leila Mohammadi, College Librarian (acknowledged in the publication). I drafted the manuscript (70%) and submitted the final version to the Journal. Professors McKinnon and Gordon respectively contributed 10%, Professor Woodman 5% and Alice Wisdom 5% to important intellectual content of the manuscript through revision. All authors approved the final version of the published manuscript.

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PROTOCOL

Interventions Targeting the Prescribing and Monitoring of Vancomycin for Hospitalized Patients: A Systematic Review Protocol

Cameron J. Phillips · Alice J. Wisdom · Ross A. McKinnon · Richard J. Woodman · David L. Gordon

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ABSTRACT

Introduction: Vancomycin remains one of our essential antibiotics after fifty years of treating serious infections such as methicillin-resistant *Staphylococcus aureus*. Vancomycin, unlike many other antibiotic agents, requires individualized dosing and monitoring of serum drug levels to ensure it is efficacious, to minimize toxicity, and to limit the development of antibiotic resistance. These issues have led to numerous vancomycin clinical practice guidelines being published in recent years including several key national guidelines. Significant resources are invested during the development of such guidelines; however, there is often little or no information about how such guidelines or other vancomycin practice improvement initiatives should be implemented. The aim of this systematic review is to identify and evaluate the effect of interventions using education, guideline implementation, and dissemination of educational resources that have sought to improve therapeutic drug monitoring and dosing of vancomycin.

Methods: A systematic review of the literature will be conducted for RCTs and observational studies where a vancomycin guideline or

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practice improvement initiative has been implemented. Electronic databases to be searched are PubMed, Medline, CINAHL, EMBASE and the Cochrane Library of Systematic Reviews. The population will be patients who have had intravenous vancomycin prescribed and monitored in hospital. The interventions will be education, implementation of guidelines or protocols, dissemination of educational materials (printed or electronic) or multifaceted interventions of the above. The comparator will be patients who have had standard-care prescribing and monitoring of vancomycin. Outcomes will be changes in prescribing and ordering of vancomycin serum tests, and serum levels attained in patients as well as reported nephrotoxicity. Two reviewers will be involved in the quality assessment and extraction of data. The Scottish Intercollegiate Guidelines Network checklist for RCTs will be used. Studies that are not randomized will be assessed for quality using the validated ROBINS-I (risk of bias in non-randomized studies of interventions) tool.

Discussion: This systematic review will identify interventions that have been used to implement guidelines and clinical practice initiatives for vancomycin. The findings of this review may be informative to those involved with the implementation of vancomycin clinical practice guidelines.

Systematic review registration: PROSPERO: CRD42016049147.

Keywords: Education; Guideline; Implementation; Intervention; Protocol; Vancomycin

INTRODUCTION

While vancomycin has been used for nearly 60 years, it remains the principal treatment for infection caused by serious Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) [1]. Vancomycin, unlike many other antibiotics, has a number of special considerations, such as the requirement for individualization of dosing and serum drug monitoring to ensure efficacy, minimize toxicity and limit the development of bacterial resistance [2–4]. These factors, in addition to increasing concerns about antimicrobial resistance [5, 6] and the need to prolong the life of our existing antibiotics, have led to the publication of a number of vancomycin guidelines [7], including important national guidelines for the dosing and or monitoring of vancomycin from the United States (US), Japan and China [8–10]. Significant effort and resources are invested in the process and preparation of such high-quality national guidelines, which are endorsed by peak professional societies in their respective countries [11, 12]. These documents provide much needed contemporary guidance on the appropriate use of vancomycin; however, there is a paucity of information about how these vancomycin guidelines and their contents should be best disseminated and implemented into practice to achieve the intended outcomes for clinicians and patients. Only one guideline, by the Chinese Pharmacological Society [10], includes some information about implementation. The implementation details associated with this guideline propose promotion via conferences, education sessions for physicians, pharmacists and nurses, and research to evaluate both the implementation and impact of the guideline on vancomycin therapeutic drug monitoring (TDM) [13].

There are numerous reports in the medical literature that highlight clinicians lack of knowledge of the contents of key guidelines in addition to an often low uptake of guidelines [14–16]. To combat this issue, adoption strategies have been recommended by a number of prominent organizational developers of guidelines such as the Australian National Health and Medical Research Council (NHMRC) [17, 18], the United Kingdom's National Institute for Health and Clinical Excellence (NICE) [19], the Scottish Intercollegiate Guideline Network (SIGN) [20], and the US Institute of Medicine (IOM) [21]. While it is prudent that any plan to implement a guideline or practice change should include an assessment of the barriers and enablers [22], there are common implementation strategies recommended by these organizations, which are widely employed. Such strategies include the provision of education about the guideline and its recommendations [23]. Educational meetings

have demonstrated changes in practice measures between 1.8% and 15.9% [24], while dissemination of guidelines and educational supporting material have been shown to have a median 8.1% improvement on care [25], although there have been recent concerns about the effectiveness of the latter [26]. Determination of the relative effectiveness of these strategies to promote the implementation of guidelines or practice change initiatives for vancomycin is important to prudently allocate supportive resources. While a systematic review on guidelines for TDM of vancomycin has been published [7], the current review aims to identify and evaluate the effect of interventions employing education, guideline implementation and dissemination of educational resources on the therapeutic drug monitoring and dosing of vancomycin.

METHODS

The steps of the systematic review to be conducted will be defining the inclusion criteria and exclusion criteria, searching for and capturing studies, and identifying studies that address the review question and are in accordance with the criteria. Defined data will be extracted and compiled. This systematic review protocol will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement [27, 28]. The PRISMA-P 2015 checklist for this review accompanies this protocol as Supplementary material 1.

Research Question

This review aims to systematically identify and determine the effect of interventions that have targeted the therapeutic drug monitoring and dosing of the intravenous antibiotic vancomycin.. The specific review question is:

Do interventions (alone or in combination) involving; education, implementation of guidelines or protocols, or dissemination of educational materials (printed or electronic) improve the prescribing, monitoring and safety of vancomycin?

Population, Interventions, Comparator and Outcome (PICO)

The review populations, interventions, comparator group and outcomes [29], to be assessed in the systematic review are presented in Table 1.

Selection of Studies and Inclusion/ Exclusion Criteria

A preliminary search suggests that there are limited RCTs on this topic, so observational, including before–after studies and interrupted time series studies, will also be included in addition to RCTs. The review will include studies that have employed documented implementation strategies for vancomycin guidelines and protocols, educational interventions (face-to-face or electronic, disseminations of educational materials (printed or electronic) or multifaceted strategies using a combination of these. Studies to be excluded will be those using population pharmacokinetic modeling of guidelines or protocols, those comparing one explicit guideline directly against another (e.g., continuous versus intermittent dosing), those with no comparison to control or baseline data, and those where the post-implementation assessment excluded patients who were not dosed in accordance with the new guideline (as this may bias and misrepresent uptake of the guideline). Studies will also be excluded if they focus solely on indication for vancomycin or duration of usage. Studies involving oral vancomycin for *Clostridium difficile* infection will be excluded as this therapy does not involve TDM.

Search Strategy and Data Storage

The search strategy was developed in collaboration with an academic medical librarian experienced in conducting searches for systematic reviews. Search strategies will employ medical subject headings (MeSH) [30], and key words pertaining to the research question. The electronic database search was initially developed for Ovid MEDLINE (full search strategy presented as Supplementary material 2). The

Table 1 PICO framework

Population	Patients who have had vancomycin prescribed and monitored in hospital
Interventions	Education, implementation of guidelines or protocols, or dissemination of educational materials (printed or electronic) or multifaceted interventions of the above
Comparators	Standard care prescribing and monitoring of vancomycin
Outcomes	*Prescribing* The proportion of patients prescribed loading doses, and prescribed maintenance doses appropriate for renal function
	Monitoring The proportion of vancomycin blood levels drawn at appropriate times, attaining specified target ranges, and in levels outside specified ranges
	Safety Frequency of reported nephrotoxicity (increase in serum creatinine of 0.5 mg/dL or $> 50\%$ from baseline on ≥ 2 or more consecutive measurements) after 2 or more days of vancomycin [8]

search strategy was then adapted for PubMed, EMBASE (Excerpta Medica Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature) and the Cochrane Library of Systematic Reviews. The search will be filtered to capture articles in the English language only. As vancomycin was first licensed with the US Food and Drug Administration in the 1950s, the search strategy will span all articles in the respective databases from inception. To further the search strategy, any relevant studies identified by members of the review team will be captured. The search will be re-performed prior to closing the review to ensure any recently published articles are captured. Publications will be stored in in a dedicated electronic library using EndNote X7.7 referencing software (Thompson Reuters, 2016), with duplicate references to be removed. Data collection will be performed using Microsoft Excel (Microsoft, 2017).

Data Analysis and Synthesis

The preliminary screening of captured articles will be performed to determine if the titles or abstracts address the review question. A second reviewer will independently review articles to determine if they are in agreement with the suitability of selected articles. Any differences will be resolved through discussion with a third member of the review team. The following stage will be accessing full text articles to determine eligibility for final inclusion, when a second reviewer will independently check that they agree with the identified articles. Any disagreement will be resolved by a third member of the review team. An assessment of the quality of articles will be performed. The SIGN checklist for RCTs will be used [20]. Studies that are not randomized will be assessed using the validated tool ROBINS-I (Risk of bias in non-randomized studies of interventions) [31].

Data variables to be collected are study demographics, authors, year, country, care setting (unit or ward) in hospital, type of study, intervention type and description of intervention, intended effect of intervention, use of any theory for the intervention, learning objectives, materials used, educational strategies, schedule, instructions and modes used, use of incentives and environment [32]. Data for outcomes will be authors' results for vancomycin prescribing, drug monitoring and nephrotoxicity. This article does not contain any new studies with human or animal subjects performed by any of the authors.

DISCUSSION

Studies have demonstrated hospital doctors do not prescribe antibiotics appropriately nearly half of the time [33], and one-quarter of hospitals in Australia have been reported as non-adherent to guidelines [34]. Determination of the

strategies that promote effective implementation should be a fundamental component of guideline development and practice improvement initiatives. The published literature on vancomycin prescribing and monitoring shows that there is considerable room for improvement for this half-century-old antibiotic. The findings from this systematic review will be summarized in tabular format providing ready interpretation and comparison of studies. We will provide a narrative synthesis of the findings from included studies structured around the type of intervention, prescriber and population characteristics and outcomes. We will also discuss the strengths and limitations of included studies. We elected not to measure clinical efficacy or microbiological outcomes, as we wanted to focus on outcomes pertaining specifically to dosing, TDM and toxicity which are highly appropriate as these are directly related to interventions providing guidance, education or dissemination of resources seeking to improve vancomycin dosing and TDM and to limit toxicity. This review will be informative in providing guidance on how successful the examined interventions are in effecting appropriate prescribing and monitoring of vancomycin. The findings of this review will help those seeking to improve the clinical use of vancomycin by selecting effective interventions to implement guidelines or other practice improvement initiatives.

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Disclosures. Cameron J. Phillips, Alice J. Wisdom, Ross A. McKinnon, Richard J. Woodman, and David L. Gordon have nothing to disclose relevant to this work.

Compliance with Ethics Guidelines. This protocol is based on preparing to search for previously conducted studies and does not involve any new human or animal subjects performed by the authors.

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2.2.2 Systematic review with meta-analysis

Phillips CJ, Wisdom AJ, McKinnon RA, Woodman RJ, Gordon DL. Interventions targeting the prescribing and monitoring of vancomycin for hospitalized patients: a systematic review with meta-analysis. Infection and Drug Resistance 2018; 11: 1-14.

Author contributions

I was responsible (80%) for the design of the review and meta-analysis, with Professors McKinnon, Gordon and Woodman and Alice Wisdom each contributing 5%. I assessed 100% of full-text articles for eligibility. As this was a dual review process, Alice Wisdom also reviewed full-text articles for eligibility for inclusion. Any disagreement of articles for inclusion was adjudicated by Professors Gordon or McKinnon. Included studies were assessed 100% by myself and the process repeated by Alice Wisdom. I performed 85% of data acquisition and Alice Wisdom 15%. Professor Woodman performed the formal statistical analysis. All authors contributed to interpretation of the results. I wrote 80% of the manuscript, each coauthor contributed (5%) to important intellectual content. All authors approved the final version of the published manuscript.

Infection and Drug Resistance

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REVIEW

Interventions targeting the prescribing and monitoring of vancomycin for hospitalized patients: a systematic review with meta-analysis

This article was published in the following Dove Press journal:
Infection and Drug Resistance

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Purpose: Vancomycin prescribing requires individualized dosing and monitoring to ensure efficacy, limit toxicity, and minimize resistance. Although there are nationally endorsed guidelines from several countries addressing the complexities of vancomycin dosing and monitoring, there is limited consideration of how to implement these recommendations effectively.

Methods: We conducted a systematic search of multiple databases to identify relevant comparative studies describing the impact of interventions of educational meetings, implementation of guidelines, and dissemination of educational material on vancomycin dosing, monitoring, and nephrotoxicity. Effect size was assessed using ORs and pooled data analyzed using forest plots to provide overall effect measures.

Results: Six studies were included. All studies included educational meetings. Two studies used implementation of guidance, educational meetings, and dissemination of educational materials, one used guidance and educational meetings, one educational meetings and dissemination of educational materials, and two used educational meetings solely. Effect sizes for individual studies were more likely to be significant for multifaceted interventions. In meta-analysis, the overall effect of interventions on outcome measures of vancomycin dosing was OR 2.50 (95% CI 1.29–4.84); $P< 0.01$. A higher proportion of sampling at steady-state concentration was seen following intervention (OR 1.95, 95% CI 1.26–3.02; $P<0.01$). Interventions had no effect on appropriate timing of trough sample (OR 2.02, 95% CI 0.72–5.72; $P=0.18$), attaining target concentration in patients (OR 1.50, 95% CI 0.49–4.63; $P=0.48$, or nephrotoxicity (OR 0.75, 95% CI 0.42–1.34; $P=0.33$).

Conclusion: Multifaceted interventions are effective overall in improving the complex task of dosing vancomycin, as well as some vancomycin-monitoring outcome measures. However, the resulting impact of these interventions on efficacy and toxicity requires further investigation. These findings may be helpful to those charged with designing implementation strategies for vancomycin guidelines or complex prescribing processes in hospitals.

Keywords: drug monitoring, education, guideline, implementation, intervention, prescribing, systematic review, vancomycin

Introduction

Vancomycin is an essential antibiotic that has been in use for six decades.[1] Despite sustained use, vancomycin remains an inherently challenging drug to prescribe, due to the need for individualized dosing and requirement for serum-concentration monitoring to ensure efficacy, minimize nephrotoxicity and limit the development of resistant organisms.[2–5] Recommendations on how to dose and monitor vancomycin have evolved over time.[6] These issues, in addition to the greater public health concern of antimicrobial

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resistance,[7] have resulted in a number of professional societies in the US, Japan, and more recently China publishing their own vancomycin guidelines. [8–10] Significant time and expert engagement goes into the development of these high-caliber guidelines,[11] which are sanctioned and advocated by their respective countries.[12,13] These guidelines provide important updated information for clinicians and seek to improve care for patients; however, there is a dearth of information as to how these guidelines should be implemented into practice to fulfill these objectives. The published protocol for the development of clinical practice guidelines for therapeutic drug monitoring (TDM) of vancomycin by the Chinese Pharmacological Society is the only one that provides any advice on implementation.[14] In addition to limited information on implementation strategies of these guidelines, there is scant evidence on which interventions may be best employed and in what combination.

There are a number of published works stating that clinicians in numerous fields of medicine often do not follow guidelines, including prescribing antibiotics for hospitalized patients.[15–18] In an effort to address these problems, strategies have been advocated by peak national bodies concerned with guideline implementation and care improvement, such as the UK National Institute for Health and Care Excellence, the US Institute of Medicine, the Australian National Health and Medical Research Council, and more broadly the Guideline International Network.[12,19–21] Examples of strategies recommended by these bodies include implementation of guidelines, educational meetings, and dissemination of educational material.[22–24] Determining optimal strategies, employed alone or in combination, is critical to inform practice initiatives seeking to translate guidelines and their recommendations into practice. This systematic review aims to evaluate the effect of interventions using education, guideline implementation, and dissemination of educational resources on the dosing and monitoring of vancomycin in hospitalized patients.

Methods

Registration and protocol

The protocol for this systematic review was registered (CRD42016049147) with PROSPERO, (International Prospective Register of Systematic Reviews, Center for Reviews and Dissemination, University of York, UK) in October 2016. A protocol for this review has been published.[25] The review has been reported in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) 2015 statement.[26,27] A PRISMA flow diagram of included studies is presented in Figure 1.

Research question

Do interventions (alone or in combination) involving education, implementation of guidelines/protocols, or dissemination of educational materials (printed or electronic) improve the prescribing, monitoring, and safety of vancomycin?

Eligibility criteria

Studies included were restricted to the English language. Due to a pilot search suggesting a limited number of randomized controlled trials, no restrictions were placed on study type, which included observational and cohort studies. There were no restrictions on year of publication, with databases searched back to their inception. The studies included required interventions to influence vancomycin prescribing and monitoring, using educational meetings (face to face, online, or continuing education), guideline or protocol implementation, dissemination of educational materials, or multifaceted interventions comprising one or more of these. These interventions were selected as they are commonly recommended implementation strategies that are not cost-prohibitive.[20,28] Excluded studies were those that used pharmacokinetic modeling based on guidelines/protocols/nomograms, compared one guideline directly with another (rather than an intervention to implement the guideline), lacked comparator or baseline data, and where postimplementation outcomes excluded patients not managed in accordance with the new guideline (so as not to bias or misrepresent uptake of the guideline). Studies employing interventions where outcomes were exclusively based on indication and/or duration of vancomycin therapy were also excluded.

Data sources

The database searches were performed in October 2016 using the predefined search strategy and method described in the published protocol of our review.[25] The following five databases were searched: Ovid Medline, PubMed, Embase, CINAHL, and the Cochrane Database of Systematic Reviews. In addition, we performed a hand search of reference lists of systematic reviews captured in the original search. We used medical subject headings,[29] and their synonyms as search terms. We used syntax suitable to detect different spelling and truncation of search terms for the various databases. Search terms principally related to interventions were "guideline/protocol", "adherence", "impact", "evaluation", "disseminate", "implement", "education", "lecture", "tuto-

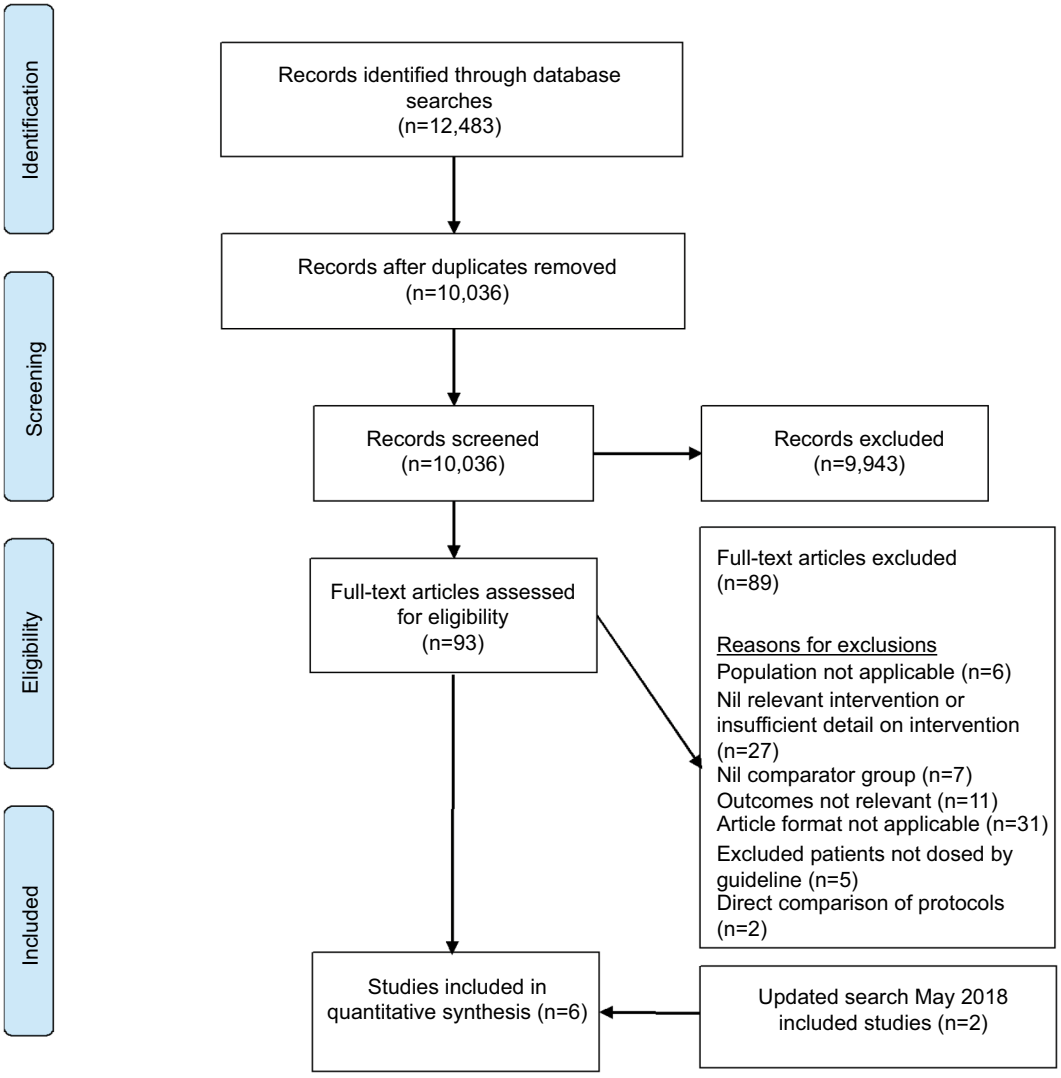

Figure 1 PRISMA study flow diagram.

rial", "seminar", "feedback", "reminder", "electronic mail", "smartphone", "computer", "personal digital assistant; and outcomes", "prescribing", "dosing", "drug monitoring", and "monitoring". This list is not exhaustive: the full search strategy is included as the Supplementary material. The search was rerun in May 2018 to identify any potentially new citations that had been published prior to submission.

Data management and extraction

All citations captured were stored in a dedicated and shared library using EndNote referencing software (version X7.7; Clarivate Analytics, Philadelphia, PA, USA). Titles and abstracts of studies were reviewed and assessed independently by two authors for suitability of inclusion. Two authors (CJP and AJW) independently reviewed the full text of relevant studies, any disagreement was resolved by a third investigator. Studies that satisfied eligibility were included for data extraction. Two authors piloted the data-extraction tool before agreeing on the final tool, which was employed using Excel (Microsoft, Seattle, WA, USA). The data-extraction tool was located in cloud storage (Dropbox version 16.4.30; Dropbox, San Francisco, CA, USA) to enable shared and remote access by authors. Data collected included author, year, country, study design, type of intervention, description of interventions, and outcome measures.

Outcome measures

Data were collected for outcome measures of vancomycin dosing. Loading dosages and maintenance dosages appropriate for renal function were as defined by individual study

authors. TDM outcomes were the timing of blood samples at steady-state concentration (ie, blood taken prior to the fourth or fifth dose with 12-hourly dosing in patients with normal renal function),[9] appropriate timing of trough levels (ie, prior to next dose),[8] attainment of therapeutic target,[8,10] and frequency of patients with supratherapeutic vancomycin concentration (>20 mg/L, at which likelihood nephrotoxicity increases steeply).[30] The safety outcome of frequency of reported nephrotoxicity was also included, defined as an increase in serum creatinine of 0.5 mg/dL or >50% from baseline on two or more consecutive measurements after ≥2 days of vancomycin therapy.[31]

Interventions

We categorized interventions according to the Cochrane Effective Practice and Organization of Care Group (EPCO) taxonomy of health-system interventions. The four categories of this taxonomy are delivery arrangement, financial arrangements, governance arrangement, and implementation strategies. Implementation strategies are further subdivided into interventions targeted at health care workers. In this subdivision, the interventions are audit and feedback, clinical incident monitoring, monitoring the performance and delivery of health care, communities of practice, continuous quality improvement, educational games, educational materials, educational meetings, educational outreach, clinical practice guidelines, interprofessional education, local consensus processes, local opinion leaders, managerial supervision, patient-mediated interventions, public release of performance data, reminders, routine patient-reported outcome measures, and tailored interventions.[32] The target cohort of interventions was hospital clinicians. For definition purposes in this review, patients treated by staff who were subject to interventions are referred to as the intervention group. Patients under the care of hospital clinicians that were not subject to interventions are referred to the usual-care group.

Risk of bias

Quality assessment of included studies was performed using ROBINS-I (risk of bias in nonrandomized studies – interventions). ROBINS-I was developed by members of the Cochrane Bias Methods Group and Non-Randomized Studies Methods Group and has been validated.[33] As all studies in this review were nonrandomized and conducted in a health care environment, the ROBINS-I tool was highly suitable. ROBINS-I contains seven domains of bias: due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurements of outcomes, and selection of reported results. ROBINS-I provides detailed guidance on categorizing each domain as low risk, moderate risk, serious, or critical risk of bias. ROBINS-I detailed guidance states that the level of risk of bias can only be as good as the highest risk obtained for any one of the seven domains, and it is unlikely that an observational study will be judged less than moderate risk.[33] Two authors (CJP and AJW) independently assessed studies for quality, with any disagreement resolved by a third author (Figure 2).

Statistical analysis

Event rates for intervention and standard care are described using frequencies and proportions and differences described using ORs with 95% CIs in Stata (version 15.1; StataCorp, College Station, TX, USA) using the epitab "cci" command. We performed random-effect meta-analyses for the various study subgroups with inverse-variance weights using the R "meta" package (version 4.9.1) with R software (version 3.4.1; Vienna, Austria). Forest plots were created using RevMan version 5.0 (Nordic Cochrane Center, Copenhagen, Denmark). Heterogeneity was assessed using τ^2 and I^2. I^2=0 represents no heterogeneity, while increasing values represent the presence of heterogeneity. I^2 values of 25%, 50%, and 75% were defined as low, moderate, and high heterogeneity respectively.[34]

Results

Search results

The search captured 12,483 records across five databases. Following duplicate removal, 10,036 citations were screened and 93 full-text articles sourced, with 89 subsequently excluded (Figure 1). Four studies met inclusion criteria. This was increased to six after the search was rerun prior to submission. All studies included were observational, and no randomized controlled studies were identified. Studies

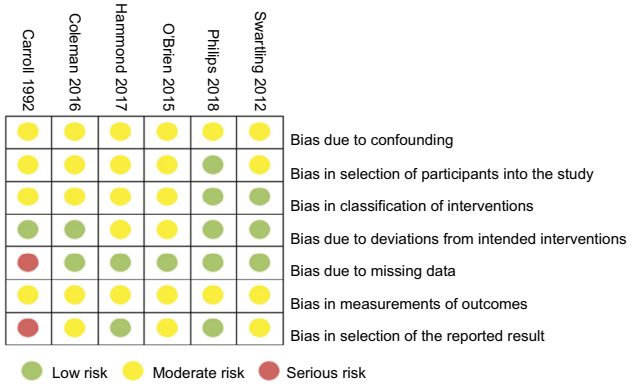

Figure 2 Quality of included studies: ROBINS-I (risk of bias assessment in nonrandomized studies – interventions).

involving interventions employing single or multifaceted interventions were included.

Quality of studies and risk of bias

Five of six included studies had at least one domain that was assessed as moderate risk of bias, and one study had a serious risk of bias for two domains. No studies had domains ranked as critical risk of bias. Figure 2 shows the assignment of risk of bias for each of the seven domains of each included study. Overall risk of bias for each study is presented in Table 1.

Characteristics of included studies

Five of the six studies were from the US[35,36,38–40] and one from Australia.[37] Three studies reported the population as number of patients, with 263 in the intervention group and 274 receiving usual care,[35–37] and one study reported treatment courses, with 200 in the intervention group and 279 receiving usual care.[38] Two studies that evaluated timing of blood samples for vancomycin assays exclusively reported only the number of concentrations: 387 in the intervention group and 288 receiving usual care.[39,40] Data on characteristics of included studies and details of intervention are summarized in Tables 1 and 2.

Interventions

All interventions involved education meetings.[35–40] Five studies employed multifaceted interventions,[35–38,40] including two or more interventions. Two studies involved implementation of guidance, educational meetings, and dissemination of educational materials.[37,38] Two studies employed guidance and education meetings,[36] one utilized education meetings and dissemination of educational material,[40] and another used educational meetings only.[39] Of the four studies using guidance, two employed a clinical practice guideline,[37,38] one a nomogram,[36] and one an undefined policy change.[35] Dissemination of educational materials was employed in three studies using a pocket reference card (Table 2).[37,38,40] Reported outcomes and effect sizes for studies employing interventions on dosing, monitoring, and nephrotoxicity outcomes are presented in Table 3. Interventions involving implementation of clinical practice guidelines, educational meetings, and dissemination of educational resources had the highest effect on dosing outcomes (effect size 2.76–7.28, $P<0.001$).[37,38] Furthermore, studies using these three interventions when assessing initial maintenance doses being prescribed appropriate for renal function demonstrated relatively consistent effect sizes: OR 2.76 (95% CI 1.66–4.58, $P<0.001$)[37] and OR 3.36 (95% CI 2.22–5.09, $P<0.001$).[38] Overwhelmingly, the studies employing a composite of implementation of guidelines, educational meetings, and dissemination of educational material also had the greatest effect on TDM outcomes. A notable exception was one study using educational meetings and dissemination of educational material, which produced a greater effect size (OR 4.2, 95% CI 1.16–15.17; $P=0.024$)[40] when compared with studies that used three interventions: OR 2.18 (95% CI 1.43–3.32, $P<0.001$)[38] and OR 1.42 (95% CI 0.87–2.32, $P=0.162$).[37]

Outcome measures

Effect of interventions on dosing of vancomycin

The overall effect of interventions on vancomycin dosing was OR 2.50 (95% CI 1.29–4.84, $P<0.01$). The heterogeneity between studies was high ($I^2=83\%$, $P<0.01$; Figure 3). Three studies measured the impact of interventions on loading doses.[35–37] The overall frequency of receiving a loading dose for patients in the intervention group (112 of 263, 42.6%) compared to those receiving usual care (69 of 274, 25.2%) was not significantly different (OR 2.08, 95% CI 0.49–8.79; $P=0.32$). High heterogeneity among those studies was present ($I^2=90\%$, $P<0.01$; Figure 3A). There were two studies that measured the effect of interventions on maintenance dosages appropriate for renal function.[37,38] There was a higher frequency of maintenance dosages prescribed for patients in the intervention group (246 of 333, 73.9%) compared to those receiving usual care (183 of 378, 48.4%; OR 3.11, 95% CI 2.26–4.28; $P<0.01$). There was low heterogeneity between these studies ($I^2=0$, $P=0.55$; Figure 3B).

Effect of interventions on monitoring of vancomycin

Three studies evaluated the effect of interventions on whether blood samples were collected at steady-state concentration.[37,38,40] There was a higher proportion of concentrations appropriately collected at steady state (196 of 356, 55.1%) for patients in the intervention group compared to those receiving usual care (122 of 314, 38.9%; OR 1.95, 95% CI 1.26–3.02; $P<0.01$) There was no significant heterogeneity between studies ($I^2=38\%$, $P=0.20$; Figure 4A). Three studies measured the effect of interventions on appropriate timing of trough blood samples for vancomycin assays prior to next dose.[35,38,39] There was no difference between patients in the intervention group (463 of 668, 69.3%) and those receiving usual care (302 of 569, 53.1%; OR 2.02, 95% CI 0.72–5.72; $P=0.18$), although there was significant heterogeneity between these studies ($I^2=94\%$, ($P<0.01$; Figure 4B).

There was no significant difference in patient attainment of therapeutic target between those in the intervention group (161 of 233, 69.1%) and those receiving usual care (144 of 225, 64%; OR 1.50, 95% CI 0.49–4.63; $P=0.48$). There was also significant heterogeneity between studies ($I^2=80\%$,

Table 1 Study design and characteristics of included studies

Study	Country	Study design	Interventions			Patients/samples (pre-; post-)	Outcome measures	Overall risk of bias (ROBINS-I)
			Guidance (guideline, protocol, nomogram)	Educational meetings (target audience)	Dissemination of educational materials			
Carroll et al[40]	USA	Retrospective, pre/postintervention	None	Nursing staff, medical officers, ward clerks, lab personnel, pharmacists	Pocket reference card	16 SVC; 32 SVC, number of patients NR	Proportion of blood samples collected at steady-state concentration	Serious
Coleman et al[39]	USA	Unspecified, pre/postintervention	None	Nursing staff	None	272 SVC; 355 SVC, number of patients NR	Percentage of appropriately timed trough blood samples prior to next dose	Moderate
Hammond et al[35]	USA	Retrospective, Pre/postintervention	Policy change	Nursing staff	None	49 patients (124 SVC); 30 patients (122 SVC)	Percentage of appropriately timed trough blood samples prior to next dose	Moderate
O'Brien et al[36]	USA	Retrospective, pre/postintervention	Nomogram	Pharmacists	None	100 patients; 100 patients, number of SVC NR	Frequency of nephrotoxicity, prescribing adherent to nomogram, attainment of therapeutic target	Moderate
Phillips et al[37]	Australia	Retrospective, pre/postintervention	Clinical practice guideline	Medical officers (interns, residents) and pharmacists	Pocket version of dosing and TDM card	125 patients (319 SVC); 133 patients (379 trough levels)	Proportion of patients receiving loading dose, proportion of appropriate maintenance doses, and frequency of nephrotoxicity	Moderate
Swartling et al[38]	USA	Prospective, pre/postintervention	Clinical practice guideline	Nursing staff & phlebotomists	Pocket version of dosing and TDM cards	279 treatment courses; 200 treatment courses	Appropriateness of initial vancomycin dosing, appropriateness of sampling of levels	Moderate

Abbreviations: NR, not reported; SVC, serum vancomycin concentrations; TDM, therapeutic drug monitoring; ROBINS-I, risk of bias in nonrandomized studies – interventions.

Table 2 Intervention details of included studies

Study	Interventions			Additional EPOC implementation strategies
	Guidance	Educational meeting	Dissemination of educational materials	
Carroll et al[40]	None	Educational intervention on basic pharmacokinetic principles, importance of samples for accurate serum drug concentration Audio recording of the talk Duration of session NR Frequency of sessions: reeducation every 3 months (number of repeat sessions NR)	Pocket reference cards distributed containing recommendations of appropriate timing of blood sampling for TDM Audio recording of the talk, distributed to all nurse-unit heads for provision to future employees	None
Coleman et al[39]	None	Educational session on clinical vancomycin use Importance of and how to collect samples appropriately and perform TDM Five multiple-choice questions for nursing staff Duration of session NR Frequency of sessions: four minimum, in five hospital units	None	None
Hammond et al[35]	Change in policy (change in hour of day for routine blood sampling, no details provided if written or verbal change)	Education verbally on dosing times and when to collect blood samples Duration of session 2–5 minutes Frequency of sessions NR	None	None
O'Brien et al[36]	Implementation of nomogram	Education on how to utilize the nomogram appropriately (and nomogram development) Details of delivery NR Duration of education NR Frequency of education NR	None	None
Phillips et al[37]	Clinical practice guideline developed and implemented to institution, guideline content adapted from US consensus guidelines[31]	Educational tutorial using clinical vignettes on vancomycin treatment, including antibiotic resistance, appropriate dosing, monitoring, and issues of vancomycin renal toxicity Delivery format face to face and PowerPoint Duration of tutorial 60 minutes Frequency three tutorials annually	Provision of pocket guideline of vancomycin dosing and TDM disseminated to medical and pharmacy staff at educational sessions and via doctors' mailboxes/pigeon holes in staff lounge Ten multiple-choice questions in one vancomycin CME for medical staff email to all interns and resident medical officers[44]	Audit and feedback of local prescribing and monitoring data Local consensus process Engagement of opinion leaders Reminder email alert from director of medical services to all medical staff advising where to find the guideline on hospital intranet and requesting adherence
Swartling et al[38]	Clinical practice guideline developed and implemented to institution, guideline content adapted from US consensus guidelines[31]	In-service education on appropriate timing and documentation of sample collection Duration of in service NR Frequency of in-service education NR	Guideline emailed to all pharmacists Provision of pocket card of vancomycin dosing and TDM information on pocket card disseminated to medical and pharmacy staff	None

Abbreviations: EPOC, Effective Practice and Organisation of Care (Cochrane); NR, not reported; CME, continuing medical education; TDM, therapeutic drug monitoring.

Table 3 Summary of interventions on dosing, monitoring, and safety outcomes

Outcome	Interventions employed	Study	Standard care to intervention, n	Percentage change in effect difference (intervention vs standard care)
Prescribing				
Loading dose	CPG/education meeting/EM	Phillips et al[37]	12/125 to 58/133	34% (9.6%–43.6%), *P*<0.001
	Nomogram and education meeting	O'Brien et al[36]	50/100 to 49/100	–1% (50%–49%), *P*=NR
	Education meeting	Hammond et al[35]	7/49 to 5/30	2.4% (14.3%–16.7%), *P*=0.68
Initial maintenance dose	CPG/education meeting/EM	Swartling et al[38]	128/253 to 155/200	27% (50.6%–77.5%), *P*<0.0001
	CPG/education meeting/EM	Phillips et al[37]	55/125 to 91/133	24.4% (44%–68.4%), *P*=0.04
Therapeutic drug monitoring				
Timing of blood sample at steady-state concentration	CPG/education meeting/EM	Swartling et al[38]	63/173 to 106/191*	19.1% (36.4%–55.5%), *P*<0.03
	Education meeting and EM	Carroll et al[40]	5/16 to 21/32*	34.3% (31.3%–65.6%), *P*<0.025
	CPG/education meeting/EM	Phillips et al[37]	54/125 to 69/133	8.7% (43.2%–51.9%), *P*=0.01
Timing of blood trough sample prior to next dose	CPG/education meeting/EM	Swartling et al[38]	64/173 to 149/191*	41% (37%–78%), *P*<0.001
	Education meeting	Coleman et al[39]	189/272 to 263/355*	4.6% (69.5%–74.1%), *P*=0.2
	Education meeting	Hammond et al[35]	49/124 to 51/122*	2.3% (39.5–41.8), *P*=0.72
Patient attainment of vancomycin therapeutic target	CPG/education meeting/EM	Phillips et al[37]	104/125 to 124/133	10% (83.2%–93.2%), *P*=0.012
	Nomogram and education meeting	O'Brien et al[36]	40/100 to 37/100	–3% (40%–37%), *P*=NR
Frequency of patients with supratherapeutic vancomycin concentrations	CPG/education meeting/EM	Phillips et al[37]	98/125 to 59/133	–9.8% (30.7%–20.9%), *P*<0.001
	Nomogram and education meeting	O'Brien et al[36]	45/100 to 43/100	–3% (45%–43%), *P*=NR
Safety				
Frequency of nephrotoxicity	Nomogram and education meeting	O'Brien et al[36]	16/100 to 14/100	–2% (16%–14%), *P*=0.197
	CPG/education meeting/EM	Phillips et al[37]	13/125 to 9/133	–3.6% (10.4%–6.8%), *P*<0.001

Note: *Indicates serum vancomycin concentrations.
Abbreviations: NR, not reported; CPG, clinical practice guideline; EM, educational meeting; EPOC, Effective Practice and Organisation of Care (Cochrane).

P=0.02; Figure 4C). No association was seen between the frequency of patients attaining potentially toxic suprathrapeutic vancomycin levels above target (>20 mg/L) in the intervention group (102 of 233, 43.8%) and those receiving usual care (143 of 225, 63.6%; OR 0.45, 95% CI 0.11–1.83; *P*=0.26). There was significant heterogeneity between these studies (I^2=92%, (*P*<0.01; Figure 5A).

Effect of interventions on frequency of nephrotoxicity

There were two studies reporting the number of patients that experienced nephrotoxicity. No association was observed between patients in the intervention group (23 of 233, 9.9%) and those receiving usual care (29 of 225, 12.9%; OR 0.75, 95% CI 0.42–1.34; *P*=0.33). There was low heterogeneity between these studies (I^2=0, *P*=0.60; Figure 5B).

Discussion

To our knowledge, this is the first systematic review with meta-analysis to explore the effect of commonly recommended interventions of educational meetings, implementation of guidance, and dissemination of educational materials on vancomycin dosing, monitoring, and nephrotoxicity. We found these interventions combined or used individually had

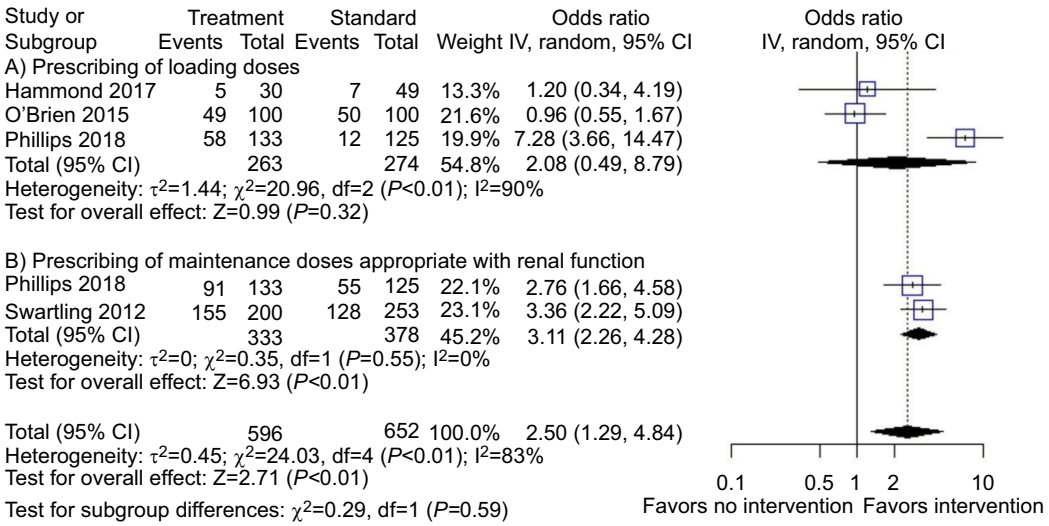

Figure 3 Effect of interventions on vancomycin dosing.

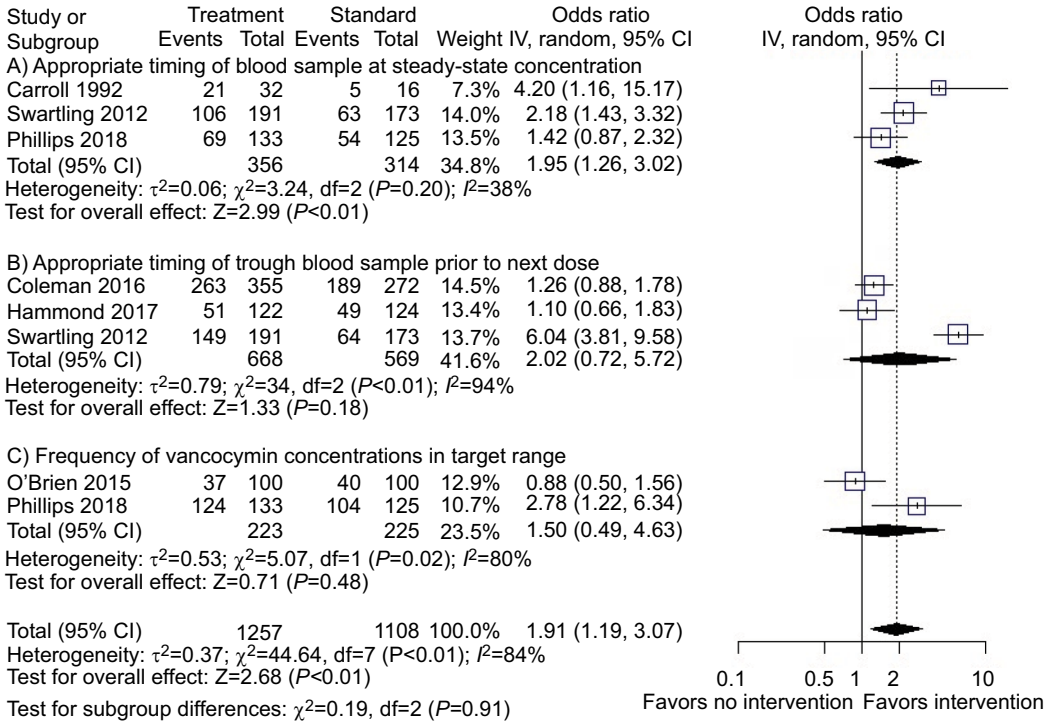

Figure 4 Effect of interventions on vancomycin therapeutic drug monitoring.

a variable effect on dosing, monitoring, and nephrotoxicity outcomes. All studies employed a constant of educational meetings. A Cochrane review on the effect of educational meetings on professional-practice health care outcomes found that educational meetings had a modest effect (median 6%, IQR 1.8%–15.9%) on these outcomes when compared to no intervention.[22] This is broadly consistent with our findings when educational meetings were the sole intervention. While no included study used dissemination of educational material exclusively as an intervention, one study that used this in conjunction with educational meetings demonstrated a much higher effect change of 34%, although this was a small study.[40] A Cochrane review of the effect of disseminating educational materials to medical officers found a minimally

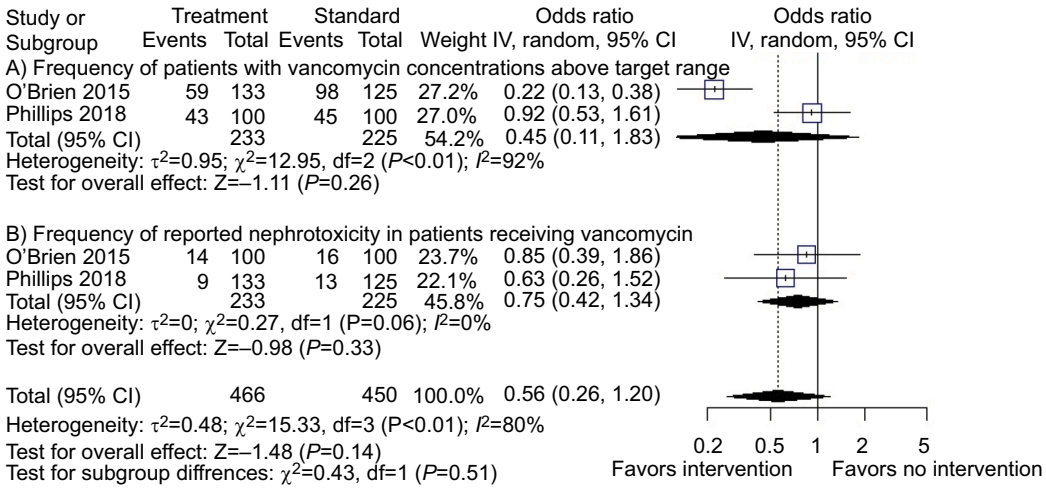

Figure 5 Effect of interventions on supratherapeutic concentrations and nephrotoxicity in patients receiving vancomycin.

increased effect (median 2%, range 0–11%) when compared to no intervention, but an increased effect (median 13%, range 16%–36%) was observed when interventions were followed up to 9 months.[41]

The US Institute of Medicine recommends promoting multifaceted interventions to implement guidelines at individual practitioner and health care system levels.[20] However, some authors have expressed strongly that multifaceted interventions are no better when compared to single interventions in changing health care professionals' behaviour.[42] This was inconsistent with our findings. Five of the six included studies used multifaceted interventions to improve dosing and monitoring of vancomycin. While the effect of individual interventions when combined do not appear to have had a proportional summative effect, those studies with interventions that specifically employed a guideline, educational meetings, and dissemination of educational materials generally had a much greater composite effect than individual interventional component effects.

Others have stated that providing printed material is a reasonable intervention to consider in any implementation strategy, as the costs are not likely to be prohibitive.[43] Based on the findings of this review, we agree with this recommendation for educational material to aid dosing and monitoring of vancomycin. Two studies[37,38] with similar interventions that produced favorable effect size changes also adapted their local vancomycin guidelines from US consensus guidelines. This may be meaningful, as guideline content and usability have also been acknowledged as variables in implementation strategies.[20] One of the included studies[37] had a very detailed description of its educational component published elsewhere[44] and stated use of additional interventions, including audit and feedback, local consensus processes, opinion leaders in development of guidelines, and email reminder.[45,46] It is possible these interventions may have augmented some of the generally large effect changes observed within that study.

Interestingly no included studies provided assessment of the local barriers and enablers to effective dosing and monitoring of vancomycin in their institution. Understanding these barriers and enablers can influence the choice of intervention, as has been reported by health care professionals conducting implementation projects in health care, including a project to improve vancomycin dosing and monitoring.[47] Additionally, no included studies provided any theoretical or behavioral basis for selecting the interventions they employed. Providing a theoretical basis for selecting interventions is increasingly acknowledged as important for any implementation program seeking to influence health-professional behaviour.[48–51] Furthermore, the results of this systematic review and meta-analysis are likely to be applicable to the selection of interventions that optimize the uptake of other health care initiatives in hospitals, particularly those relating to more complex prescribing processes. Another strategy used to implement changes in clinical practice for antibiotic dosing has been the use of clinical decision-support software.[52] However, a Cochrane review found that while this was useful for the dosing and monitoring of some antibiotics, there was no evidence for vancomycin.[53] Implementing a vancomycin nomogram utilizing computerized prescriber-order entry systems has shown to be useful and results in an increased likelihood

of prescribers ordering initial regimens that are nomogram adherent.[54] For institutions operating electronic prescribing, computerized prescriber-order entry is likely to be seen more in the future. Furthermore, smartphone applications provide ready access to contemporary guidance on the use of antibiotics, including vancomycin.[55] However, data are lacking on whether access to smartphone applications improves dosing and monitoring of vancomycin.

Our study has some limitations. Our search was restricted to English-language citations, so it is possible we did not capture all relevant studies. While we designed a systematic search with the assistance of an experienced medical liaison librarian, the final number of included studies was low, and thus our conclusions are derived from a small number of studies. There was considerable heterogeneity among included studies, in particular for sample size, duration of intervention, details of hospital environment, attitudes, and qualifications and experience of health care professionals. The sustainability of effects once the interventions have concluded is an important question that we were unable to answer in this review. Details about the interventions were at times minimal, limiting utility of comparisons between interventions. Additionally, with the data from this review, we are unable to determine the impact of the various interventions on clinical outcomes, aside from nephrotoxicity. Lastly, in an effort to account for heterogeneity among studies, a random-effect model with weighting using inverse-variance methods was used.[56]

Conclusion

Prolonging the working life of vancomycin is critical in our armamentarium of antibiotics in this era of antimicrobial resistance. Interventions that have favorable effects on dosing and monitoring of vancomycin should be adopted at an individual professional level and more broadly, across health systems, as inappropriate dosing can lead to therapeutic failure, nephrotoxicity, and the emergence of organisms resistant to vancomycin. When designing implementation strategies targeting the dosing and monitoring of vancomycin, multifaceted interventions are more effective. Consideration should also be given to the local barriers and enablers that will have an impact on practice initiatives seeking to improve the use of vancomycin. This review found that multifaceted interventions including guideline implementation, face-to-face educational meetings, and dissemination of educational resources in the form of pocket dosing and TDM cards had a favorable effect on the dosing and monitoring of vancomycin in hospitalized patients.

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Author contributions

CJP was responsible for study design, acquisition of data, analysis and interpretation of data, initial drafting, and revision of the manuscript; AJW study design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for intellectual content; RAM study design, analysis and interpretation of data, and critical review of the manuscript for intellectual content; RJW study design, analysis and interpretation of data, statistical analysis, and critical review of the manuscript for intellectual content; and DLG study design, acquisition of data, analysis and interpretation of data, and critical review of the manuscript for intellectual content. All authors have read and approved the final version of the manuscript. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material
Search strategy for Ovid Medline

1. Vancomycin/
2. (vancocin or vancomycin).tw,kw.
3. 1 or 2
4. education, continuing/or education, medical, continuing/or education, nursing, continuing/or education, pharmacy, continuing/or education, professional, retraining/
5. Practice Guideline/or Guideline/or Guideline Adherence/
6. guideline*.tw,kw.
7. (guideline* adj3 (adherenc* or evaluat* or introduct* or impact* or effect* or disseminat* or implement* or integrat*)).tw,kw.
8. Electronic Mail/
9. ((writte* or print* or oral or online* or educat*) adj2 (information or material*)).tw,kw.
10. (face to face or face-to-face or train* or lectur* or tutor* or seminar* or workshop* or academic detail*).tw,kw.
11. (opinion leader* or facilitator* or "linking agent*" or champion or "changing agent*").mp.
12. ((knowlege or research) adj2 (translant* or transfer* or disseminat* or implement* or broker*)).tw,kw.
13. remind*.tw,kw.
14. Feedback/
15. feedback.tw,kw.
16. chart review.tw,kw.
17. Program Evaluation/
18. Quality Improvement/
19. Clinical Protocols/
20. (protocol* or algorithm* or leaflet* or pamphlet*).tw,kw.
21. computers, handheld/or minicomputers/
22. (mobile* or "cell phone*" or "smart phone*" or smartphone*).tw,kw.
23. ((app$1 or application*) adj3 (phone* or mobile* or cell*)).tw,kw.
24. Drug Monitoring/
25. (prescri* or monitor* or dosag* or dosing).ti.
26. or/4-25
27. 3 and 26
28. limit 27 to english language
29. (note or letter or editorial or comment).pt.
30. 28 not 29

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Chapter 3: Role of a theory framework in designing interventions in health

Numerous researchers have called for the use of theory in studies seeking to influence clinician behavioural change, in both the design and implementation of interventions in health. (99, 114) This call has especially been in relation to improving antibiotic prescribing. (115) A taxonomy for behaviour change has been developed (116), which has been used by the National Institute of Health and Care Excellence (NICE) UK, in their review of interventions in healthcare involving behavioural change. (117) These resources were useful in identifying potential implementation strategies for the published work of this thesis.

In determining what implementation strategies may be beneficial for a multifaceted intervention targeting the prescribing and monitoring of vancomycin, consideration was given to the importance of using a theoretical approach that would be well suited to implementation in a clinical care setting. The Theoretical Domains Framework (TDF) was selected as a tool to inform the design and implementation of a multifaceted strategy to improve the prescribing and monitoring of vancomycin presented in this thesis.

3.1 The Theoretical Domains Framework (TDF)

The TDF was developed by behavioural scientists and implementation researchers through a collaborative expert consensus process. (118) The Framework draws on psychological and organizational theory (119), and has recently been updated. (120) The TDF has been validated prospectively in studies implementing interventions and assessing the design of interventions. (121, 122) The TDF employed at the time of this work comprised 14 domains; 1) knowledge, 2) skills, 3) social/professional role identify, 4) beliefs about capabilities, 5) optimism, 6) beliefs about consequences, 7) reinforcement, 8) intentions, 9) goals, 10) memory, attention and decision processes, 11) environmental context and resources, 12) social influences, 13)

emotion and 14) behavioural regulation. (121) The TDF has undergone subsequent iteration and has now been consolidated to 12 domains. (123)

3.2 Application of Theoretical Domains Framework to the design of a multifaceted intervention targeting vancomycin dosing and monitoring

Junior doctors typically perform the majority of prescribing and monitoring of medicines including antibiotics in hospitals. (124-126) When undertaking a review of the barriers and enablers to implementing and accessing contemporary vancomycin recommendations, clinicians including junior doctors in our health network, were asked what they perceived the key barriers were. The barriers reported by junior doctors were collated and principally involved five domains of the TDF. These domains were knowledge, skills, beliefs about consequences, environmental context and resources. Responses from clinicians were used to inform design of our multifaceted intervention targeting vancomycin dosing and monitoring.

3.2.1 Knowledge

In responding to the identified domains; knowledge was addressed by delivering face-to-face educational sessions to doctors, and by provision of continuing professional development (CPD) modules for both junior doctors and pharmacists.

3.2.2 Skills

Skills were identified as practical ability to interpret serum vancomycin levels in relation to time of dosing, and use of this information to calculate the next dosing regimen. These practical skills were developed through doctors participating in clinical vignettes in the face-to-face educational sessions. These practical skills were reinforced in the online CPD modules.

3.2.3 Beliefs about consequences

Beliefs about consequences manifested in two predominating views by junior doctors regarding 1) the likelihood their patients could experience renal impairment when treated inappropriately with vancomycin (excessive dosing); and 2) could subtherapeutic dosing of vancomycin promote the emergence of resistant bacteria in their patient? Both issues were well summarised in one comment from a junior doctor, *"Does it really matter if I get the dose a bit wrong or forget to take a patient's blood test, or delay changing the dose (if it's too high or low)?* Whilst vancomycin is not as nephrotoxic as earlier thought (127, 128), nephrotoxicity remains a serious adverse effect of vancomycin. (129, 130) Persistent subtherapeutic vancomycin levels can result in the emergence of *S. aureus* colonies in infection which are no longer treatable with vancomycin or at least, have reduced susceptibility to vancomycin. (24, 131) Both of these key points were addressed in the content of face-to-face educational sessions, and CPD module.

3.2.4 Environmental context and resources

The domain of environmental context and resources was identified in interviews with junior doctors. Junior doctors reported having difficulty accessing computers in the clinical area of the hospital in real-time, limiting their ability to download the institutional vancomycin dosing and monitoring guideline when reviewing a patient they were treating with vancomycin. Acknowledging that computers were often in high demand, limiting intranet access to the guideline, a pocket version of the guideline was made available to all doctors and pharmacists in the institution.

3.2.5 Memory, attention and decision processes

As hospital staff could not be expected to remember all guideline content, the guideline was

available via hospital intranet. A pocket version of the guidelines was provided to prompt memory recall. The decision support table for dosing and monitoring within the guideline was refined and beta-tested for ease of use by a cohort of junior doctors and final year medical students (n=12). Each member of the beta-test group was independently provided the same clinical vignette and required to answer questions about what dose to prescribe, and when the next blood sample should be collected for TDM using the guideline. Their comments about interpreting the dosing table were used to refine the tool. An electronic vancomycin dosing support tool (incorporating body weight and renal function) was developed and added to a medication dosing application accessible on the hospital intranet.

3.3 Experience using the Theoretical Domains Framework

3.3.1 Introductory comments

This article was a qualitative study that investigated how clinician researchers engaged in implementation of interventions in healthcare, perceived and used the TDF. This paper has been included in this thesis as it demonstrates that I used the TDF in my research to improve the prescribing and monitoring of vancomycin in tertiary care. (132) The article also demonstrates collaborative research I led, which sought to better understand the utility of the TDF in healthcare research. As the TDF was a relatively new tool at the time of this research, I engaged the collaboration of an expert in health psychology and behavioural change, Professor Susan Michie from University College London as she is published widely on employing theory in the design of interventions to influence clinician behavior change (133-135), including interventions seeking to improve antibiotic use. (115)

3.3.2 Aim

The aim of this study was to explore the experience of clinician researchers from multiple disciplines who have used the TDF in projects seeking to effect behavioral change of healthcare professionals.

3.3.3 Hypothesis

We hypothesised that there would be considerable variance in how clinicians viewed the utility and application of the TDF, and that it would be helpful identifying barriers and enablers to project implementation projects in healthcare. We postulated that the findings from this study would be informative to others clinician researchers seeking to use the TDF in implementation projects.

Our first hypothesis was correct in that there was considerable variance in the way the TDF was used in implementation projects. Some clinicians used the TDF to assess the barriers and enablers to effect change, while others used it prospectively to inform their projects. There was considerable agreement in the utility of the 14 domains of the TDF being relevant to their research. Lastly, we postulated that our research on this topic would be informative to others clinician researchers considering using the TDF, and it would seem this was correct. Our 2015 publication has been cited 58 times in Scopus and 93 times in Google Scholar as of November 2019.

3.3.4 Publication

Phillips CJ, Marshall AP, Chaves NJ, Jankelowitz SK, Lin I, Loy CT, Rees G, Sakzewski L, ThomaS, The-Phung T, Wilkinson SA, Michie S. Experience of using the Theoretical Domains Framework across diverse clinical environments: a qualitative study. Journal of

Multidisciplinary Healthcare 2015: 8; 139-146.

Author contributions

I led this work from inception to publication. I conceived the study and was substantively involved in the design (70%) with coauthors contributing 30%. I was involved in development of the interview questions (35%) equally with Professor Andrea Marshall (35%) and Dr Gwyneth Rees (30%). Professor Marshall and Dr Chaves conducted the interviews acquiring the data with data analysis performed by Professor Marshall, Dr Wilkinson, Dr Lin and Dr Chaves 25% each. Professor Loy performed statistical analysis (100%). I principally wrote the first draft of the manuscript (90%), incorporated coauthors' comments and finalised the manuscript for submission

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ORIGINAL RESEARCH

Experiences of using the Theoretical Domains Framework across diverse clinical environments: a qualitative study

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Background: The Theoretical Domains Framework (TDF) is an integrative framework developed from a synthesis of psychological theories as a vehicle to help apply theoretical approaches to interventions aimed at behavior change.

Purpose: This study explores experiences of TDF use by professionals from multiple disciplines across diverse clinical settings.

Methods: Mixed methods were used to examine experiences, attitudes, and perspectives of health professionals in using the TDF in health care implementation projects. Individual interviews were conducted with ten health care professionals from six disciplines who used the TDF in implementation projects. Deductive content and thematic analysis were used.

Results: Three main themes and associated subthemes were identified including: 1) reasons for use of the TDF (increased confidence, broader perspective, and theoretical underpinnings); 2) challenges using the TDF (time and resources, operationalization of the TDF) and; 3) future use of the TDF.

Conclusion: The TDF provided a useful, flexible framework for a diverse group of health professionals working across different clinical settings for the assessment of barriers and targeting resources to influence behavior change for implementation projects. The development of practical tools and training or support is likely to aid the utility of TDF.

Keywords: barriers and enablers, behavioral change, evidence-based practice, implementation, health care, Theoretical Domains Framework

Introduction

Implementation science promotes the systematic uptake of research findings into clinical practice with the aim of improving patient care and health care outcomes. Implementation of evidence-based practice requires behavior change, but changing behavior is difficult.[1,2] Attempts at implementing evidence-based interventions that are tailored to the particular context have yielded mixed results.[3] A number of factors can influence the uptake of an evidence-based intervention, and the success of implementation efforts depends on a careful assessment of barriers to and enablers of the behavior to be changed. A theory-based assessment allows for the systematic identification of such factors, can guide implementation and evaluation design,[4] and may provide the basis for a better understanding of behavior change processes.[5–7] There are a multitude of theoretical models which explain various behaviors,[8] however, these are often difficult to access and understand by health professionals who do not have a psychology background.[9]

An integrative framework, the Theoretical Domains Framework (TDF),[10] has been designed as a vehicle to help apply theoretic approaches to interventions aimed

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at behavioral change.[11,12] The TDF was developed through an expert consensus process, including factor analysis and validation to identify psychological and organizational theory relevant to health practitioner clinical behavior change.[10] Following further refinement, it now comprises of 14 domains and 84 constructs that allows synthesis of a multitude of coherent behavior change theories into a single framework that allows assessment and explanation of behavioral problems and associated barriers and enablers, and inform the design of appropriately targeted interventions.[11,13] The TDF domains and their descriptors are outlined in Table 1; the 14 domains are 1) knowledge, 2) skills, 3) social/professional role and identity, 4) beliefs about capabilities, 5) optimism, 6) beliefs about consequences, 7) reinforcement, 8) intentions, 9) goals, 10) memory, attention, and decision processes, 11) environment context and resources, 12) social influences, 13) emotion, and 14) behavioral regulation.[11]

Table 1 The domains of the Theoretical Domains Framework (TDF)

TDF domain	Description
Knowledge	An awareness of the existence of something
Skills	An ability or proficiency acquired through practice
Social/professional role and identity	A coherent set of behaviors and displayed personal qualities of an individual in a social or work setting
Beliefs about capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use
Optimism	The confidence that things will happen for the best, or that desired goals will be attained
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behavior in a given situation
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus
Intentions	A conscious decision to perform a behavior or a resolve to act in a certain way
Goals	Mental representation of outcomes or end states that an individual wants to achieve
Memory, attention and decision processes	The ability to retain information, focus selectively on aspects of the environment, and choose between two or more alternatives
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behavior
Social influences	Those interpersonal processes that can cause an individual to change their thoughts, feelings, or behaviors
Emotion	A complex reaction pattern, involving experiential, behavioral, and physiological elements, by which the individual attempts to deal with a personally significant matter or event
Behavioral regulation	Anything aimed at managing or changing objectively observed or measured actions

Note: Data from Cane et al.[11]

The TDF has been used prospectively to facilitate implementation of health care interventions[14–16] and retrospectively in theory-based process evaluation.[11,14,17] Most studies have relied on qualitative analyses of interview or focus group data, which are time consuming, although questionnaire measures of the TDF have recently been published.[18–20] Evaluation of the use of the TDF in everyday practice by those implementing projects in the clinical environment is limited, therefore we aimed to explore the experiences of health care practitioners from various disciplines using the TDF. This included examining the perceived relevance and utility of the TDF domains in identifying barriers to evidence uptake and when designing implementation strategies to facilitate behavior change in a variety of clinical settings. We anticipated that insights from this cohort would be useful to clinicians or researchers using or contemplating using the TDF.

Materials and methods

Design

Mixed methods were used to examine the experiences, attitudes, and perspectives of health professionals in understanding and use of the TDF in healthcare implementation projects.

Participants

Participants were health professionals from a variety of medical, nursing and allied health disciplines who were implementing healthcare improvement projects. Participants were identified from a cohort of Australian National Health and Medical Research Council (NHMRC) Translating Research into Practice (TRIP) Fellows (http://www.nhmrc.gov.au/grants/apply-funding/translating-research-practice-trip-fellowships) who had received training on the TDF. Training consisted of a 1-day master class on theories and frameworks to assess barriers and enablers to evidence-based health service change, including an introduction to the TDF. Participants were recruited via the email distribution network of the 2012 NHMRC TRIP Fellows. All ten prospective participants who used the TDF in their implementation projects were invited and consented to participate in the study.

Materials

Interview questions were theoretically informed by the TDF and formulated by three researcher-participants

(AM, CP, and GR). They were further refined after external review by one author (SM) and three experts on the TDF. Interview questions (available from authors on request) focused on the characteristics of participants, and their understanding and use of TDF in their project. A survey was developed based on the 14 domains of the TDF (available from authors on request) to evaluate perceived usefulness and relevance of each TDF domain to identify barriers in each participants' organization to inform implementation strategies to change clinical practice behavior. The participants were instructed to rate on a 7-point Likert scale (1 being least relevant and 7 the most relevant) the relevance and usefulness of the 14 theoretical domains to their individual health care projects.

Procedure

This study was approved by the Griffith University Human Research Ethics Committee (Southport, QLD, Australia: NRS/15/13/HREC). Informed consent was obtained prior to interview commencement. The questions and survey were sent to participants in June 2013 to allow them sufficient time to consider their responses prior to the interview. Respondents submitted survey responses via email. Telephone interviews were conducted by two authors (AM and NC) during July and August 2013. An interview guide was used to ensure consistency of data collection. The duration of each interview was approximately 45 minutes. No interviews were repeated. Interviews were recorded and transcribed verbatim.

Analysis

Demographic data collected in the telephone interview were summarized using descriptive statistics. Descriptive statistics were calculated to summarize frequency of responses about the relevance and usefulness of the 14 domains of the TDF. Distribution of responses was examined using histograms. Qualitative analysis involved the complementary methods of deductive content[21] and thematic analysis.[22] Deductive content analysis was led by NC and thematic analysis by AM, SW, and IL, each who individually identified then discussed broad themes within the data. Group discussion was then used to further refine the themes.

Results

Ten health professionals participated (Table 2). The mean age of participants was 40 years (32–43 years). Seven participants held higher research degrees at the doctoral level and three held Masters level qualifications or equivalent. Participants were employed at tertiary hospitals (n=7; 70%), primary care (n=2; 20%), or residential care services (n=1; 10%). Health disciplines were diverse comprising medical specialists (n=3), pharmacists (n=2), physiotherapists (n=2), psychology researcher (n=1), dietitian (n=1), and occupational therapist (n=1). Clinical practice areas included pediatrics, neurology, maternal health, aged care, quality use of medicines, infectious diseases, clinical education, and musculoskeletal health.

Table 2 Participants characteristics and aims of implementation project

Discipline	Aim of implementation project	Setting
Academic health psychology	Integrate psychosocial care into low vision rehabilitation services	Community
Dietetics	Implement nutrition practice guidelines for women with gestational diabetes	Tertiary hospital
Medical	Reduce antipsychotic use in patients with Huntington disease in residential care	Residential care
Medical	Implement an antimicrobial stewardship program in an intensive care unit	Tertiary hospital
Medical	Improve the use of secondary prevention medications after stroke	Tertiary and secondary hospital
Occupational therapy	Increase intensive upper limb training for children with hemiplegia	Community
Pharmacy	Improve vancomycin prescribing and monitoring	Tertiary hospital
Pharmacy	Improve management of medications when patients are fasting or nil by mouth	Tertiary hospital
Physiotherapy	Implement self-management approaches for lower back pain, to educate health practitioner	Community
Physiotherapy	Implement guidelines to prevent falls for patients after hip fracture	Tertiary hospital

Seven participants used the TDF prospectively to inform their projects; three participants used the TDF retrospectively either to formally analyze data or to help understand challenges with implementation. There was little difference in how participants rated relevance and usefulness of individual TDF domains for their implementation projects, therefore only usefulness ratings are presented in Figure 1. The small sample size precluded further statistical testing but a number of domains (eg, knowledge and skills) show Likert scale ratings skewed toward the higher (more useful) range.

Thematic analysis of interview transcripts identified three main themes and associated subthemes including: 1) reasons for use of the TDF (increased confidence, broader

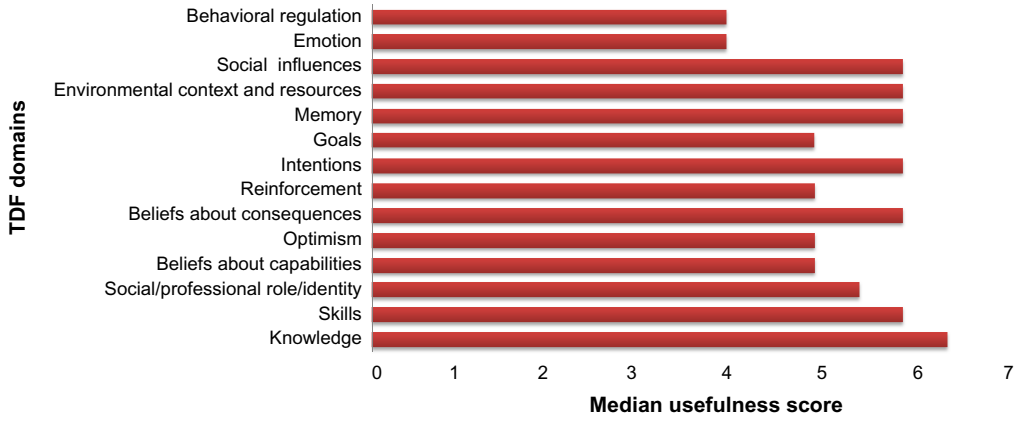

Figure 1 Median Likert score by TDF domain.
Abbreviation: TDF, Theoretical Domains Framework.

perspective, and theoretical underpinnings); 2) challenges using the TDF (time and resources, operationalization of the TDF); and 3) future use of the TDF.

Theme 1: reasons for use of the TDF

Most participants were influenced to use the TDF following attendance at a master class that introduced the TDF; one participant (academic health psychologist; GR) had previous knowledge of and experience with using the TDF.

Increased confidence

Participants reported that their confidence in undertaking their projects increased when using the TDF. They reported using the TDF to ensure that unwarranted assumptions about barriers and enablers were not made and also used the TDF to double-check decisions already made. The TDF was used to ensure "all aspects of possible influences" were considered in specific projects and "to ensure that I captured the most significant barriers or enablers to implementation". For one participant this provided "confidence that I wasn't missing something in the process" something that was considered difficult "without using some kind of framework". Many of the participants described the TDF as a "systematic approach" to identifying barriers and enablers that then allowed the researcher "to make sure that the interventions … put into place were appropriate".

Broad perspective

The use of the TDF to identify a wide variety of possible barriers and enablers to behavior change was seen as key to the development of targeted interventions that were likely to bring about change. With barriers and enablers systematically identified, participants were able to select and tailor interventions to the specific context in which they were working. This was considered a good strategy to "better identify where to invest … time and resources".

Theoretical underpinnings

The theoretical underpinnings of the TDF were considered an important and often mentioned strength. While other theoretical approaches were considered by some participants, the fact that the TDF provided a synthesis of concepts from a number of psychological theories of behavior change was seen as particularly appealing because it meant that you did not have to try "to put a square peg in a round hole" and it helped by "broaden(ing) the understanding of the barriers of how to develop an intervention".

Theme 2: challenges faced when using the TDF

Although all participants acknowledged the benefits of using the TDF, they identified several challenges including time and resources issues, and steps in operationalization of the TDF.

Time and resource issues

The time taken and resources required to use the TDF were amongst the most frequent challenges described by participants. Almost all participants had used qualitative methods in their projects, thus associated interviewing, transcribing, and analyzing data were considered time consuming and resource intensive. Some used the TDF retrospectively (applied to previous data) and acknowledged the trade-off between rigor and feasibility with one participant commenting "… I would have loved to have used [the TDF] prospectively … but I just didn't have the time to do that,

so I used a retrospective approach". Using the retrospective approach (because of time restraints) was considered a limitation because there was a lack of certainty whether "I really covered all the domains and identified all possible influences". For another participant, using the TDF was considered time effective because it was believed that this approach would assist in streamlining the investment of time and resources required for implementation.

Challenges to operationalization of the TDF

Some participants described operationalization of the TDF as challenging because of a perceived lack of familiarity with the framework. There were considerable variations in the reported understanding of the framework. Developing a clear understanding of the domains and associated constructs for each domain was complicated by lack of clear operational definitions such that one participant commented that "the language is a bit different to what I'm used to … It's just that some [constructs] I still don't really understand … I don't have a strong conceptual understanding". The use of the TDF was also challenging because of perceived "overlap" between domains that resulted in repetition. For one participant it was as though the "huge overlap" made the domains "blend into each other" and made it hard to "tease out what I was trying to do".

Difficulty understanding the domains and associated constructs was reinforced by another participant who commented, "it wasn't exactly clear to me how the domains should be interpreted". The constructs that were listed gave me "… a bit more of an idea …" however the perceived language complexity was considered "frustrating". The number of constructs within and across domains was also considered an issue with one participant describing this about being "… far too complicated … and unwieldy" and another indicating being selective about what aspects of the TDF informed survey development because of the concern that using the TDF in its entirety would "… push the envelope …" and be burdensome to the participants. One participant described interpretation of the domains and constructs as a subjective exercise that "… comes down to the interpretation of the TDF …" that was influenced by "… what sort of lens you are looking [through]…"

As the TDF is informed in part by psychological theories, some participants felt disadvantaged by not having a background in psychology. One participant said it "took a little while to really get my head around it". Attempting to develop further understanding of the domains and constructs through reading literature did not always assist with a clearer understanding because "what [an author] interpreted as a particular domain was completely not what I'd interpreted as a particular domain". In contrast, the two participants with postgraduate qualifications in psychology did not articulate any specific challenges in understanding the domains or constructs within the TDF. For one, reading "… quite broadly around the TDF" helped to "… [understand] that each of the constructs fleshed out what was in the domain". However, the other acknowledged that "it's all a bit open to interpretation" although this wasn't viewed as problematic. It was suggested that an established and validated process to analyze the TDF would have been helpful during analysis because "it was difficult to code …". Once coding was completed it was then challenging to determine which domains in the data were most important.

Unfamiliarity with psychological constructs meant that, for some participants, their collaborators or participant groups were hesitant in accepting the TDF framework for their implementation projects. For example, one participant's supervisor said, "I think that's going to be far too complicated for the (surgeons) – they'll get a bit scared …" Another challenge in operationalization of the TDF related to uncertainties in how to apply the results to effect change. One participant commented, "… having the domains is really helpful, but I think there needs to be a better way to compare … them". One participant made the observation that if you were using the TDF to explore individual behavior then you might overlook other important factors including "systems level" considerations (eg, cultural change and leadership) although acknowledged that the TDF might pick up these issues used to evaluate barriers and enablers at the organizational level.

Uncertainties with application of the TDF were also related to published studies that had very modest effects or failed to affect behavioral change despite being theoretically informed[14,17] "… I just have to say that I'm a bit disheartened that even though something might be theory informed there's no guarantees that it is going to be translating to great impact or great success. That's the only thing because we recently read an article [...] it was a spectacular failure … It was the exact same department, the exact same sort of method of rollout, and things like that".

Demonstrating the influence the TDF might have on the results of implementation projects was seen as challenging and although all participants believed that the TDF enhanced their ability to comprehensively identify possible barriers and enablers, the extent to which it positively influenced study outcomes was less certain. One participant commented, "I'm getting good results but with a multidimensional intervention it's hard to know if using the TDF to hone my intervention and dissemination, whether that is the result of the TDF. So the

TDF, I think it's helped me to make some informed choices upstream and the results I'm getting downstream at this point look quite good but it'll be difficult to draw the association between good results and use of the TDF".

Theme 3: thoughts on future use of the TDF

All participants stated they would use the TDF in future projects and seven suggested strategies they felt could help in its future use. Two participants suggested developing an instrument through which the TDF constructs could be evaluated. A questionnaire was considered a way of quantifying the results of the TDF and could also "take some of the time burden away from using it, because it was incredibly time consuming". The disadvantage of restricting the TDF to a questionnaire was limiting the "richness of information that you would [get] using an … interview approach". Others suggested development of resources to support use of the TDF (eg, formalized training, practical written guidelines).

Discussion

This study provides insight into how the TDF was operationalized, used, and experienced by health professionals to implement evidence-based changes in practice across a range of clinical settings. Our findings highlight that the TDF is considered a useful approach providing a systematic, comprehensive, and theory-derived process to identify barriers to clinical practice change that can help identify target behaviors for change and inform implementation strategies. However, even in this group of experienced health professionals who had received some training in the TDF, challenges remain regarding the comprehension and independence of domains, the feasibility of using such an in-depth procedure prospectively in clinical practice, and how best to use findings to direct implementation activities.

Our study found that the TDF was a flexible tool that could be used across different settings and in different ways to understand implementation issues and plan implementation activities. The TDF was used both prospectively and retrospectively using interview, observational, and survey data. All the domains proved to be relevant to understanding barriers across all contexts and could be applied to identify issues at the individual, team, or organizational level. These findings concur with a review of 50 qualitative studies exploring clinicians' perceptions and experiences of clinical quality improvement interventions, which found that all TDF domains were relevant and accounted for barriers and enablers to clinical practice change. Consistent with our findings, the TDF was flexible enough to be applied across clinical quality interventions and the authors proposed that it may form the basis for a model of clinical quality policy implementation.[23]

Our findings suggest that there is likely to be considerable variation in how researchers and practitioners interpret and use the TDF and highlight that if the TDF is to move significantly beyond the academic literature on implementation science toward a tool that can be routinely used in practice, more needs to be done to inform healthcare professionals of the domains and constructs. Even within our sample of professionals who had received tutorials on theories and frameworks to systematically inform interventions, confusion was still present. Some participants struggled with the complexity of the TDF language and the perceived lack of independence between the domains. These findings are not entirely new, as similar challenges have previously been reported.[18,24,25] The resource intensive nature of using the TDF has been previously reported as a challenge in its use, although may be balanced with achievement of sustainable behavior change.[26] Perhaps, this is not surprising given that the validation of the TDF was conducted via recruitment of eligible participants who possessed a good understanding of psychological theory.[11]While our participants did receive limited training, most had no previous experience in utilizing theories or frameworks to guide implementation interventions. Some participants had already commenced their projects prior to the training on behavior change. Therefore it may be argued that the study cohort is more representative of health care professionals/researchers on-the-ground with limited or no behavior change theory experience and without the benefit of a behavior change expert on their project team. Previous authors have recommended that research teams include a health psychologist in order to utilize the TDF[10] and many published studies on the TDF have one or more behavioral change experts as an author.[14,15] Unfortunately, when dealing with implementation issues in practice this is often not the case with a lack of access, resourcing, and time as described in our study. Accessible training (eg, online) including tangible examples of the TDF domains across a variety of settings that can demonstrate subtle differences between constructs would be useful for healthcare professionals/researchers. Workshops have been conducted since March 2013 (subsequent to the current study) in the United Kingdom (http://yhahsn.org.uk/improvement-academy/trainng-workshops/ and http://www.ucl.ac.uk/behavior-change) to support use of the TDF.

One strength of our study was its reach across a range of clinical settings and health care professionals involved in

the implementation of current evidence-based health care interventions. However, a number of limitations need to be acknowledged. Firstly, as a cohort of NHMRC TRIP Fellows, the authors of this paper were the designers of the study, the interview guide, and participants. Furthermore, participants were interviewed by their peers. Interview responses (and the delivery of interview questions), therefore, may have been more strongly influenced by social desirability bias and confirmation bias than if the participant was completely independent from the research process. Secondly, our interview did not probe deeply into beneficial aspects of the TDF. Whilst most participants reported that the TDF was useful and they would use it again, the reasons for this were not fully elucidated. Thirdly, it was not possible in this study to determine in detail, exactly which domains were considered (accepted or rejected) and how the TDF directly influenced implementation strategies and the process by which participants linked domains of the TDF to target behaviors for change. It was also not possible to identify specifically which domains were considered to be overlapping or confusing. This is an important area for future research to explore in order to improve the utility of the TDF for researchers and health care practitioners more widely. Finally, this study was conducted prior to the participants having completed their implementation projects. So while the findings provide us with some insight into how useful the TDF was in assisting health professionals to design implementation projects, it is not possible to comment on the overall success of the projects that utilized the TDF.

Our study demonstrated that the TDF is a useful, flexible framework for health professionals managing implementation that assists by providing a structured framework for the assessment of barriers and enablers and targeting of resources to influence behavioral change. The TDF is appropriate to be used by a variety of healthcare disciplines, across a range of clinical settings, and to aid in the development of implementation projects. To overcome the challenges regarding comprehension of the TDF, as well as to enhance the feasibility of using such an in-depth procedure prospectively in clinical practice, practical tools, and training or support is likely to aid the utility of TDF so it can be used most effectively by health care professionals and researchers on-the-ground in the design and implementation of health care projects.

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Author contributions

All authors were involved in the concept and design of this study. Interview questions were developed by APM, CJP, and GR. Interviews were conducted by APM and NJC and analysis was performed by APM, SAW, IL, and NJC. Statistics were performed by CTL. All authors contributed to the writing of the manuscript and read and approved the final version.

Disclosure

The authors report no conflicts of interest in this work.

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Chapter 4: Clinical practice guidelines for vancomycin

4.1 Development of clinical practice guidelines

As described in Chapter 1, the prescribing and monitoring of vancomycin has been reported to be poor or suboptimal at best. (136-140) In seeking to improve this, we sought to distil the core messages of the North American consensus vancomycin guideline (141), with adaptation of the Australian Therapeutic Guidelines on vancomycin (43), into a local clinical practice guideline for vancomycin dosing and monitoring. This guideline was trialled in an earlier pilot study conducted on a single unit at Flinders Medical Centre and subsequently refined for the studies in this thesis. (142)

It has been documented that guidelines alone are not enough to change practice, and that doctors often do not follow guidelines, including guidelines for antibiotics. (87, 89, 143, 144) Others have also commented specifically that provision of vancomycin guidelines alone is insufficient to effect change. (145)

Leading developers and funders of guidelines around the world such as Australia's National Health and Medical Research Council (NHMRC), the English National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guideline Network (SIGN), the Guideline International Network (G-I-N) and the United States Institute of Medicine (IOM) produce guidance on how to implement guidelines. The are no 'magic bullet' interventions to improve Professional practice in health, however multifaceted interventions have been recommended to implement guidelines (95), including providing educational sessions (146), continuing professional education (91, 92), provision of printed material (147), and engagement of opinion leaders to promote guidelines uptake. (148, 149) Reminders have also been shown to reinforce

physician adoption of guidelines. (150) Our study sought to examine the effect of a multifaceted intervention implementing vancomycin dosing and monitoring guidelines.

4.2 Initial study: implementing contemporary vancomycin guidance in hospital

4.2.1 Introductory comments

This initial study was undertaken to examine the effectiveness of implementing a clinical practice guideline (CPG) on vancomycin prescribing, monitoring, patient safety (nephrotoxicity) and clinical cure rate of infection. The implementation consisted of a multifaceted intervention of educational sessions, case-based discussions, email reminders, and provision of a pocket guideline to support the hospital wide introduction of the CPG.

4.2.2 Aim

To examine the impact of a multifaceted intervention to implement clinical practice guidelines for vancomycin dosing and monitoring across multiple units within a tertiary hospital.

4.2.3 Hypothesis

We hypothesised that this intervention would have a favourable effect on prescribing and monitoring of vancomycin.

4.2.4 Summary

The findings from this study demonstrated the multifaceted intervention caused a proportional improvement in all primary outcomes as well as clinical cure rates, however effects on most outcomes were non-significant. The trends in the data were modest yet encouraging. Based upon these results we decided a larger, adequately powered study, conducted over a longer

duration of time was required to determine if the interventions were effective to improve vancomycin prescribing and monitoring, and if any effects could be sustained over time (Chapter 7).

4.2.5 Publication

Phillips CJ, and Gordon DL. Pharmacist-led implementation of a vancomycin guideline across medical and surgical units: impact on clinical behavior and therapeutic drug monitoring outcomes. Integrated Pharmacy Research and Practice 2015; 4: 145-152.

Author contribution

The study was designed collaboratively by myself (90%) and Professor Gordon (10%). I drafted and submitted the application for ethical approval. I principally acquired the data (95%) with contribution from Professor Gordon (5%). Both authors interpreted the data, myself 80% and Professor Gordon 20%. I performed the statistical analysis and wrote the manuscript (90%) with Professor Gordon making important intellectual contributions (10%).

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ORIGINAL RESEARCH

Pharmacist-led implementation of a vancomycin guideline across medical and surgical units: impact on clinical behavior and therapeutic drug monitoring outcomes

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Background: Vancomycin is the antibiotic of choice for the treatment of serious infections such as methicillin-resistant *Staphylococcus aureus* (MRSA). Inappropriate prescribing of vancomycin can lead to therapeutic failure, antibiotic resistance, and drug toxicity.

Objective: To examine the effectiveness of pharmacist-led implementation of a clinical practice guideline for vancomycin dosing and monitoring in a teaching hospital.

Methods: An observational pre–post study design was undertaken to evaluate the implementation of the vancomycin guideline. The implementation strategy principally involved education, clinical vignettes, and provision of pocket guidelines to accompany release of the guideline to the hospital Intranet. The target cohort for clinical behavioral change was junior medical officers, as they perform the majority of prescribing and monitoring of vancomycin in hospitals. Assessment measures were recorded for vancomycin prescribing, therapeutic drug monitoring, and patient outcomes.

Results: Ninety-nine patients, 53 pre- and 46 post-implementation, were included in the study. Prescribing of a loading dose increased from 9% to 28% (P=0.02), and guideline adherence to starting maintenance dosing increased from 53% to 63% (P=0.32). Dose adjustment by doctors when blood concentrations were outside target increased from 53% to 71% (P=0.12), and correct timing of initial concentration measurement increased from 43% to 57% (P=0.23). Appropriately timed trough concentrations improved from 73% to 81% (P=0.08). Pre-dose (trough) concentrations in target range rose from 33% to 44% (P=0.10), while potentially toxic concentrations decreased from 32% to 21% (P=0.05) post-implementation. Infection cure rates for patients increased from 85% to 96% (P=0.11) after the guideline was implemented.

Conclusion: The implementation strategy employed in this study demonstrated potential effectiveness, and should prompt additional larger studies to optimize strategies that will translate into improved clinical practice using vancomycin.

Keywords: antibiotics, Australia, behavioral medicine, clinical guidelines, implementation, intervention, pharmacists

Introduction

Vancomycin, after nearly 60 years of use, is still the intravenous antibiotic of choice for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection.[1–3] Inappropriate prescribing of vancomycin is associated with therapeutic failure, antibiotic resistance, and kidney toxicity.[4] Therapeutic drug monitoring in patients receiving vancomycin has been shown to significantly increase clinical efficacy and to decrease the rate of kidney toxicity.[5] A small number of newer antibiotics for the treatment of

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MRSA infection have been licensed by the US Food and Drug Administration (FDA) in recent years; however, it is critical to reserve these agents for when vancomycin fails.[6] Development of clinical practice guidelines (CPGs) has been identified as a way to improve the utilization of vancomycin.[7] Education and dissemination of CPGs on vancomycin prescribing and monitoring are measures to ensure best standard of care for patients receiving this antibiotic.[8] A previous pilot study where a pharmacist implemented vancomycin dosing and monitoring guideline in a single surgical unit in our institution, Flinders Medical Centre, Bedford Park, South Australia, produced favorable and statistically significant results.[9] It was unclear if a similar implementation strategy targeting physicians working in all medical and surgical units across our institution would produce similar results to the pilot. The aim of the current study was to examine the impact of implementation of a CPG for vancomycin dosing and monitoring across all medical and surgical units in our institution.

Methods

Study design and procedure

The present study was approved by the Southern Adelaide Clinical Human Research Ethics Committee (approval 12312/51711). The ethics application for this study contained a waiver of consent as participants were not going to be exposed to an increase risk of harm. The waiver of consent was consistent with the National Statement of Ethical Conduct in Human Research. The study was an observational pre–post design undertaken at Flinders Medical Centre, a teaching hospital with a wide variety of medical and surgical specialties, located in metropolitan South Australia. The study was comprised of three phases. Phase 1 was a retrospective audit of medical records of patients receiving vancomycin therapy over a 3-month consecutive period (pre-implementation). Phase 2 was an education program delivered to junior medical officers (JMOs) and registered pharmacists, dissemination of a pocket version of the guideline to these two groups, and release of the CPG to the hospital Intranet.

Pharmacists received education due to their supportive role to improve antibiotic use at organizational and practice level, which has been well documented.[10] Release of the CPG was accompanied by a formal email sent from the hospital Trainee Medical Officer Unit to all JMOs advising them of the new guideline and requesting their adherence to it. Phase 3 was a subsequent audit of medical records of patients receiving vancomycin over a 3-month period of the following year (post-implementation) depicted in Figure 1. The same months were selected for audit pre- and post-implementation to avoid seasonal variance in the use of vancomycin. Resource allocation for implementation in this study was principally funded through partial salary support.

Participants

JMOs

Medical officers (year 1 post-completion of medical school) registered with the Trainee Medical Officer Unit in our institution were included in the current study. JMOs were the chosen target cohort to measure behavioral change in their clinical practice, as they are the medical staff principally involved in prescribing, ordering of pathology tests, and interpreting test results to inform subsequent prescribing and monitoring of the intravenous antibiotic vancomycin.

Patients

Patients ≥18 years of age receiving vancomycin therapy were identified from vancomycin blood concentrations recorded in

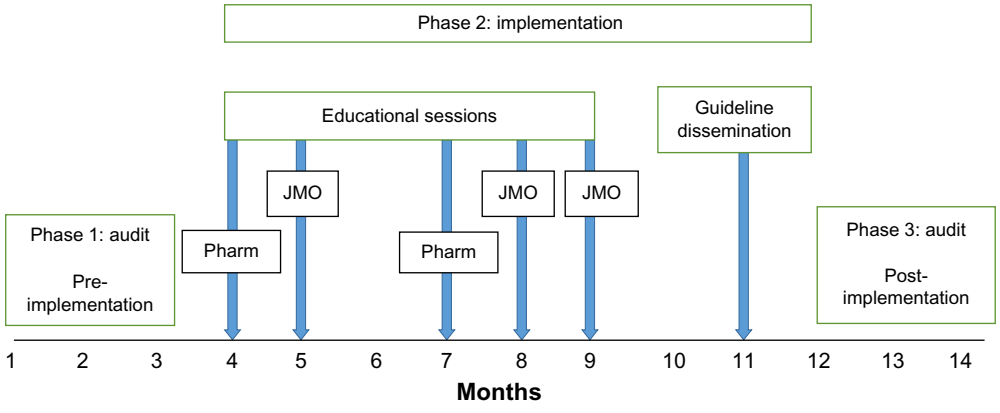

Figure 1 Temporal schematic of audits and implementation of vancomycin clinical practice guideline.
Abbreviations: JMO, junior medical officers; Pharm, registered pharmacist.

the daily hospital therapeutic drug monitoring report. Patients were eligible for inclusion if they had at least one measurable vancomycin concentration and had received more than one dose of vancomycin.

Intervention

CPG

The vancomycin dosing and monitoring guideline for adults that was implemented in this project was a modified version of the guideline used in a prior pilot study at our institution.[9] Modifications to the guideline were: 1) an improved decision support table to assist prescribers to adjust the dose in response to results of vancomycin blood concentrations and kidney function; and 2) inclusion of an embedded hyperlink to a hospital Intranet-based creatinine clearance calculator (glomerular filtration rate [GFR] + calculator; Southern Adelaide Health Service, Adelaide, SA, Australia) to aid doctors to choose an appropriate individualized dose. Also included were general explanatory notes on how to use the guideline. The amended guideline underwent beta-testing by eight JMOs and two final-year medical students from Flinders University School of Medicine, co-located in our hospital, to ensure the guideline was "fit for purpose". All JMOs and pharmacists were sent an email advising them of the release of the guideline and how to access it via the Intranet.

Key features of guideline

Prescribing was as follows: a loading dose of 25 mg/kg actual body weight (maximum 2 g vancomycin). Maintenance dosing was determined by creatinine clearance (CrCl): >90 mL/min, 1.5 g vancomycin 12 hourly; CrCl 60–90 mL/min, 1 g vancomycin 12 hourly; CrCl 20–59 mL/min, 1 g vancomycin 24 hourly; CrCl <20 mL/min, 1 g vancomycin every 2–7 days.

Therapeutic drug monitoring was as follows: The time initial blood concentration was to be measured was determined by CrCl; CrCl >60 mL/min required bleeding the patient before the fourth dose; CrCl 20–59 mL/min required bleeding the patient before the third dose; CrCl <20 mL/min required bleeding the patient at 48 hours post-dose. Subsequent monitoring was stipulated every 48 hours until stable blood concentration was achieved (target, 15–20 mg/L); thereafter, patients were to be bled twice weekly. Pre-dose (trough) blood concentrations were to be taken approximately 1 hour pre-dose.

Implementation process

Education

Three 60-minute face-to-face education sessions on vancomycin prescribing and monitoring were provided to JMOs. Pharmacists received two educational sessions. Attendance at all education sessions was voluntary, with no incentives offered. The tutorial contained content on contemporary vancomycin treatment covering issues of antibiotic resistance – specifically how subtherapeutic dosing can promote bacterial resistance to vancomycin, the need for appropriate dosing, monitoring, issues of vancomycin kidney toxicity, and practical advice using clinical vignettes on how to determine an appropriate dosage regimen, how to monitor, interpret blood concentration results, and how to use this information to amend subsequent dosing. Education was delivered by the principal investigator, who has expertise in clinical education, antibiotics, and therapeutic drug monitoring. Fidelity of the education sessions was ensured by using the same content, and clinical vignettes were conducted over the same duration for all sessions.

Provision of printed material

A pocket laminated version of the guideline (10 cm ×6 cm), suitable for attachment to hospital identification badges, was provided to all JMOs and pharmacists.

Email alert

All JMOs and pharmacists were sent an email advising them of the existence of the guideline and how to access it via the Intranet.

Assessment measures

Patient characteristics

Medical records were used to extract details of patients; residence, comorbidities, and colonization with multi-resistant bacterial organisms. Indication for vancomycin, dosage, time of dose, and duration were recorded. Concomitant aminoglycoside antibiotic use was also recoded, as was the treating team (medical or surgical), length of stay in hospital, whether surgery was required to help resolve the infection, in addition to data on cure and readmission to hospital for the same infection. Laboratory data collected included serum creatinine (to determine kidney function), vancomycin blood concentrations, and microbiological data of organism and source of isolate. Vancomycin minimum inhibitory concentration (MIC) was determined using a Vitek® 2 compact (bioMerieux Inc., Durham, NC, USA) on MRSA isolates (when performed by a laboratory).

Clinical behavior of medical officers

Prescribing of vancomycin and ordering of pathology blood tests for vancomycin concentrations was assessed by audit

of drug charts and medical records. Measurement was conducted on the proportion of patients prescribed: 1) a loading dose, 2) maintenance doses adherent to the guideline, 3) appropriate dose adjustment (ie, increase or decrease) by prescriber in response to blood concentrations of vancomycin outside target range, 4) measurement of initial vancomycin blood concentration adherent with the guideline (ie, after the appropriate number of doses), and 5) appropriately timed drawing of blood for vancomycin pre-dose (trough) blood concentration in relation to the time of last dose.

Patient outcomes

Electronic hospital pathology database and medical records were used to measure: 1) the number of days until patients attained a measured vancomycin blood concentration in target range, 2) the proportion of vancomycin concentrations patients attained within target range, 3) infection cure rates, and 4) the frequency of kidney toxicity.

Educational attendance and guideline measurement

The number of JMOs and pharmacists that attended educational sessions on vancomycin dosing and monitoring was recorded, as was the frequency of downloads of the guideline from the hospital Intranet.

Definitions

Guideline target range for vancomycin blood concentrations was 15–20 mg/L.[11,12] Kidney toxicity was defined as a rise in serum CrCl of ≥50% or 0.5 mg/dL on 2 or more consecutive days of vancomycin therapy from baseline.[13,14] Clinical cure was resolution of all clinical and laboratory signs and symptoms of infection.[15]

Statistical analysis

Data were stored in Microsoft Excel, and descriptive statistics were used to report results. The IBM Statistical Package for the Social Sciences (SPSS) version 22 was used to perform statistical testing. The Student's *t*-test was performed to compare continuous variables, and the chi-square test was used to compare categorical variables to measure difference between the two groups. Observed difference were considered statistically significant when $P<0.05$.[16]

Results

Patients

There were 99 patients included in this study, with 53 pre- and 46 post-implementation. The median patient age was 75 years vs 63 years, respectively, and median weight was 78 kg vs 77 kg in the pre- and post-implementation groups, respectively. Patient characteristics are presented in Table 1, while indication for treatment and microbiological data are presented in Table 2.

Table 1 Baseline characteristics of patients receiving vancomycin treatment

	Pre-implementation n=53 n, (%)*	Post-implementation n=45 n, (%)*
Characteristic		
Age years; median (IQR)	75 (59–82)	63 (46–75.5)
Male sex	32 (60.32)	31 (67.39)
Residence in RACF	20 (37.73)	10 (67.39)
Prior admission to hospital ≤12 months	39 (73.58)	31 (67.39)
Prior colonisation with MRO		
In ≤12 months		
MRSA	20 (37.74)	13 (28.26)
VRE	11 (20.75)	8 (17.39)
CrCL; median (IQR) (mL/min)	77.28 (47.07–109.68)	103.4 (70.63–129.8)
Comorbidities		
Diabetes	18 (33.96)	10 (21.74)
Congestive heart failure	6 (11.30)	6 (13.04)
Ischemic heart disease	10 (18.87)	8 (17.39)
Valvular disease	5 (9.43)	5 (10.87)
Malignancy	6 (11.32)	12 (26.09)
Medication		
Concomitant aminoglycoside	8 (15.09)	15 (32.61)
Penicillin/beta-lactam allergy	20 (37.74)	10 (21.74)
Treating team		
Medical	21 (39.62)	25 (54.35)
Surgical	32 (60.38)	21 (45.65)

Note: *Unless otherwise stated.
Abbreviations: IQR, interquartile range; RACF, residential aged care facility; MRO, multi-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant Enterococcus; CrCl, creatine clearance; min, minute.

Clinical behavior of medical officers

Prescribing of vancomycin loading doses increased significantly from five (9.43%) to 13 (28.27%) doses (P=0.02). The proportion of maintenance doses prescribed that were adherent to the guideline increased without significance from 52.83% to 63.04% (P=0.32). The frequency of prescribers amending (increasing or decreasing) a dose when a vancomycin blood concentration was either low or high, increased non-significantly from 53.85% pre-implementation to 70.59% post-implementation (P=0.12). The appropriate timing when the initial vancomycin blood concentration was measured (after the correct number of doses based on kidney function) increased from 43.40% to 56.52% post-implementation (P=0.23). Appropriately

Table 2 Infection site requiring vancomycin treatment and microbiological data

	Pre-implementation n=53 n, (%)*	Post-implementation n=45 n, (%)*
Infection site		
Bacteremia	15 (11.32)	16 (34.72)
Synovial/orthopedic	3 (5.66)	2 (4.34)
CNS/cranial	5 (9.43)	1 (2.17)
Skin and soft tissue infection	17 (32.08)	14 (30.43)
Osteomyelitis	5 (9.43)	6 (13.04)
Urinary	1 (1.89)	4 (8.70)
Respiratory	6 (11.32)	7 (15.21)
ENT	1 (1.89)	0
GI/abdominal infection	7 (13.2)	2 (4.35)
Pyrexia of unknown origin	6 (11.32)	3 (6.52)
Bacterial organism#		
MRSA	18/56 (32.14)	13/49 (26.53)
MIC (mg/L) performed	11/18 (61)	11/13 (85)
≤0.5	4/11 (36)	4/11 (36)
1.0	5/11 (45)	7/11 (63)
2.0	2/11 (18)	0
Enterococcus spp	6/56 (10.71)	8/49 (16.33)
CoNS	4/56 (7.14)	5/49 (10.20)
Staphylococcus epidermis	4/56 (7.14)	5/49 (10.20)
MSSA	4/56 (7.14)	3/49 (6.12)
Streptococcus spp	5/56 (8.92)	0
Other	13/56 (23.2)	8/49 (16.33)
No growth detected	13/56 (23.2)	8/49 (16.33)

Notes: *Unless otherwise stated; #note, some patients had infection with more than one organism. Not all MRSA isolates had MIC performed.

Abbreviations: GI, gastrointestinal; Spp, bacterial species; MRSA, methicillin-resistant *Staphylococcus aureus*; CoNS, coagulate negative *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; MIC, minimum inhibitory concentration; CNS, central nervous system; ENT, ear nose and throat.

measured pre-dose (trough) vancomycin blood concentrations in relation to the time the previous dose was administered improved non-significantly from 72.57% to 80.57% (P=0.08) (Table 3).

Patient outcomes

The median time for patients to attain an in-target vancomycin trough concentration in their blood decreased from 5 (interquartile range [IQR] 4.25–13.75) to 4 (IQR, 3–5.5) days (P=0.12) post-implementation. The proportion of vancomycin blood concentrations in our CPG target range (15–20 mg/L) increased non-significantly from 32.93% to 42.55% (P=0.10), while the proportion of concentrations in the lower shoulder range (10–14.9 mg/L) remained unchanged at 20.73% pre-implementation and 20.57% post-implementation. Potentially kidney toxic concentrations (>20 mg/L) decreased from 52 (31.37%) to 30 (21.28%) post-implementation (P=0.05). The incidence of nephrotoxicity observed did not change from 11.32% pre- and 10.87% post-implementation.

Sub-analysis found eight of the eleven (72.73%) participants (four of six pre-and four of five post-implementation) with nephrotoxicity had one or more potentially toxic vancomycin concentrations >20 mg/L. In contrast, in the 87 participants without nephrotoxicity, 37 of 87 (42.53%) (14 pre- and 23 post-implementation) had one or more vancomycin concentrations >20 mg/L (P=0.31).

All cures of infection for which vancomycin was prescribed increased from 84.48% pre-implementation to 95.83% post-implementation (P=0.11) (Table 3). Sub-analysis of the three of eleven (27.27%) infections that failed to respond to therapy (two pre- and one post-implementation) involved patients that had one or more sub-therapeutic vancomycin concentrations <10 mg/L. No association was observed between clinical failure and vancomycin concentrations <10 mg/L (P=0.33).

Educational attendance and guideline process measures

Fifty-one of 75 (68%) JMOs registered with the hospital Trainee Medical Officer Unit had documented attendance at voluntary educational sessions provided on vancomycin dosing and monitoring. Thirty-five of 47 (74%) pharmacists from the study site attended an education session. From uploading the guideline to the hospital Intranet until the close of the study, the guideline had a monthly download mean of 86.5 (standard deviation [SD] 21.06).

Discussion

The implementation of a vancomycin CPG across medical and surgical units was associated with a statistically significant increase in the number of patients being prescribed loading doses. This result is meaningful, as a recent systematic review found that doctors prescribing loading doses of vancomycin enabled their patients to more rapidly attain blood target levels of vancomycin known to kill bacteria.[17] There was a non-significant trend to an increase in adherent measurement of pre-dose (trough) blood concentrations. This result is also meaningful, as it has been previously reported that vancomycin concentrations collected at inappropriate times produce spurious results, leading doctors to make incorrect treatment decisions.[18] There was a substantial reduction of borderline significance in the proportion of potentially toxic concentrations (>20 mg/mL), which have been associated with kidney toxicity.[19–21] This finding warrants further investigation to confirm this observation. Doctors' prescribing of appropriate vancomycin maintenance doses increased from approximately half to nearly two-thirds (63%) that were guideline-adherent. This compares closely with 64% appropriate maintenance

Table 3 Clinical behavior of medical officers and patient outcomes

	Pre-implementation n=53 n, (%)*	Post-implementation n=45 n, (%)*	*P*-values
Clinical behaviour			
Prescribing a loading dose	5 (9.43)	13 (28.27)	0.02
Adherent maintenance dose	28 (52.83)	29 (63.04)	0.32
Dosage adjusted correctly	21/39 (53.85)	24/34 (70.59)	0.12
Adherent timing of initial conc	23 (43.40)	26 (56.52)	0.23
Adherent pre-dose conc	164 (72.57)	26 (80.57)	0.08
Patient outcomes			
Days of admission; median (IQR)	20 (10.5–32.5)	16 (9–29.5)	0.13
Days of vanco treatment; median (IQR)	10 (4.25–13.75)	6 (4–16.5)	0.31
Days until first conc in target; median (IQR)	5 (4.25–13.75)	4 (3.5–5.5)	0.12
Conc in target range	54 (32.93)	60 (42.55)	0.10
Potentially kidney toxic conc	52 (31.37)	30 (21.28)	0.05
Sterile site cure	27/30 (90)	19/19 (100)	0.27
Non-sterile site cure	22/28 (78.57)	27/29 (93.10)	0.14
All cure of infection	49/58 (84.48)	46/48 (95.83)	0.11
Kidney toxicity	6 (11.32)	5 (10.87)	1.0

Note: *Unless otherwise stated.
Abbreviations: Conc, blood vancomycin concentration; Vanco, vancomycin; IQR, interquartile range.

dosing achieved in another study post-implementation of vancomycin guidelines,[22] and is considerably better than (50%) the result that was reported in a study conducted in a Hong Kong teaching hospital.[23] Post-implementation in the current study, there was a much larger improvement in dosage adjustments, from 54% pre-implementation to 71% post-implementation, made by JMOs when trough concentrations were outside target range, suggesting patients were more closely monitored in the current study.

Adherence to the CPG for measurement timing when pre-dose (trough) blood concentrations were taken (relative to time of preceding dose) increased in excess of 80% post-implementation in the present study and compared similarly (78%) to a study conducted in California that implemented vancomycin guidelines.[24] While the effect size of provision of pocket guidelines is unknown, a Cochrane review on the effect of printed educational material on professional practice and health care outcomes found providing written material to health care staff did have a beneficial effect.[25] The effect of implementation on the proportion of vancomycin concentrations in the target range (43%) did reproduce the result observed in the pilot study (44%),[9] but was non-significant in the current study. Forty-three percent of all concentrations within our CPG target range highlights the fact that there is still considerable work to be done to improve this result; however, some authorities use a wider target range (10–20 mg/L),[26] and when our results were measured against this range, some 63% of our concentrations were within range.

The rates of nephrotoxicity observed in the present study remained encouragingly unchanged despite the post-implementation group receiving many more loading doses, and having double the percentage of patients concomitantly receiving aminoglycoside antibiotics, which are also known to cause kidney toxicity.[27,28] Since the introduction of the CPG, the median duration of vancomycin therapy decreased from 10 days pre-implementation to 6 days post-implementation. It is not possible to determine if this reduction was due to reasons such as the prescribing of more loading doses, thus enabling the antibiotic to act more rapidly, or because doctors were requesting blood tests more promptly and were adherent to the guideline. The cure rate for both sterile and non-sterile infections also improved somewhat post-implementation.

A strength of the guideline implemented in this study is that it was based on contemporary international and national vancomycin consensus guidelines.[11,29] The guideline was developed and endorsed by local opinion leaders in the fields of pharmacy, infectious diseases, and clinical pharmacology from the hospital it was implemented in. This is meaningful, as a systematic review of the influence of local opinion leaders showed that their influence was successful in promoting evidence-based practice.[30] Importantly, the CPG was beta-tested on JMOs and final-year medical students, who were the target audience, and the outcomes used to measure the impact of guideline implementation were highly objective. Finally, details of the implementation were provided. This is important, as it has been reported that studies involving guideline implementation often do not provide enough information

about the implementation process to be informative to others seeking to change practice.[31] Further, it has been reported that there is an imperfect evidence base in guideline dissemination and implementation studies, with little consideration given to resource allocation.[32] The current study adds to the evidence base on this topic.

Limitations

The present study has a number of limitations. Review of "usual clinical care" paper-based medical records and medication charts is problematic, as data extraction can be difficult; however, the accuracy of research assistants performing data collection was audited and was found to be of high accuracy. While the educational component of implementation included JMOs assigned to various different medical and surgical units, the study was conducted in a single hospital, and thus, the findings may not necessarily be generalizable. The small sample size is a clear limitation. While there was improvement in some outcome measures, there is still substantial room for improvement. From the attendance records, we were unable to confirm if some JMOs or pharmacists went to more than one education session, thus potentially reducing the total count of professionals receiving education. In addition, there may be selection bias in effect, as those professionals that were interested to improve their knowledge and skills were the ones that attended the educational sessions.

Conclusion

The pharmacist implementation of a CPG across medical and surgical units significantly increased the proportion of loading doses prescribed by doctors for patients receiving vancomycin. A larger-powered study may help determine if proportional improvements observed in other measures of prescribing and monitoring vancomycin translate into statistically significant changes in clinical behavior and meaningful outcomes for patients and their doctors.

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Disclosure

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Chapter 5: Knowledge and self-confidence of health professionals to clinically use vancomycin

It is important for health professionals to be prepared, competent and up to date with contemporary practice in their field. Drug therapy is a core and often complex area for both pharmacists and junior doctors. (151, 152) Knowledge of how to prescribe and monitor antibiotics safely and effectively is even more challenging, as inappropriate use of antibiotics can lead to the emergence of bacteria that are less susceptible or resistant to antibiotics. (153)

5.1 Impact of a continuing professional development module on pharmacists' preparedness to provide contemporary advice on the clinical use of vancomycin

5.1.2 Introductory comments

Providing advice on prescribing, dosing and monitoring of medicines is a core role of pharmacists. (154) This is also true for antibiotics. (155) After the introduction of the internationally accepted North American vancomycin consensus guidelines (88), it was unclear how prepared Australian pharmacists would be to provide contemporary advice based on the content of these guidelines. Additionally, it was also unclear how well pharmacists would score in a knowledge assessment after completing a continuing professional development (CPD) module based on the content from the guidelines and a clinical vignette. In this study, we assessed pharmacists' preparedness (measured by self-reported confidence) to answer numerous questions on vancomycin and provide contemporary advice on vancomycin to healthcare colleagues. We developed and disseminated a CPD module based on core elements of the vancomycin guideline and performed a knowledge assessment of pharmacists' understanding of guideline recommendations post-completion of the CPD.

5.1.3 Aim

The study aim was to assess the preparedness of a cohort of Australian pharmacists to provide contemporary advice on the clinical use of vancomycin. A secondary aim was to evaluate pharmacists' knowledge scores post completion of a locally developed CPD module on vancomycin.

5.1.4 Hypothesis

Pharmacists would have variable levels of self-confidence when providing contemporary advice on the clinical use of vancomycin to health professional colleagues, and knowledge scores would be higher post completion of a CPD module.

5.1.5 Summary

We found that pharmacists generally had high self-reported confidence to provide advice on the clinical use of vancomycin to other health professionals. However, this was less so for providing advice on intravenous administration rates, and on how to manage an infusion related reaction (red man syndrome), which have been reported by others to be problematic areas of confidence for nursing staff. (22, 156) When knowledge scores were assessed post CPD, we found that attained scores were very high >90% for all but two questions. The responses to these two questions, were similarly low to responses about self-reported confidence for these topics, which provides opportunity for future work to improve this preparedness and knowledge gap of pharmacists. The strong knowledge scores attained post CPD provided an impetus for developing a similar CPD module on vancomycin for junior doctors (Chapter 5.2).

5.1.6 Publication

Phillips CJ, Wisdom AJ, Eaton VS, Woodman RJ, McKinnon RA. The impact of a pilot

continuing professional development module on hospital pharmacists' preparedness to provide contemporary advice on the clinical use of vancomycin. SpringerPlus 2016; 5:331

Author contributions

I developed the concept and study design (90%) with Vaughn Eaton (10%). I developed the survey questions (80%) and the CPD module (80%) with each coauthor contributing 5%. Review of the CPD module was provided by Professor David Gordon and Associate Professor Matthew Doogue acknowledged in the publication. I collected the data (100%). Data was analysed by Professor Richard Woodman (70%), Professor Ross McKinnon (5%), Alice Wisdom (5%) and myself (20%). I wrote the manuscript (80%) with coauthors all contributing importantly for intellectual content (5%). All authors approved the final manuscript which I submitted for publication.

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The impact of a pilot continuing professional development module on hospital pharmacists' preparedness to provide contemporary advice on the clinical use of vancomycin

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Abstract

Background: Revised international clinical guidelines for the antibiotic vancomycin have changed the advice pharmacists need to provide to medical and nursing colleagues.

Objectives: (1) To determine the self-reported confidence of hospital pharmacists to provide contemporary advice on vancomycin and (2) to evaluate hospital pharmacists' knowledge to provide contemporary advice on vancomycin following a pilot continuing professional development (CPD) module.

Methods: The study was a prospective two-phase design in an Australian teaching hospital. Phase one: a survey of pharmacist self-reported confidence to eight questions on providing contemporary advice on vancomycin. Responses were recorded using a Likert scales. Phase two: The provision of a pilot online CPD module on vancomycin containing knowledge-based assessment based on a clinical vignette. Likert scales recorded self-reported confidence were reported as median and interquartile range (IQR). Knowledge assessment was reported using descriptive statistics. The main outcome measure were the self-reported confidence, and knowledge of pharmacists regarding provision of contemporary advice on clinical vancomycin use.

Results: Response rates for surveys; confidence n = 35 (72.9 %) and knowledge n = 31 (58.5 %). Phase one: confidence was highest regarding vancomycin dosing and monitoring with 71.4–81.6 % of respondents agreeing or strongly agreeing that they were confident in these domains. Respondents agreeing or strongly agreeing were least confident regarding intravenous administration and infusion related reactions, 57.1 and 45.7 % respectively. Respondents who provided advice on vancomycin >10 times in the prior 12 months reported significantly higher confidence in; therapeutic range 1 (IQR 1–2) versus 2 (IQR 1–3) p = 0.02; amending dosage based on therapeutic drug monitoring results 2 (IQR 1–3) versus 3 (IQR 2–3) p = <0.001, and providing general advice to prescribers on vancomycin 2 (IQR 1–3) versus 2 (IQR 2–4) p = <0.009. Knowledge questions were answered correctly post CPD by >75 % of pharmacists.

Conclusion: Pharmacists' self-reported confidence to managing vancomycin was variable but generally high. Knowledge scores were consistently high after pharmacists completed a pilot CPD module on vancomycin. These data

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provides impetus for a randomised controlled study across multiple sites to determine the extent to which pharmacist knowledge on vancomycin can be attributed to completion of an online CPD.

Keywords: Antibiotic, Confidence, Continuing education, Continuing professional development, Knowledge, Vancomycin

Background

Confidence and knowledge are important components for healthcare professionals' ongoing competence to practice. Australian national law requires registered health practitioners to undertake continuing professional development (CPD) with the intention of ensuring knowledge is contemporary (Australian Health Practitioners Regulation Agency 2014). Participating in CPD can meaningfully change knowledge, skills and attitudes of healthcare professionals (Cervero and Gaines 2015). Professional pharmacy organisations in Australian and internationally affirm the importance of maintaining currency of knowledge through CPD (International Pharmaceutical Federation 2002; The Society of Hospital Pharmacists of Australia 2012; Pharmaceutical Society of Australia 2010; Driesen et al. 2007).

Vancomycin is an intravenous antibiotic used for nearly 60 years in the treatment of Gram-positive infections and remains the therapy of choice for methicillin resistant *Staphylococcus aureus* (MRSA) infection (Rybak et al. 2013). While a small number of newer antibiotics to treat MRSA have been licenced by the United States Food and Drug Administration in recent years, it remains vital to reserve these agents for clinical situations when vancomycin fails (Yu et al. 2014). In an era of increasing antibiotic resistance, necessitating higher therapeutic target concentrations and more aggressive dosing of vancomycin (Lomaestro 2011), it is imperative to ensure the ability of pharmacists' to confidently provide accurate contemporary advice to medical and nursing colleagues. This is important as there have been reported lack of confidence by pharmacists' post evaluation of programs where pharmacists are required to provide clinical and therapeutic advice, which has led pharmacists to call for more training (Rosenthal et al. 2010).

A North American consensus clinical practice guideline devised by medical and pharmacy experts and revised Australian guidelines on vancomycin have changed the nature of the advice pharmacists provide to medical and nursing staff (Rybak et al. 2009a; Antibiotic Expert Group 2010). Amongst a number of changes in these guidelines, doctors need to frequently prescribe loading doses and larger subsequent doses to achieve a higher serum therapeutic targets and be more cautious with monitoring (Rybak et al. 2009b). Nursing staff are required to infuse vancomycin over revised durations of time to accommodate larger doses (Wilson and Estes 2011; Karch 2012), while being more vigilant in observing for adverse effects, particularly infusion related reactions such as 'red man syndrome' (Hoelen et al. 2007).

Since these new recommendations for vancomycin have come into effect, it is unclear how confident pharmacists are in recommending these changes to their professional colleagues. Furthermore, it is uncertain to what extent pharmacists' confidence in their ability to provide contemporary advice is consistent with their actual knowledge of the revised recommendations for vancomycin.

The aims of this study were threefold. Firstly, to assess pharmacist baseline self-reported confidence in their ability to provide contemporary advice on vancomycin. Secondly, to assess pharmacist knowledge scores after completion of an online vancomycin CPD module. Lastly, to explore any association between pharmacists self-reported confidence scores on providing vancomycin management advice with actual assessed knowledge scores post-completion of a CPD module on vancomycin dosing and monitoring.

Methods

This pilot study was a prospective two phase design. The study was conducted at Flinders Medical Centre (FMC), a 580-bed university teaching hospital located in Adelaide, South Australia. Study participants were identified from the register of pharmacists employed in the Division of Pharmacy at FMC.

The primary outcomes for the study were (1) to determine if the years of experience as a registered pharmacist have an effect on the self-reported confidence of pharmacists to provide advice on the management of patients receiving vancomycin; and (2) if providing advice on vancomycin more than ten times in the prior 12 months resulted in greater pharmacist self-reported confidence to provide advice on vancomycin management. The secondary outcome was to report pharmacist knowledge scores following a structured online Continuing Professional Development (CPD) module on vancomycin dosing and monitoring.

Phase one: confidence survey

In June 2012 all identified FMC pharmacists (n = 48) were sent an email inviting them to participate in a

survey assessing their confidence in providing vancomycin management advice. The survey was designed to capture self-reported confidence levels in providing advice on effective and safe management of patients receiving vancomycin. Questions were provided on core domains of pharmacists' involvement in vancomycin management; dosing, therapeutic drug monitoring and intravenous drug administration (see Additional file 1). The survey questions were structured as statements of confidence on the various domains. The degree to which the pharmacists agreed or disagreed with each statement was recorded using a five-point Likert scale (Likert 1932). The following responses represent each point of the Likert scale: Strongly agree (1), agree (2), not sure (3), disagree (4) and strongly disagree (5). The phase one survey was hosted online by Survey Monkey, Portland, OR, USA (www.surveymonkey.net). No incentives were offered to complete the confidence survey.

Phase two: CPD and knowledge assessment

In February 2013, all identified FMC pharmacists (n = 53) were emailed an invitation to undertake an electronic CPD on Vancomycin Dosing and Monitoring designed by local experts and opinion leaders from FMC. The email contained the CPD with questions (see Additional file 2), a copy of our institutions vancomycin clinical practice guideline, and a link to assessable questions based on a practical clinical vignette which were also hosted on Survey Monkey.

The vancomycin CPD module had formal learning objectives; (1) to familiarise pharmacists with new institutional clinical practice guidelines on vancomycin dosing and monitoring, secondly, (2) to understand the importance of the provision of appropriate and individualised advice on vancomycin in clinical practice to medical and nursing colleagues, (3) to understand how to provide contemporary advice on vancomycin. The CPD module was endorsed by the Society of Hospital Pharmacists of Australia and the Australian Pharmacy Council for accreditation (number S2013/4) for 4 CPD credits. CPD credits accrue toward the Pharmacy Board of Australia's mandatory requirement for compulsory ongoing professional development. Forty CPD credits are required annually to maintain registration in Australia (Pharmacy Board of Australia 2010). The opportunity to obtain CPD credits was the only incentive offered to undertake the CPD module and complete the assessable questions.

The CPD module contained background on vancomycin regarding; the development of the vancomycin clinical practice guideline, efficacy, safety and reduced bacterial susceptibility to vancomycin along with pharmaceutical formulations available from the state wide pharmacy service that supplies our local health network. Evidence-based, contemporary material was presented to cover all aspects of a pharmacists' role in providing advice in the management of patients receiving vancomycin. The CPD included a clinical vignette with ten assessable multiple choice questions, with only one correct answer from a choice of four answers. The questions covered similar domains to the confidence survey undertaken in phase one. Supplementary questions were asked of participants' regarding the relevance of the CPD content and delivery mode (see Additional file 1. The study was granted full ethics approval from the Southern Adelaide Clinical Human Research Ethics Committee (approval number 123.12).

Statistical analysis and sample size

Data was analysed using the IBM Statistical Package for the Social Sciences (SPSS) version 22.0. Confidence scores recorded in a Likert scale were expressed as a median and IQR, and knowledge was reported using percentage of correctly answered responses for each question. Mann-Whitney U tests were used to compare median confidence scores where applicable with a p value of <0.05 considered statistically significant (Peacock and Peacock 2011). Required sample size was based on 80 % power to detect a mean difference of 0.5 in each Likert scale response between two groups, assuming a standard deviation of 0.55 for each Likert scale response, using a Mann Whitney U test for analysis and an underlying normal distribution of the responses. The means and medians for our data were all similar suggesting a normal distribution and the standard deviations ranged from 0.5 to 1.0 for each question.

Results

Phase one: confidence survey

All 48 pharmacists employed in June 2012 in the Division of Pharmacy were sent the confidence survey of which 35 completed (72.9 % response rate). There were 22 (62.9 %) pharmacists with greater than 5 years of practice experience. (Table 1). From the 35 responding pharmacists, 51.4 % reported providing advice on vancomycin to health professionals more than 10 times in the prior 12 months. The majority of respondents agreed or strongly agreed that they possessed confidence in providing advice on vancomycin to health professionals. Median confidence scores ranged from 2 (IQR 1–2) to 3 (IQR 2–3) across the eight questions. Pharmacists' self-reported confidence was poorest in regards to provision of advice on vancomycin administration rates and the management of infusion related reaction. Pharmacists with less than 5 years of experience were significantly more confident in providing advice on the timing of first

Table 1 Hospital pharmacists' mean self-reported confidence scores providing vancomycin management advice by years of practice experience

Confidence domains	Median (IQR) confidence scores			p value[1]
	All respondents n = 35	<5 years of experience n = 13	>5 years of experience n = 22	
Therapeutic target range	2 (1–2)	1 (1–3)	2 (1–3)	0.04
Timing of first blood concentration	2 (1–2)	1 (1–3)	2 (1–4)	0.02
General advice to prescribers	2 (2–2)	2 (1–3)	2 (1–4)	0.32
Loading dose	2 (2–2)	2 (1–3)	2 (1–4)	0.13
Amending dosing based on TDM	2 (2–3)	2 (1–3)	2 (1–3)	0.10
Frequency of blood concentrations	2 (2–3)	2 (1–4)	2 (1–3)	0.83
Administration rate	2 (2–3)	3 (1–5)	2 (1–4)	0.13
Management of infusion related reactions	3 (2–3)	3 (1–5)	3 (1–5)	0.36

1 = strongly agree, 2 = agree, 3 = not sure, 4 = disagree, 5 = strongly disagree

TDM therapeutic drug monitoring, *IQR* interquartile range, [1] Using Mann-Whitney

vancomycin blood concentrations median score of 1 (IQR 1–3) versus 2 (IQR 1–4) (p = 0.02); and knowing the therapeutic target range 1 (IQR 1–3) versus 2 (IQR 1–3) (p = 0.04) compared to pharmacists with more than 5 years of experience. The years of practice experience had no significant effect on the mean confidence scores for the remaining seven questions (Table 1).

The confidence of pharmacists with recent experience in providing vancomycin management advice, defined as providing advice greater than ten times in the past 12 months is presented in Table 2. Pharmacists with more recent experience had significantly higher confidence in providing general advice on vancomycin to prescribers, median 2 (IQR 1–3) versus 2 (IQR 2–4) (p = <0.009). These pharmacists also reported a statistically significant greater awareness of the therapeutic target range, median 1 (IQR 1–2) vs 2 (IQR 1-3) (p = 0.02), and confidence to amending vancomycin doses based on sub or supra-therapeutic drug monitoring results compared to pharmacists with less experience, median 2 (IQR 1–3) versus 3 (IQR 2–3) (p = <0.001) (Table 2).

Phase two: CPD and knowledge assessment

In February 2013, all FMC pharmacists (n = 53) were invited to complete a structured CPD module on vancomycin with knowledge assessment. A total of 31 pharmacists (58.5 % response rate) undertook the CPD module and completed the ten assessable questions. There were 17 (54.8 %) pharmacists with greater than 5 years of practice experience. Some 22 (71 %) female participants

Table 2 Hospital pharmacists' mean self-reported confidence scores on providing vancomycin management advice by recent experience with vancomycin

Confidence domains	Median (IQR) confidence scores		p value[1]
	Provided advice <10 times in last 12 months n = 17	Provided advice >10 times in last 12 months n = 18	
Therapeutic target range	2 (1–3)	1 (1–2)	0.02
Timing of first blood concentration	2 (1–4)	2 (1–3)	0.11
General advice to prescribers	2 (2–4)	2 (1–3)	0.009
Loading dose	2 (1–4)	2 (1–3)	0.10
Amending dosing based on TDM	3 (2–3)	2 (1–3)	<0.001
Frequency of TDM	2 (1–3)	2 (1–4)	0.85
Administration rate	2 (1–4)	2 (1–5)	0.75
Management of infusion related reactions	3 (1–5)	2.5 (1–5)	0.63

1 = strongly agree, 2 = agree, 3 = neutral, 4 = disagree, 5 = strongly disagree

TDM therapeutic drug monitoring, *IQR* interquartile range, [1]Using Mann-Whitney

that completed the questions. Eight of the ten questions elicited correct responses ranging from 93.6–100 %. Questions regarding intravenous administration and management of adverse reactions were answered correctly with a relatively lower frequency of 77.4 % each (Table 3). All respondents agreed or strongly agreed that the CPD activity was of a high educational quality, well presented, up to date, worthwhile and achieved the stated learning objectives. All respondents agreed that the online CPD format suited them.

Table 3 Hospital pharmacists' knowledge scores for domains on providing vancomycin management advice post continuing professional development

Knowledge domain	*n* (%)
Therapeutic target range	31 (100)
Timing to take first blood concentration (in renal impairment)	31 (100)
Frequency of blood concentration following dose stabilisation	30 (96.8)
Timing of blood concentration following dose adjustment	30 (96.8)
Amending dosing based on TDM	30 (96.8)
Subsequent maintenance dose	30 (96.8)
Loading dose	29 (93.6)
Timing of first blood concentration	29 (93.6)
Administration rate	24 (77.4)
Management of infusion related reaction	24 (77.4)

TDM therapeutic drug monitoring

Confidence versus knowledge

Those pharmacists that self-reported 1 (strongly agree) or 2 (agree) on the Likert scale to questions about confidence in phase one were considered confident. The responses from phase one were plotted against the knowledge scores attained in phase two. Percentage scores were higher for all domains post-completion of CPD as measured by knowledge scores (Fig. 1).

Discussion

This study sought baseline self-reported confidence of pharmacists to provide contemporary advice on vancomycin clinical management to health professional colleagues in light of revised recommendations. In addition, this study set out to assess knowledge of vancomycin management after completion of a CPD on the topic. There are several strengths to this study. Firstly, the survey questions were designed to capture responses to key domains of vancomycin management reflected in expert consensus guidelines (Rybak et al. 2009a). Secondly, the CPD was developed by local experts and opinion leaders in clinical pharmacy, clinical pharmacology, infectious diseases and clinical education, which is meaningful as a Cochrane review on the effect of local experts on professional practice found that local experts can successfully influence evidence-based practice (Flodgren et al. 2011). Lastly, the questions designed to assess

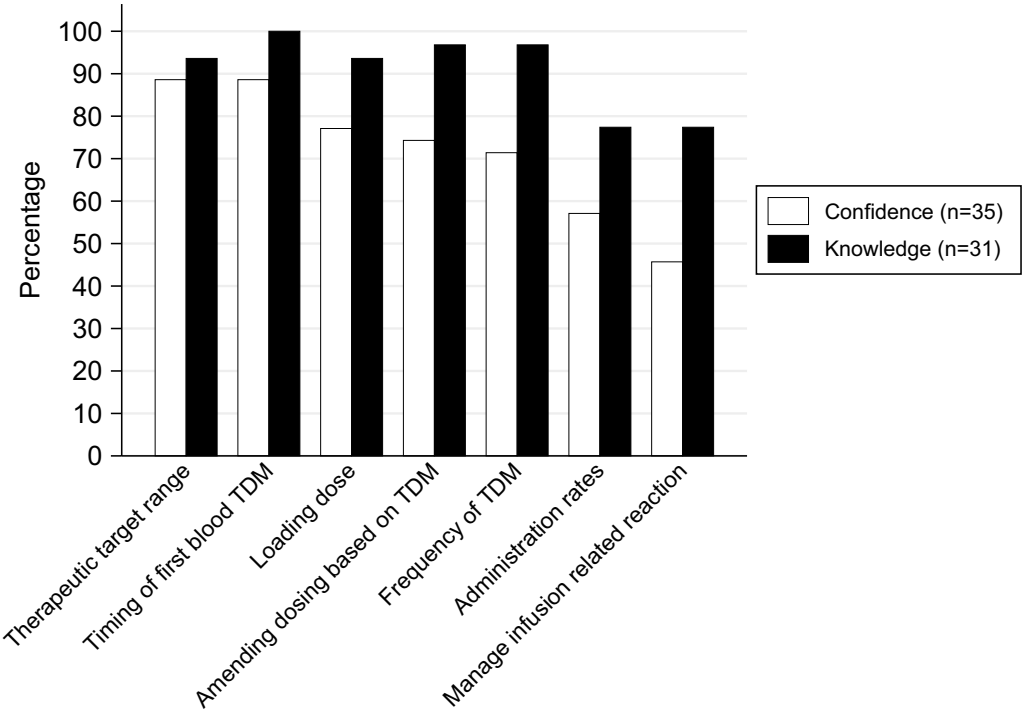

Fig. 1 Percentage of hospital pharmacists who agreed or strongly agreed they were confident to provide advice on vancomycin and correct knowledge scores for the same domains post continuing professional development. *TDM* therapeutic drug monitoring

pharmacist knowledge post CPD were derived from a clinical vignette with very practical every-day application to interprofessional advice directly affecting patient care. The use of clinical vignettes in online continuing education has been associated with health professionals being more likely to make evidence-based decisions (Casebeer et al. 2010).

An overall response rate of more than fifty percent of the invited pharmacists was observed in both phases of the study. A number of online surveys of pharmacists related to CPD have attracted lower response rates than those obtained in this current study (Ang et al. 2013; Power et al. 2011, 2008). Specifically the response rate of 73 % obtained in phase one is more than that reported (67 %) by other authors examining pharmacist self-reported confidence (Awaisu et al. 2015). A response rate of 59 % was achieved in phase two which is also greater than that obtained (44 %) from another pharmacist knowledge assessment conducted post CPD in our department (Grzeskowiak et al. 2015). While barriers have been reported to undertaking CPD online (Donyai et al. 2011), this did not seem to be overly problematic for this CPD, with all respondents agreeing the online mode suited them. The only potential incentive to participate was in phase two where CPD credits were available post-completion of the module. The department did not overly encourage pharmacist participation in the study. FMC Pharmacy Department has a view to encourage and support participation in CPD while acknowledging that ultimately it is the responsibility of the individual. Pharmacists must ensure they are competent and capable of discharging their duties as luminaries on pharmacy CPD have recently stated (Tofade et al. 2015). Further, pharmacists should undertake CPD to meet educational needs for their scope of practice (McMahon 2015).

Overall, pharmacists reported greatest self-confidence in the domains of therapeutic drug monitoring, followed by dosing advice and least confident to providing advice on intravenous administration of vancomycin and managing infusion related reactions. Interestingly there was no difference in self-reported confidence for those with less than 5 years' experience except regarding when to draw the first blood sample to measure a vancomycin concentration. This is noteworthy as it has been reported that if patients have blood drawn too early in the treatment (i.e. serum levels are not at stead-state concentration), this can lead to medical staff misinterpreting concentrations and subsequently prescribing inappropriate dosages (Morrison et al. 2012). What impacted most on pharmacist confidence was recent experience providing advice on vancomycin rather than their years of practice experience. Pharmacists that had provided advice on more than ten occasions in the prior year reported significantly more confidence regarding; provision of general advice on vancomycin to doctors, knowing the therapeutic target range and interpreting concentrations to amend dosage regimens.

After completion of the vancomycin CPD, more than three-quarters of pharmacists surveyed answered all knowledge questions correctly. A score in excess of ninety per cent was obtained for the majority of questions. These results compare similarly to those of other authors where a high knowledge score was attained post completion of a targeted continuing pharmacy education program. (Charpentier et al. 2012).

Questions about managing infusion-related problems and intravenous administration rates generated the lowest self-reported confidence and knowledge scores. These findings are concerning as vancomycin features prominently in medication errors made by nursing staff with intravenous administration errors rating highly (Hoefel et al. 2008; Fahimi et al. 2008). Further, the rate of administration of vancomycin infusion can directly precipitate an infusion related reaction such as red man syndrome (Lilley and Guanci 1995; Garrelts and Peterie 1985; Wallace et al. 1991; Sivagnanam and Deleu 2003; Bauters et al. 2012). This finding suggests more can be done to ensure pharmacist competency in the provision of advice on administration rates and management of infusion-related problems. While baseline confidence on a number of questions was high, a greater knowledge score was attained for all questions post CPD, which is likely to reflect favourably on the content and practical nature of the CPD as was confirmed in responses to supplementary questions.

The results of this study suggest that years of practice as a pharmacist do not routinely translate into higher confidence regarding provision of advice on vancomycin management. Based on these findings, completing a vancomycin CPD module such as the one developed for this study may be of value to pharmacists irrespective of their years of experience if it is clinically relevant to their scope of practice.

Limitations

Considering potential limitations of this study. The confidence survey in phase one and CPD in phase two were sent to the same departmental email distribution list, however due to workforce issues the absolute number of pharmacists employed varied between the phases of the study. Participants in each phase are thus not necessarily the same individuals. The study was not a before and after design and was conducted in a single centre. However, as more than half the pharmacists employed in our institution participated in each phase of the study, the results are likely to be reflective of the wider cohort.

Lastly, selection bias may have been in effect in that those pharmacists who were more confident with contemporary practice or more amendable to improving their knowledge may have chosen to participate, while those in greatest need of updating their knowledge may have elected not to participate.

Conclusion

Pharmacists provide an important and valuable role assisting their medical and nursing colleague by providing contemporary guidance on medication management. Pharmacists' ability to provide advice on revised recommendations on vancomycin management is important to ensure the clinically safe and efficacious use of this essential antibiotic. This study adds to the literature on pharmacists' confidence and knowledge to provide clinical advice. Pharmacists self-reported a variable but generally high degree of confidence in the use of vancomycin. After completion of a pilot online CPD on vancomycin, pharmacists achieved consistently high scores in knowledge assessment. Our results need to be interpreted with caution. A larger and randomised multi-centre study is required to determine if these findings are reproducible.

Additional files

Additional file 1. Vancomycin Continuing Professional Development with knowledge assessment.

Additional file 2. Questions on pharmacists' confidence to provide advice on contemporary vancomycin management.

Authors' contributions

CJP and VSE designed the study. CJP, AJW, RAM and RJW analysed the data. CJP developed the Continuing Professional Development module. All authors contributed to the manuscript generation and editing. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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5.2 Junior doctors' preparedness to prescribe, monitor and treat patients with vancomycin

5.2.1 Introductory comments

Junior doctors have been reported as being under prepared to prescribe in a number of areas of clinical practice (157-159), including antimicrobials. (160, 161) Education has been shown to increase doctors' knowledge and competency in prescribing medicines including antibiotics. (162-164) Provision of dosing cards to junior doctors has been found to improve their preparedness to prescribe. (165) Thus we sought to use an intervention involving face-to-face education, CPD and provision of a pocket guideline to increase doctors' preparedness and knowledge to treat patients with vancomycin.

5.2.2 Aims

1) The aim of this study was to assess junior doctors' preparedness to prescribe and monitor vancomycin.

2) Determine if an intervention involving an educational program comprised of face-to-face education, a locally developed CPD module on vancomycin and dissemination of a pocket guideline influenced junior doctors' preparedness and knowledge to clinically use vancomycin.

5.2.3 Hypothesis

Based on the published literature (and my experience delivering numerous lectures on antibiotics to junior doctors), we hypothesised that junior doctors would have a greater degree of preparedness (measured by self-reported confidence) to treat patients with vancomycin after undergoing the intervention compared with not being exposed to the intervention.

5.2.4 Summary

We found that junior doctors had greater confidence to use vancomycin after undergoing an intervention. Those doctors who attended a face-to-face educational session or were in possession of a pocket guideline reported more confidence in a number of key areas of vancomycin clinical management. However, this was not true for all areas. Regarding junior doctors who completed the online CPD with knowledge questions, there was no difference in attainment of knowledge scores, whether they attended a face-to-face session or were in possession of a pocket guideline. This finding surprised us and raised questions about the utility of online CPDs as a tool to improve clinician use of vancomycin. However, the number of doctors in each category of comparison was low which may have limited the ability to determine if there were any differences between those who did and did not complete the CPD on vancomycin. Furthermore, it is possible that junior doctors who elected not to attend an educational session, did so as they felt much more comfortable with the topic and likewise were not in possession of a pocket guideline for the same reason. This paper demonstrated that interventions involving face-to-face education and provision of a pocket guideline do have a role to increase the preparedness of doctors to prescribing and monitoring vancomycin for their patients.

5.2.5 Publication

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Author contributions:

The study was principally conceived and designed by myself (90%) with input from Professors

Gordon and McKinnon, 5% each. I performed data collection and interpretation (100%), with formal statistical analysis performed by Professor Woodman (100%). I wrote the first draft of the manuscript and finalised the submission (85%) with each coauthor contributing 5% to important intellectual content.

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Junior doctors' preparedness to prescribe, monitor, and treat patients with the antibiotic vancomycin in an Australian teaching hospital

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Purpose: We aimed to assess the preparedness of junior doctors to use vancomycin, and to determine whether attending an educational session and being provided pocket guidelines were associated with self-reported confidence and objective knowledge. **Methods:** This was a 2-component cross-sectional study. A 60-minute educational session was implemented and pocket guidelines were provided. Preparedness was evaluated by a self-reported confidence survey in the early and late stages of each training year, and by continuing medical education (CME) knowledge scores. **Results:** Self-confidence was higher among those later in the training year (n = 75) than in those earlier (n = 120) in the year for all questions. In the late group, vancomycin education was associated with higher self-confidence regarding the frequency of therapeutic drug monitoring (P = 0.02) and dose amendment (P = 0.05); however, the confidence for initial monitoring was lower (P < 0.05). Those with pocket guidelines were more confident treating patients with vancomycin (P < 0.001), choosing initial (P = 0.01) and maintenance doses (P < 0.001), and knowing the monitoring frequency (P = 0.03). The 85 respondents who completed the knowledge assessment scored a mean ± standard deviation of 8.55 ± 1.55 on 10 questions, and the interventions had no significant effect. **Conclusion:** Attending an educational session and possessing pocket guidelines were associated with preparedness, as measured by higher self-reported confidence using vancomycin. High knowledge scores were attained following CME; however attending an educational session or possessing pocket guidelines did not significantly increase the knowledge scores. Our findings support providing educational sessions and pocket guidelines to increase self-confidence in prescribing vancomycin, yet also highlight the importance of evaluating content, format, and delivery when seeking to improve preparedness to use vancomycin through education.

Keywords: Drug monitoring; Continuing medical education; Prescriptions; Self report; Vancomycin

Introduction

The ability to prescribe safely and effectively is a core requirement of doctors [1]. Concerns have been reported about how well junior doctors are prepared for prescribing [2]. A recent report by the UK General Medical Council on 'Being Prepared' defined preparedness for new doctors as including readiness, competence, being fit for purpose, and being fit to practice. This report stated that over 13% of junior doctors felt forced to deal with clinical problems beyond their competence or experience on a daily basis, and that antibiotics were a class of medicines that nearly 10% of doctors felt unprepared to use [3]. A number of medicines have been identified as error-prone for prescriptions by junior doctors, with antibiotics being associated with many documented errors [4]. The antibiotic vancomycin is inherently challenging to prescribe, as it requires individualisation of dosing and measurements of serum drug levels to monitor for both

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efficacy and toxicity [5,6]. After 50 years, however, vancomycin is still widely used and is the treatment of choice for serious infections such as methicillin-resistant *Staphylococcus aureus* [7].

In Australia, junior doctors (medical postgraduates 1–2 years and above who have not completed specialist training) undergo semi-structured teaching in public hospitals guided by the Australian Curriculum Framework for Junior Doctors. Under the domain of clinical management, this framework lists prescribing, therapeutics, and treating infections as core areas for junior doctors [8]. There is modest evidence supporting educational interventions to improve antibiotic prescribing in hospitals, which can be considered as belonging to the field of antimicrobial stewardship [9], and in general to improve prescribing by junior doctors [10]. However, no current study, to our knowledge, has evaluated the impact of educational interventions on junior doctors' preparedness to prescribe and treat patients with vancomycin. As junior doctors perform the great majority of prescribing in teaching hospitals, the aim of this study was to assess the preparedness of this group to prescribe and monitor vancomycin, and to determine whether an educational program and the provision of pocket guidelines were associated with self-reported and objective knowledge of vancomycin prescribing.

Methods

Setting

The study was conducted at Flinders Medical Centre (FMC), a 580-bed government teaching hospital in Adelaide, Australia.

Subjects

The participants of the study were junior doctors identified from the register of the Trainee Medical Officer (TMO) Unit, FMC. The potential cohorts of junior doctors available to participate comprised 72 doctors in 2012, 73 in 2013, and 74 in 2014.

Study design

This was a cross-sectional study assessing confidence and knowledge about prescribing and monitoring vancomycin conducted between 2012 and 2014. The study comprised 2 components each year. Component 1 was a self-reported confidence survey (Supplement 1), and component 2 was an online continuing medical education (CME) module on vancomycin with knowledge assessment questions (Supplement 2). The 8 survey questions relating to self-reported confidence were analysed individually, but were first subjected to a content validity assessment to assess topic coverage via a factor analysis to determine dimensionality and an analysis using the Cronbach alpha to assess internal reliability. Content validity was assessed by 4 experts (2 pharmacists and 2 physicians). Following the adaptation of several questions, agreement was reached that the questions covered all relevant aspects of the construct. We used factor analysis, with maximum likelihood used to determine whether the questions could be considered as all relating to a single confidence domain. The 8 questions provided solutions with between 1 and 4 factors. The lowest Bayesian information criterion (BIC) was obtained for that with 2 factors (BIC = 109.7) but the solution with a single factor was very similar (BIC = 110.0). In addition, the first factor was the only one of the 4 factors with an eigenvalue greater than 1, and it alone explained 69.4% of the variability in the data, indicating that the 8 questions could be thought of as relating to a single domain. The internal reliability as assessed by the Cronbach alpha was alpha = 0.929. The knowledge component questions were also assessed for content validity by the same panel of 4 experts. The knowledge questionnaire comprised 10 multiple-choice questions, which were given equal weighting for a total score ranging from 0 to 10. Agreement on the correct answer for each question was also assessed by the experts who each took the test alone before obtaining concurrence on the correct answer.

Component 1: the self-confidence survey required respondents to use a 5-point Likert scale of (1) strongly agree, (2) agree, (3) not sure, (4) disagree, and (5) strongly disagree for a series of questions. The survey was disseminated to doctors in both the early and late part of each year. In Australia, the hospital teaching year is January to December, and the survey was disseminated and completed by participants in a 4-week period commencing in January (early in the training year) and a 4-week period running from November to December (late in the training year) in 2012, 2013, and 2014. The self-confidence survey was available to complete on paper and electronically via Survey Monkey (San Mateo, CA, USA).

Component 2: the CME and knowledge assessment were provided over 3 consecutive years during the period of June to December. The CME module was disseminated to doctors via email with a link to the online knowledge assessment, also hosted via Survey Monkey. No incentives were offered to complete the self-confidence survey or CME knowledge assessment.

The study included educational support in the form of a 60-minute, face-to-face, non-compulsory educational session and the provision of pocket guidelines (Supplement 3). The educational sessions contained core information and practical advice on prescribing and monitoring, with content selected by a multidisciplinary group of local experts. The sessions were delivered 3 times each year in an effort to capture rotating doctors. Sessions began early in participants' training year, with repeat sessions offered mid-way through the year. The laminated pocket guidelines (6 × 10 cm) contained the essential features of the institutional guidelines. The pocket guidelines were disseminated at educational sessions and via the TMO Unit.

Statistical analysis

Differences in the mean Likert scale confidence scores between the early and late training groups were assessed using the independent t-test. In addition, amongst the late in training year group alone,

we also compared the difference in mean confidence scores for those who attended an educational session and those who did not, and also the difference in mean confidence scores for those who possessed pocket guidelines and those who did not. The differences in the proportion of respondents correctly answering CME knowledge questions according to vancomycin prescribing experience, attendance at an educational session, and possession of pocket guidelines were assessed in a univariate analysis using the Fisher exact test. In addition, we also assessed whether these 3 factors were independent predictors of a correct response using multivariate binary logistic regression. Finally, multivariate linear regression was used to assess whether any of these 3 factors predicted total knowledge scores, as defined by the number of correct responses across the 10 questions.

Sample power

We had 80% power to detect a difference in Likert scale confidence scores of 0.4, assuming a standard deviation in confidence for each question of 1.0 for each group (n = 120 and n = 75). In regard to assessing differences in the proportion of correctly answered CME knowledge questions, we had 80% power to detect a difference of 18%, assuming that approximately 80% of subjects correctly answered each question between 2 groups of size n = 27 and n = 58 (pocket guidelines groups) and 82% power for 2 groups of size n = 40 and n = 45 (educational session groups) for those who completed the CME knowledge questions. All analyses were performed using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA).

Ethical approval

This study received full ethics approval from the Southern Adelaide Clinical Human Research Ethics Committee, Australia (approval 123.12).

Results

Component 1: self-reported confidence survey

A total of 195 completed surveys were received over 2012–2014 (120 from the early group and 75 from the late group). Raw data are available in Supplement 4. The work position and experience of junior doctors is presented in Table 1. Self-reported confidence in prescribing vancomycin improved across the 8 domains between the early and late groups (P < 0.001) (Table 2).

The association of attending an educational session with self-reported confidence in prescribing vancomycin was evaluated in respondents who responded late in their year of training (n = 75). Those who had attended an educational session had a higher degree of con-

Table 1. Position of junior doctors and their experience prescribing vancomycin by training period (early versus late)

Junior doctors' characteristics	Early in training year (n = 120)	Late in training year (n = 75)	P-value[a]
Hospital position			0.83
PGY1	115 (95.8)	73 (97.3)	
PGY2	3 (2.5)	2 (2.7)	
Other	2 (1.7)	0	
How many times prescribed vancomycin			< 0.001
≤ 10 times	108 (90.0)	49 (65.3)	
11–20 times	9 (7.5)	16 (21.3)	
21–30 times	1 (0.8)	7 (9.3)	
> 30 times	0	3 (4.0)	
Missing	2 (1.7)	-	

Values are presented as number (%).
PGY, postgraduate year.
[a]Early in the training year versus late in the training year, using the Fisher exact test.

Table 2. Junior doctors' mean self-reported confidence scores by training period (early versus late)

Confidence domains "do you feel confident to"	Early in training year (n = 120)	Late in training year (n = 75)	P-value[a]
Treat patients with VAN?	3.2 ± 0.98 (3.1–3.4)	2.3 ± 0.76 (2.1–2.5)	< 0.001
Choose an initial VAN dose?	3.1 ± 0.99 (2.9–3.3)	1.9 ± 0.67 (1.8–2.1)	< 0.001
Choose a maintenance VAN dose	3.1 ± 0.88 (3.0–3.3)	2.0 ± 0.74 (1.9–2.2)	< 0.001
Know when the first blood level of VAN should be measured?	3.2 ± 0.90 (3.0–3.3)	2.1 ± 0.70 (2.0–2.3)	< 0.001
Know how often blood levels of VAN should be taken once the patient has reached therapeutic range?	3.3 ± 0.87 (3.1–3.4)	2.26 ± 0.73 (2.1–2.4)	< 0.001
Know the target therapeutic range for VAN?	3.1 ± 1.1 (2.9–3.3)	2.1 ± 0.81 (1.9–2.3)	< 0.001
Interpret high or low VAN levels to use that information to amend the dose or interval?	3.2 ± 0.94 (3.0–3.3)	2.2 ± 0.91 (2.0–2.4)	< 0.001
Manage an infusion-related reaction to VAN (red man syndrome)?	3.8 ± 0.98 (3.6–4.0)	3.2 ± 1.1 (2.9–3.4)	< 0.001

Values are presented as mean ± standard deviation (95% confidence interval). Likert score 1 = strongly agree, 2 = agree, 3 = not sure, 4 = disagree, 5 = strongly disagree.
VAN, vancomycin.
[a]Early in the training year versus late in in the training year, using the unpaired t-test.

fidence in terms of knowing how often blood levels of vancomycin should be taken once the therapeutic target range is attained; Likert score, mean (95% confidence interval [CI]) 2.2 (2.0–2.4) versus 2.5 (2.1–2.9); (P = 0.02). There was a trend for significance in interpreting high or low vancomycin levels to amend the dosing among those who attended the educational session, with a mean score (95% CI) of 2.1 (1.8–2.3) versus 2.5 (2.1–2.9); (P = 0.05). Surprisingly, respondents were more confident knowing when to take the first blood level of vancomycin if they had not attended an educational session, with a mean score (95% CI) of 1.9 (1.8–2.1) versus 2.4 (2.1–2.8); (P ≤ 0.005) while there were no significant differences for the other remaining questions (Table 3). The association of possessing pocket guidelines with self-reported confidence in prescribing vancomycin was also evaluated in respondents from the late group (n = 75). Those who possessed pocket guidelines had a higher degree of confidence in terms of treating patients with vancomycin, choosing an initial dose, choosing a maintenance dose, and knowing how often to take vancomycin blood levels (Table 4).

Component 2: continuing medical education knowledge assessment

Preparedness to prescribe, monitor, and treat patients was determined by knowledge scores obtained after completion of an online CME module on vancomycin. Eighty-five respondents completed the CME questions. Demographic factors and experience prescribing vancomycin are presented in Table 5. The mean and standard deviation for the total knowledge score was 8.55 ± 1.55 from a maximum achievable score of 10. Scores were not influenced by prescrib-

Table 3. Comparison of self-reported confidence scores between those who did and do not attend a face-to-face vancomycin educational session (late in the training year only)

Confidence domains "do you feel confident to"	Did not attend prior educational session (n = 25)	Attended prior educational session (n = 49)	P-value[a]
Treat patients with VAN?	2.5 ± 0.9 (2.1–2.9)	2.2 ± 0.7 (2.0–2.4)	0.09
Choose an initial VAN dose?	2.0 ± 0.6 (1.7–2.3)	1.9 ± 0.7 (1.7–2.1)	0.47
Choose a maintenance VAN dose	2.2 ± 0.9 (1.8–2.6)	1.9 ± 0.7 (1.7–2.1)	0.15
Know when the first blood level of VAN should be measured?	1.9 ± 0.6 (1.8–2.1)	2.4 ± 0.8 (2.1–2.8)	< 0.05
Know how often blood levels of VAN should be taken once the patient has reached therapeutic range?	2.5 ± 0.9 (2.2–2.9)	2.1 ± 0.6 (2.0–2.3)	0.02
Know the target therapeutic range for VAN?	2.0 ± 0.7 (1.8–2.2)	2.3 ± 0.9 (1.9–2.7)	0.13
Interpret high or low VAN levels to use that information to amend the dose or interval?	2.5 ± 1.1 (2.1–2.9)	2.1 ± 0.8 (1.8–2.3)	0.05
Manage an infusion-related reaction to VAN (red man syndrome)?	3.4 ± 1.3 (2.8–3.9)	3.1 ± 1.0 (2.8–3.4)	0.28

Values are presented as mean ± standard deviation (95% confidence interval). Likert score: 1 = strongly agree, 2 = agree, 3 = not sure, 4 = disagree, 5 = strongly disagree.
VAN, vancomycin.
[a]Attendance versus non-attendance, using the unpaired t-test.

Table 4. Comparison of self-reported confidence scores between those with and without pocket guidelines (late in training year group only)

Confidence domains regarding vancomycin "do you feel confident to"	JMO without pocket guidelines (n = 17)	JMO with pocket guidelines (n = 58)	P-value[a]
Treat patients with VAN?	2.9 ± 0.9 (2.4–3.3)	2.1 ± 0.6 (1.9–2.2)	< 0.001
Choose an initial VAN dose?	2.3 ± 0.7 (1.9–2.6)	1.8 ± 0.6 (1.6–2.0)	0.01
Choose a maintenance VAN dose	2.6 ± 0.8 (2.2–2.9)	1.9 ± 0.7 (1.7–2.1)	< 0.001
Know when the first blood level of VAN should be measured?	2.4 ± 0.8 (2.0–2.8)	2.0 ± 0.6 (1.9–2.2)	0.06
Know how often blood levels of VAN should be taken once the patient has reached therapeutic range?	2.6 ± 0.7 (2.1–3.0)	2.2 ± 0.7 (2.0–2.3)	0.03
Know the target therapeutic range for VAN?	2.3 ± 0.8 (2.0–2.7)	2.0 ± 0.8 (1.8–2.2)	0.13
Interpret high or low VAN levels to use that information to amend the dose or interval?	2.7 ± 1.1 (2.1–3.3)	2.1 ± 0.8 (1.8–2.3)	0.01
Manage an infusion-related reaction to VAN (red man syndrome)?	3.0 ± 1.1 (2.7–3.2)	3.8 ± 1.2 (3.2–4.4)	< 0.01

Values are presented as mean ± standard deviation (95% confidence interval). Likert score 1 = strongly agree, 2 = agree, 3 = not sure, 4 = disagree, 5 = strongly disagree.
VAN, vancomycin.
[a]Using the unpaired t-test.

Table 5. Demographics of respondents (n = 85) who completed the online VAN continuing medical education knowledge assessment

Medical officer characteristic	No. of all respondents (%)
Sex (female)	46 (54.1)
Hospital position	
PGY1	53 (62.4)
PGY2	14 (16.5)
PGY3	10 (11.8)
Other	8 (9.4)
Hospital	
Flinders Medical Centre	66 (77.6)
Repatriation General Hospital	13 (15.3)
Noarlunga Health Service	6 (7.1)
How many times prescribed VAN	
≤ 10 times	57 (67.1)
11–20 times	16 (18.8)
21–30 times	5 (5.9)
> 30 times	5 (5.9)
Missing	2 (2.3)
Attended an educational session on vancomycin earlier in the year	45 (52.9)
Possess pocket vancomycin guidelines	58 (68.2)

VAN, vancomycin; PGY, postgraduate year.

ing experience, attending an educational session, or possession of the pocket vancomycin guidelines (Table 6). In multivariate linear regression, there were no significant effects for experience prescribing vancomycin (β = 0.09 ± 0.36, P = 0.82), attending an educational session (β = –0.56 ± 0.35, P = 0.12) or possessing pocket guidelines (β = 0.62 ± 0.38, P = 0.11). The range of correctly answered individual knowledge questions is presented in Table 6, with no differences observed for those who attended a prior educational session, were in possession of pocket guidelines, or had more experience prescribing vancomycin. However, in multivariate logistic regression, the odds of correctly answering the question about the loading dose were unexpectedly lower than in those with more experience prescribing vancomycin than in those with less experience (odds ratio [OR], 0.17; 95% CI, 0.04 to 0.81; P = 0.02), and was higher for those with a pocket guide than for those without (OR, 6.3; 95% CI, 1.11 to 36.2; P = 0.04). The odds of correctly answering the question related to managing initially elevated vancomycin levels were lower for those who attended the educational session than for those who did not (OR, 0.20; 95% CI, 0.05 to 0.83; P = 0.03). Experience prescribing vancomycin, prior attendance of an educational session, and possessing pocket guidelines were

Table 6. Number and percentage of correct scores attained by respondents (n = 85) completing the online continuing medical education knowledge assessment

Knowledge questions on VAN from clinical vignettes	All	Prescribed VAN ≤ 10 times (n = 57)	Prescribed VAN > 10 times (n = 26)	P-value[a]	Did not attend prior educational session (n = 40)	Attended prior educational session (n = 45)	P-value[a]	No pocket guidelines (n = 27)	Possession of pocket guidelines (n = 58)	P-value[a]
What loading dose would you prescribe?	75 (88.2)	55 (93)	20 (77)	0.06	37 (92.5)	38 (84.4)	0.32	22 (81.5)	53 (91.4)	0.28
What subsequent maintenance dose would you prescribe?	77 (89.4)	51 (86)	25 (96)	0.26	38 (95.0)	38 (84.4)	0.16	24 (88.9)	52 (89.7)	1.00
Before which dose should you take the first VAN level?	81 (95.3)	55 (93)	26 (100)	0.31	39 (97.5)	42 (93.3)	0.62	26 (96.3)	55 (94.8)	1.00
If the patient had a creatinine clearance of 30 mL/min, before which dose would you take the first VAN level?	77 (89.4)	51 (86)	23 (88)	1.00	32 (80.0)	42 (93.3)	0.10	21 (77.8)	53 (91.4)	0.10
What is the therapeutic range (intermittent infusion) for vancomycin recommended by the pathology laboratory?	81 (95.3)	55 (93)	26 (100)	0.31	38 (95.0)	43 (95.6)	1.00	26 (96.3)	55 (94.8)	1.00
A patient's initial VAN levels returns as 23.2 mg/L; what dosing regimen will you prescribe?	70 (82.4)	47 (80.0)	23 (88.5)	0.54	36 (90.0)	34 (75.6)	0.10	20 (74.0)	50 (86.2)	0.15
When should the patient's next VAN trough level be checked?	77 (89.4)	53 (89.8)	24 (92.3)	1.00	37 (92.5)	40 (88.9)	0.72	24 (88.9)	53 (91.4)	0.71
How often should a VAN level be measured once the patient is in the target range (provided stable renal function)?	79 (92.9)	54 (91.5)	25 (96.1)	0.66	38 (95.0)	41 (91.1)	0.68	26 (96.3)	53 (91.4)	0.66
If a patient develops red man syndrome, what changes will you make to the VAN infusion rate?	51 (60)	36 (61.0)	14 (53.8)	0.63	25 (62.5)	25 (55.6)	0.66	14 (51.9)	36 (62.1)	0.48
How many consecutive VAN levels within the target range will the patient require prior to discharge home for outpatient antimicrobial therapy with VAN?	65 (76.5)	46 (78.0)	18 (69.2)	0.42	30 (75.0)	34 (75.6)	1.00	20 (74.0)	44 (75.9)	1.00

Values are presented as number (%). Likert score: 1 = strongly agree, 2 = agree, 3 = not sure, 4 = disagree, 5 = strongly disagree.
VAN, vancomycin.
[a]Using the 2-sided Fisher exact test.

not predictors of a correct response for any of the other questions.

Discussion

This study examined a pertinent topic with a pragmatic design employing educational interventions in the challenging environment of an authentic clinical context. During this study, we observed that junior doctors' self-reported confidence was higher for all questions when asked later in the hospital teaching year. While it could be argued that increased confidence occurs simply with increasing experience over the year spent working as a doctor, some two-thirds of doctors reported very limited experience, having prescribed vancomycin as little as 10 or fewer times. In the current study, those doctors who had attended an educational session were more confident in the domain of therapeutic drug monitoring of vancomycin; specifically, knowing when to measure blood levels and how frequently to monitor them once the patient is in the target range, and borderline significance was found for confidence in the more complex task of interpreting vancomycin blood results to amend dosing. These are important findings, as measuring blood levels at the wrong time and frequency can result in misinterpretation of the results and lead to incorrect dosage adjustment [11]. As our educational intervention was multifaceted, we are unable to determine the effect of individual components; thus, we cannot say if future resources should be directed to face-to-face sessions, online CME, or provision of pocket guidelines. The CME with knowledge questions was developed with considerable input from pharmacy, infectious diseases, and clinical pharmacology to ensure that the CME content was contemporary. The time required to prepare the CME with questions was significantly in excess of the time required for preparation and delivery of the face-to-face sessions, yet the CME, once prepared, can be disseminated to a large audience if required. Getting junior doctors to take time out of their busy schedule for an educational session is challenging, but during an internal evaluation of these sessions, junior doctors overwhelmingly agreed or strongly agreed that attending the sessions was useful to their clinical practice.

The junior doctors who received pocket guidelines were significantly more confident on 6 of the 8 questions about dosing and monitoring vancomycin, suggesting strongly that provision of the pocket guidelines improved their confidence. These finding are meaningful, as a systematic review found that low levels of confidence had a negative impact on the preparedness of junior doctors, as did deficiencies in areas such as prescribing [12]. Furthermore, perceived confidence has been reported to have a significant effect on the clinical behaviour of medical graduates [13].

The proportions of correct responses to the online CME knowledge questions on vancomycin were generally very high, for all but 1 question regarding the management of red man syndrome. Interestingly, pharmacists have also scored low on formal CME questions about the management of red man syndrome [14]. Experience in prescribing vancomycin, attendance at a prior educational session, or possessing pocket guidelines did not increase the total knowledge scores. The multivariate analysis of answers to individual CME questions provided some unexpected findings. Those with more experience prescribing vancomycin had a lower likelihood of answering the question about the loading dose correctly than those with less experience. Similarly, the question about managing elevated vancomycin levels produced a surprising result. Those who attended an educational session were paradoxically less likely to answer this question correctly than those who did not. This counter-intuitive performance may potentially be explained by the possibility that those with more experience were less inclined to consult the guidelines for advice before prescribing. Alternatively, the educational content for these areas may have been unclear or potentially confusing, or it may be that doctors who chose to attend the educational sessions did so because they felt less informed than those who did not attend. Nevertheless, these findings emphasise the importance of careful review of the content, format, and delivery of educational interventions, as well as the need for those with educational expertise and content knowledge to evaluate them rigorously.

There are some limitations to this study. As it was cross-sectional in design, we cannot infer causality. In particular, the differences observed for those attending or not attending the educational session and those with and without pocket guidelines may be due to reverse causality. This study did not assess actual vancomycin prescriptions written by these doctors, so we do not know if their clinical behaviour changed after the educational intervention. Further studies assessing educational support to improve junior doctors' preparedness to clinically use vancomycin should involve the rigorous evaluation of such interventions, using more programmatic approaches implemented across multiple sites with numerous sources of stakeholder input to avoid the constraints of self-reported data, as has recently been proposed by others [15]. Larger sample sizes are required to detect some of the smaller but non-significant improvements in knowledge that were observed in the study. Noteworthy, however, is that our study contained more subjects than many of the randomised and non-randomised studies included in a systematic review on educational interventions to improve prescribing for junior doctors [10].

In conclusion, to our knowledge, this is the first evaluation of junior doctors' preparedness to prescribe the antibiotic vancomycin. Possession of pocket guidelines was associated with significantly higher self-reported confidence to use vancomycin, while attending an educational session was associated with higher self-reported confidence to perform therapeutic drug monitoring. Generally high knowledge scores were obtained by those completing an online CME assessment on vancomycin. However, no apparent effect on knowledge scores was associated with attending an educational session, possessing pocket guidelines, or having increased experience prescribing vancomycin. Based on our findings, future initiatives to improve the preparedness of junior doctors to prescribe vancomycin could include

education and the provision of pocket guidelines; however, careful design and close evaluation of educational content, usability, and format require the utmost consideration.

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Conflict of interest

The authors declare they have no potential conflict of interest

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Supplementary Materials

Supplement 1. Self-confidence survey.

Supplement 2. Vancomycin continuing medical education with knowledge assessment.

Supplement 3. Vancomycin pocket guidelines.

Supplement 4. Data file is available from https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi%3A10.7910%2FDVN%2FGLCXW5.

Supplement 5. Audio recording of the abstract.

Authors' contributions

Conceptualization: CJP, DLG, RAM. Data Curation: CJP. Formal analysis: RJW. Funding acquisition: CJP. Methodology: CJP, DLG, RAM, RJW. Writing—original draft: CJP. Writing—review & editing: DLG, RAM, RJW

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Chapter 6: Using optimal vancomycin minimum inhibitory concentration cut-points to inform treatment decisions

6.1 Role of minimum inhibitory concentration in antibiotic selection

The USA Clinical Laboratory Standards Institute (CLSI) define *Staphylococcus aureus* isolates as susceptible to vancomycin treatment if the MIC is ≤2mg/L. (46) However, there have been studies which demonstrate clinical outcomes are worse when patients are infected with MRSA strains that have a vancomycin MIC >1mg/L. (48) Concern over the MIC breakpoint, where vancomycin ceases to be a viable antibiotic, is further exacerbated by the methodology used to determine susceptibility. (56, 166, 167) Depending on the susceptibility method employed, a differing value may be determined. There are several widely used susceptibility methods for MIC determination. Although broth-microdilution (BMD) is commonly referred to as the gold standard, it is impractical to use in a diagnostic laboratory due to being a slow and laborious method, whereas gradient diffusion methods such as E-test® and automated susceptibility methods such as VITEK2® are widely used. (168) Since the reference standard for vancomycin susceptibility uses BMD methodology, results from the more widely available susceptibility tests such as E-test® and Vitek2® need to be correlated and compared. Whilst discordance has been reported between these methods (55), the performance and accuracy of MIC testing should be a core consideration when using an MIC result to inform whether vancomycin is suitable to treat an MRSA infection. For example, an MIC of 2mg/L obtained via E-test® (with a reference BMD of 1mg/L) may dissuade some clinicians from using vancomycin based on CLSI definitions. Unnecessary abandonment of vancomycin in this setting is likely to lead to premature use of newer antibiotics (i.e. linezolid, daptomycin, telavancin). (169) Any exposure of bacterial infection to an antibiotic, may theoretically increase the risk of emerging resistance to that agent, thus selecting a first-line antibiotic (i.e. vancomycin), with less spectrum of

activity is a prudent approach to prolong the arsenal of effective antibiotics. (170)

6.2 Optimizing the detection of methicillin-resistant *Staphylococcus aureus* with elevated vancomycin minimum inhibitory concentration within the susceptible range

6.2.1 Introductory comments

This study measured the diagnostic accuracy of different susceptibility methods of MIC determination in a cohort of clinical MRSA isolates sourced from a diagnostic laboratory. The study sought to assess whether sensitivity and specificity of MIC methods E-test® and VITEK2® for detection of an MIC ≥1mg/L by BMD might guide clinicians' interpretation of MIC results to inform vancomycin treatment.

6.2.2 Aims

This aims of this study were to measure the diagnostic accuracy of two laboratory methods (E-test® and VITEK2®) to measure vancomycin MIC against the gold standard of BMD.

6.2.3 Hypothesis

Our hypothesis was that there would be variance in the diagnostic accuracy of MIC methods. We further hypothesised that sensitivity and specificity analyses of these methods may provide guidance interpreting MIC results to inform vancomycin treatment.

6.2.4 Summary

We found there was weak overall agreement in diagnostic accuracy and correlation of susceptibility methods used to determine MIC. The specificity and sensitivity analysis of susceptibility methods provided some guidance as to the best MIC cut-points to use in

interpreting results from these commonly used methods of obtaining MIC.

We examined the impact of different vancomycin MIC cut-off points for MRSA clinical isolates by E-test® and VITEK2®. Sensitivity and specificity results of detection of less susceptible MRSA isolates determined an optimal E-test® and VITEK2® criteria (compared against BMD) that detects clinically important reduced susceptibility. These findings assist clinical decision-making regarding vancomycin selection based on the results of routine susceptibility tests. As these results are predicated on a relatively small sample, they require testing on a larger dataset for confirmation.

6.2.5 Publication

Phillips CJ, Wells NA, Martinello N, Smith S, Woodman RJ, Gordon DL. Optimizing the detection of methicillin-resistant *Staphylococcus aureus* with elevated vancomycin minimum inhibitory concentration within the susceptible range. Infection and Drug Resistance 2016; 9:87-92.

Author contributions

I principally conceptualised and developed the study design (80%), with input from Professors Gordon, Woodman, Dr Martinello and Nicholas Wells (5% respectively). I wrote the application for ethical approval. I performed wet-lab MIC determination of MRSA isolates (50%), collected and interpreted data with Dr Martinello (20%), Nicholas Wells (20%) and Dr Simon Smith (10%). Professor Woodman performed formal statistical analysis (100%). I wrote and submitted the manuscript for publication (75%) with each coauthor contributing 5% for important intellectual content.

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ORIGINAL RESEARCH

Optimizing the detection of methicillin-resistant *Staphylococcus aureus* with elevated vancomycin minimum inhibitory concentrations within the susceptible range

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Background: Determination of vancomycin minimum inhibitory concentration (MIC) can influence the agent used to treat methicillin-resistant *Staphylococcus aureus* (MRSA) infection. We studied diagnostic accuracy using *E*-test and VITEK® 2 against a gold standard broth microdilution (BMD) methodology, the correlation between methods, and associations between vancomycin MIC and MRSA phenotype from clinical isolates.

Methods: MRSA isolates were obtained from April 2012 to December 2013. Vancomycin MIC values were determined prospectively on all isolates by gradient diffusion *E*-test and automated VITEK® 2. The Clinical and Laboratory Standards Institute reference BMD method was performed retrospectively on thawed frozen isolates. Diagnostic accuracy for detecting less susceptible strains was calculated at each MIC cutoff point for *E*-Test and VITEK® 2 using BMD ≥1 µg/mL as a standard. The correlation between methods was assessed using Spearman's rho (ρ). The association between MRSA phenotype and MIC for the three methods was assessed using Fisher's exact test.

Results: Of 148 MRSA isolates, all except one (*E*-test =3 µg/mL) were susceptible to vancomycin (MIC of ≤2 µg/mL) irrespective of methodology. MICs were ≥1.0 µg/mL for 9.5% of BMD, 50.0% for VITEK® 2, and 27.7% for *E*-test. Spearman's ρ showed weak correlations between methods: 0.29 *E*-test vs VITEK® 2 (P=0.003), 0.27 *E*-test vs BMD (P=0.001), and 0.31 VITEK® 2 vs BMD (P=0.002). The optimal cutoff points for detecting BMD-defined less susceptible strains were ≥1.0 µg/mL for *E*-test and VITEK® 2. *E*-test sensitivity at this cutoff point was 0.85 and specificity 0.29, while VITEK® 2 sensitivity and specificity were 0.62 and 0.51, respectively. Multiresistant MRSA strains tended to have higher MIC values compared to nonmultiresistant MRSA or epidemic MRSA 15 phenotypes by *E*-test (Fisher's exact P<0.001) and VITEK® 2 (Fisher's exact P<0.001).

Conclusion: Overall diagnostic accuracy and correlations between MIC methods used in routine diagnostic laboratories and the gold standard BMD showed limited overall agreement. This study helps optimize guidance on the effective use of vancomycin.

Keywords: MIC, MRSA, sensitivity, specificity, susceptibility, vancomycin

Background

Vancomycin remains the antibiotic of choice for treating serious infection with methicillin-resistant *Staphylococcus aureus* (MRSA) and other serious Gram-positive infections despite its continuous use for over half a century.[1,2] However, some have called into question "how long vancomycin may remain an effective therapy".[3,4] In recent years, there have been a number of new agents licensed by the US Food and Drug

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Administration to treat resistant infection with Gram-positive bacteria, including MRSA; however, it is essential to reserve these agents for when vancomycin is no longer effective.[5,6]

Prudent management of the way in which vancomycin is used in therapy is by prompt identification of the organism and testing of antibiotic susceptibility, which, along with optimizing dosing and serum concentration monitoring, may help ensure that vancomycin is not abandoned prematurely.[7] There are a number of methods used to determine minimum inhibitory concentration (MIC); however, broth microdilution (BMD) remains the gold standard.[8] The MIC along with vancomycin exposure measured as area under the concentration curve is the key pharmacokinetic–pharmacodynamic index used to optimize bacterial killing and clinical outcomes with vancomycin therapy.[9,10] An area under the concentration curve/MIC index target of 400 mg/L × hour is recommended for contemporary vancomycin dosing.[11] In the mid-2000s, the US Clinical Laboratory Standards Institute (CLSI) redefined the vancomycin MIC susceptibility breakpoint for *S. aureus* to ≤2 μg/mL.[12] However, since that time, there have been a number of individual studies that have demonstrated associations between isolates with vancomycin MIC in the susceptible range and patient outcomes.[13] Varying methods for determining MIC have been used in these studies, which makes extrapolation of results to routine clinical management challenging. Important consideration must be given to the method used to determine MIC, and decisions for treatment should be based upon the optimal cutoff points for the various methods. A meta-analysis of 14 papers with 2,439 patients with susceptible MRSA infection clearly defined high vancomycin MIC as ≥1 μg/mL by BMD and ≥1.5 μg/mL by *E*-test. This meta-analysis, which included patients with bloodstream and nonbloodstream infection, found a treatment failure risk ratio of 1.40 (95% confidence interval =1.15–1.71) and overall mortality risk ratio of 1.42 (confidence interval =1.08–1.87) for those with high vancomycin MIC.[14]

Although BMD remains the gold standard for measuring vancomycin MIC, this method is time consuming, labor intensive, and requires a high level of skill for consistent results. Alternative methodologies to determine vancomycin MIC such as the automated VITEK® 2 (BioMérieux Inc, Durham NC, USA) and gradient diffusion *E*-test are frequently used in diagnostic laboratories; however, these methods produce varying results in comparison to each other and to BMD.[15]

Inappropriate interpretation and overestimation of the MIC may cause unnecessary use of other agents when vancomycin would still be effective. Assessing the diagnostic accuracy of commonly used MIC methods compared against BMD would assist in meaningful interpretation of MIC values from each method and application of this information to treatment. Unnecessary abandonment of vancomycin for newer antibiotics in patients with MRSA infection with higher yet susceptible MICs (≥1 and ≤2 μg/mL) will potentially promote the emergence of resistance to these agents. Furthermore, the strength of the association among the vancomycin method, MIC, and MRSA phenotype is unclear.

The aim of this study was to measure the diagnostic accuracy of *E*-test and VITEK® 2 vancomycin MIC determination for clinical MRSA isolates compared against a BMD standard. A secondary aim was to explore the strength of the association between MIC and MRSA antibiotic resistance phenotype.

Materials and methods

Study design, data collection, and ethical approval

MRSA clinical isolates were obtained from hospitalized patients aged ≥18 years during the process of usual care between April 2012 and December 2013. The study was conducted at Flinders Medical Centre, a 550-bed teaching hospital in Adelaide, Australia. The pathology database ULTRA Laboratory Information System, Release 2.5C (Cirdan, Lisburn, Northern Ireland) was used to identify patient isolates during the study period. The study was approved by the Southern Adelaide Clinical Human Research Ethics Committee (approval number 123.12). A waiver of consent was granted with the approval as the participants were not exposed to any risk of harm. The waiver of consent was consistent with the Australian Government National Statement of Ethical Conduct in Human Research 2007.

Susceptibility testing

All MRSA isolates were tested to determine the vancomycin MIC. Isolate susceptibility to vancomycin was defined by the CLSI breakpoint of MIC ≤2 μg/mL. Automated VITEK® 2 System Version 05.04 (BioMérieux Inc.) sensitivity testing was performed on fresh isolates during routine processing. Gradient diffusion *E*-test (BioMérieux Inc.) was used according to the manufacturer's instructions. Reading of *E*-test was conducted independently by a senior medical scientist, with the result confirmed by a medical microbiologist; any disagreement was adjudicated by a third reader. BMD was performed using thawed frozen isolates. Frozen isolates were stored (−20°C for 6–12 months) to enable batched processing. Vancomycin hydrochloride (Sigma-Aldrich, St. Louis, MO, USA) was sourced to prepare the stock solution.

Susceptibility was tested at vancomycin concentrations 0.25–8.0 μg/mL in twofold dilutions according to the CLSI methodology.[16]

Validation of MIC results obtained using BMD method was performed concurrently using *S. aureus* ATCC 29213 and *Escherichia coli* ATCC 25922 as controls for every set of tests. MICs were determined after a period of 24 hours of incubation at 35°C in oxygen. Reading of BMD was performed independently by a senior medical scientist, a medical microbiologist, and a specialist pharmacist. Where a difference in reading the MIC occurred, a consensus of two readers was required.

MRSA resistance phenotype

Phenotyping was determined from antibiogram testing using VITEK® 2 AST-612 (BioMérieux Inc.). Three distinct phenotypes were recognized. Nonmultiresistant MRSA isolates were defined as those resistant to <3 non-β-lactam antibiotic classes, while multiresistant MRSA (mMRSA) isolates were defined as those resistant to ≥3 non-β-lactam antibiotic classes.[17] Epidemic MRSA 15 was separately defined by resistance to ciprofloxacin ± erythromycin antibiotic.[18]

Statistical analysis

Data were stored in Microsoft Excel and were reported using descriptive statistics. Spearman's rho (ρ) correlation coefficients were used to assess the strength of the association between the methods used to determine MIC. Specificity, sensitivity, and area under the receiver operating characteristic curve measured as *C*-statistic were used to calculate diagnostic accuracy for VITEK® 2 and *E*-test MIC methods for detecting strains with MIC ≥1 μg/mL by using BMD as the reference MIC value. The *C*-statistic is a measure of discrimination and reports the global test accuracy, ie, for all cutoff points combined. The reference MIC methodology (BMD) and MIC value were selected as they were shown to be independent predictors of poor clinical outcomes.[14,19] Fisher's exact test was used to assess whether MRSA phenotype was associated with MIC concentrations for each of the three MIC methods. Stata version 14.0 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses.

Results

A total of 148 isolates were obtained from 111 patients during the study period. The clinical isolates were sourced from multiple anatomical sites, with skin and soft tissue and respiratory sites featuring prominently and 10% of isolates being from blood or central nervous system (Table 1). All MRSA isolates, with the exception of one isolate with *E*-test of 3 μg/mL (1 μg/mL by VITEK® 2 and BMD), were susceptible to vancomycin (≤2 μg/mL) by all the three methods. The distribution of MIC values by methodology is shown in Table 2. The percentage of isolates with MIC ≤0.5 μg/mL was 90.5%, 50%, and 28% by BMD, VITEK® 2, and *E*-test, respectively. MIC values ≥1 μg/mL were observed in 9.5% by BMD, 50% by VITEK® 2, and 72% by *E*-test.

Correlation of MIC methodologies

Spearman's rho (ρ) correlation coefficients between the three methods were significant but weak; 0.29 for *E*-test vs VITEK® 2

Table 1 Anatomical region clinical isolate obtained

Specimen site	n	%
Skin and soft tissue	94	63.5
Respiratory	26	17.6
Blood/CSF	15	10.1
Sterile body cavity	8	5.4
Urine	3	2.0
Other	2	1.4
Total	148	100

Abbreviation: CSF, cerebrospinal fluid.

Table 2 Distribution of vancomycin minimum inhibitory concentrations (MICs) by three methods in 148 clinical isolates

MIC method	0.25	0.38	0.5	0.75	1	1.5	2	3	All	MIC range (μg/mL)
E-test	N/A	3	17	21	54	41	11	1	148	0.38–3
VITEK® 2	N/A	N/A	74[a]	N/A	72	N/A	2	N/A	148	≤0.5–2
BMD	18	N/A	111	5	14	N/A	N/A	N/A	148	0.25–1

Note: [a]Lowest dilution reported by VITEK® 2 is ≤0.5 μg/mL.
Abbreviations: BMD, broth microdilution; N/A, not applicable.

Table 3 Sensitivity and specificity of *E*-test and VITEK® 2 for detection of a minimum inhibitory concentration (MIC) ≥1 μg/mL by broth microdilution (BMD)

MIC method (μg/mL)	Sensitivity	Specificity	*C*-statistic
E-test			0.54
Cutoff point			
≥0.38	1.00	0.0	
≥0.5	1.00	0.02	
≥0.75	1.00	0.15	
≥1.0	0.85	0.29	
≥1.5	0.31	0.64	
≥2	0.08	0.93	
≥3	0.08	1.00	
VITEK® 2			0.58
Cutoff point			
≥0.5	1.00	0.00	
≥1.0	0.62	0.51	
≥2.0	0.08	0.99	

(*P*=0.003), 0.27 for *E*-test vs BMD (*P*=0.001), and 0.31 for BMD vs VITEK® 2 (*P*=0.002).

The *C*-statistic was weak for both *E*-test (0.5428) and VITEK® 2 (0.5815) (Table 3). Sensitivity and specificity for detection of an MIC ≥1 μg/mL by BMD were calculated for each possible cutoff point for the *E*-test and VITEK® 2 methods (Table 3). The optimum cutoff point for the *E*-test was ≥1.0 μg/mL, with a sensitivity of 0.85 and specificity of 0.29, while the optimum cutoff point for VITEK® 2 was also ≥1.0 μg/mL, with corresponding values of 0.62 and 0.51, respectively.

Breakdown by phenotype

There was no significant association between MRSA phenotype and the BMD MICs (*P*=0.15), although it appeared that there were relatively fewer mMRSA phenotypes than expected at BMD =0.25 μg/mL (2.3%), and relatively more mMRSA than expected at BMD =0.75 μg/mL (6.8%) based on observed percentages for both epidemic MRSA 15 and nonmultiresistant MRSA (Table 4). There was a significant association between MRSA phenotype and the VITEK® 2 MIC categories (*P*<0.001), with a lower than expected percent of mMRSA at VITEK® 2 =0.5 μg/mL (27.3%) and a higher than expected percent of mMRSA at VITEK® 2 =1.0 μg/mL (70.5%) based on the observed percentages for the other two MRSA phenotypes. There was also a significant association between phenotype and the *E*-test MICs (*P*<0.001), with a lower than expected percent of mMRSA at *E*-test =0.5 μg/mL MICs and 0.75 μg/mL MICs (0%–7%) and a higher than expected percent of mMRSA at *E*-test =1.5 μg/mL and *E*-test =2 μg/mL (39% and 14%) based on the observed percentages for the other two MRSA phenotypes.

Table 4 Relationship between vancomycin minimum inhibitory concentration (MIC) by methodology and methicillin-resistant *Staphylococcus aureus* (MRSA) phenotype

MIC (μg/mL)	EMRSA-15	mMRSA	nmMRSA	Total
Broth microdilution method, n (%)				
0.25	5 (15.2)	1 (2.3)	12 (17.4)	18 (12.3)
0.5	25 (75.8)	36 (81.8)	50 (72.5)	111 (76.0)
0.75	0 (0.0)	3 (6.8)	2 (2.9)	5 (3.4)
1.0	3 (9.1)	4 (9.1)	5 (7.3)	12 (8.2)
Total	33 (100)	44 (100)	69 (100)	146 (100)
VITEK® 2 method, n (%)				
0.5	28 (84.9)	12 (27.3)	33 (47.8)	73 (50)
1.0	5 (15.2)	31 (70.5)	35 (50.7)	71 (48.6)
2.0	0.00	1 (2.3)	1 (1.5)	2 (1.4)
Total	33 (100)	44 (100)	69 (100)	146 (100)
E-test method, n (%)				
0.38	0 (0.0)	0 (0.0)	3 (4.4)	3 (2.1)
0.5	5 (15.2)	0 (0.0)	12 (17.4)	17 (11.6)
0.75	8 (24.2)	3 (6.8)	10 (14.5)	21 (14.4)
1.0	16 (48.5)	17 (38.6)	20 (29.0)	53 (36.3)
1.5	3 (9.09)	17 (38.6)	21 (30.4)	41 (28.1)
2.0	1 (3.03)	6 (13.6)	3 (4.4)	10 (6.9)
3.0	0 (0.0)	1 (2.3)	0 (0.0)	1 (0.7)
Total	33 (100)	44 (100)	69 (100)	146 (100)

Note: n=146 (two isolates were unable to be sourced when phenotyping performed).

Abbreviations: EMRSA-15, epidemic MRSA; mMRSA, multiresistant MRSA; nmMRSA, nonmultiresistant MRSA.

Discussion

In this study of MRSA isolates that were susceptible to vancomycin, we found only a weak level of agreement between the accepted gold standard BMD and two commonly used methods to determine vancomycin MIC (VITEK® 2 and *E*-test). This weak agreement is consistent with the findings of other authors.[20] Although some authors have reported that *E*-test does not produce higher MIC than other methods,[21] we found higher *E*-test MIC values than either BMD or VITEK® 2, which concurs with the results of other studies.[22,23]

Patient outcomes are worse for MRSA infection with susceptible yet higher vancomycin MICs. Van Hal et al[24] in a systematic review of 22 papers on the significance of vancomycin MIC reported that MIC ≥1.5 μg/mL was associated with worse clinical outcomes than those with <1.5 μg/mL; however, this MIC range was not ascribed to any one MIC method. In this study, we used valid statistical approaches to compare susceptible MIC values that are obtained in routine care from several commonly used methods.

As BMD is acknowledged as the gold standard method for MIC testing, and a BMD MIC ≥1 μg/mL has been associated with poor clinical outcomes,[14,19] we compared the diagnostic accuracy of VITEK® 2 and *E*-test using BMD ≥1 μg/mL as the defined cutoff point for indicating reduced susceptibility. The value of sensitivity and specificity was assessed at the various *E*-test and VITEK® 2 MIC categories. For the MRSA strains used in this study, the optimum *E*-test and VITEK® 2 cutoff points for detection of reduced susceptibility were achieved at ≥1 μg/mL (*E*-test: sensitivity 0.85, specificity 0.29; VITEK® 2: sensitivity 0.62, specificity 0.51). These cutoff points need confirmation in a larger and more diverse dataset but provide novel and practical guidance toward assessing MIC results obtained from differing methodologies. These findings should prove useful to both diagnosticians and clinicians in evaluating test results for commonly employed MIC methodologies.

In our study, we observed significant variations in vancomycin MIC by phenotype using *E*-test and VITEK® 2, but not with BMD. Specifically, mMRSA strains had higher MIC

values than expected. Since mMRSA strains are more likely to be hospital associated, these strains are likely to spread in an environment of higher vancomycin usage than the other "community-acquired" strains. It is unclear why these differences were not detected by BMD, but the clustering of BMD MICs at 0.5 μg/mL may have limited the ability to detect strain differences.

Guidance on treatment of MRSA infection is based on clinical response to vancomycin rather than MIC.[25] However, if vancomycin MIC is a determinant of antibiotic selection, our findings provide useful guidance to better understanding of MIC results obtained through reference and routine laboratory methods.

The main limitations of our study were that the clinical isolates were obtained from a single geographical region (hospital catchment) and that there were also a relatively small number of isolates which were all in the susceptible range.

Conclusion

The level of agreement between MIC determination by BMD, *E*-test, and VITEK® 2 was relatively weak. The estimated sensitivity and specificity of the methods provide guidance on the best MIC cutoff points to use to interpret the results of each method. This permits more objective evaluation of test results obtained from routine methods and selection of vancomycin when appropriate.

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Author contributions

CJP, NAW, and DLG designed the study. CJP, NAW, SS, and MM collected data and performed laboratory work. RJW performed statistical analysis. All authors were involved in the drafting and approval of the final manuscript.

Disclosure

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Chapter 7: Impact of ongoing interventions on prescribing and monitoring vancomycin

7.1 Sustained improvement in vancomycin dosing and monitoring post-implementation of guidelines: Results of a three-year follow-up after a multifaceted intervention in an Australian teaching hospital.

7.1.2 Introductory comments

The findings from our initial exploratory study presented in Chapter 4 show proportional increases in appropriate prescribing and monitoring of vancomycin, and a decrease in nephrotoxicity, however these were predominantly statistically non-significant findings. As the sample size for the initial study was small, we conducted a larger powered study over a longer time period.

7.1.3 Aim

To determine the effectiveness of a multifaceted intervention to implement vancomycin dosing and monitoring guidance across all medical and surgical units throughout a tertiary care facility.

7.1.4 Hypothesis

We hypothesised that a multifaceted intervention would increase the appropriate prescribing and monitoring of vancomycin and reduce nephrotoxicity in patients treated with vancomycin.

7.1.5 Summary

We found the multifaceted intervention had a significant effect on all measured prescribing outcomes, key monitoring outcomes including the proportion of patients with measured vancomycin levels in target range and a reduction in nephrotoxicity. However, while the multifaceted intervention improved the proportion of patients with vancomycin levels in target range, overall there were still >50% of patients who did not attain this. This poses important considerations for future work in this field on how to improve this outcome further, and what interventions may help achieve this.

7.1.6 Publication

Phillips CJ, McKinnon RA, Woodman RJ, Gordon DL. Sustained improvement in vancomycin dosing and monitoring post-implementation of guidelines: Results of a three-year follow-up after a multifaceted intervention in an Australian teaching hospital. Journal of Infection and Chemotherapy 2018; 24:103-109.

Author contributions

I principally conceived and designed the study (85%), with input from coauthors (5% each). I wrote and submitted the application for ethical approval (100%). I collected and interpreted data (80%). Professor Woodman performed formal statistical analysis (100%). I wrote the manuscript and submitted the manuscript (85%) with important intellectual contributions from Professors McKinnon, Gordon and Woodman.

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Original Article

Sustained improvement in vancomycin dosing and monitoring post-implementation of guidelines: Results of a three-year follow-up after a multifaceted intervention in an Australian teaching hospital☆

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ABSTRACT

Introduction: Despite vancomycin being in use for over half-a-century, it is still not dosed or monitored appropriately in many centers around the world. The objective of this study was to determine the effectiveness of a multifaceted intervention to implement a vancomycin dosing and monitoring guideline across multiple medical and surgical units over time.

Methods: This was an observational before-and-after interventional cohort study. The pre-intervention period was August to December 2010–2011 and the post-intervention period was September to November 2012–2014. The implementation strategy comprised: face-to-face education, online continuing medical education, dissemination of pocket guideline and email reminder. Outcome measures included: appropriate prescribing of loading and maintenance doses, therapeutic drug monitoring, time to attain target range and nephrotoxicity.

Results: Post-implementation prescribing of loading doses increased (10.4%–43.6%, *P*=<0.001), guideline adherent first maintenance dose (44%–68.4% *P* = 0.04), correct dose adjustment from (53.1%–72.2%, *P* = 0.009). Beneficial effects pre and post-implementation were observed for adherent timing of initial concentration (43.2%–51.9%, *P* = 0.01), concentrations in target range (32.6%–44.1%, *P* = 0.001), time to target range (median 6–4 days, *P*=<0.001), potentially nephrotoxic concentrations (30.7%–20.9%, *P*=<0.001) and nephrotoxicity (10.4%–6.8%, *P*=<0.001).

Conclusions: A multifaceted intervention to implement a vancomycin dosing and monitoring guideline significantly improved prescribing, monitoring, pharmacokinetic and safety outcomes for patients treated with vancomycin over an extended period. However, increased guideline adoption by clinicians is required to maximize and prolong the utility of this important agent.

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Abbreviations: CME, continuing medical education; FMC, Flinders Medical Center; GIN, Guideline International Network; ICCU, Intensive and critical care unit; IOM, Institute of Medicine; JMO, junior medical officer; MRSA, methicillin-resistant *Staphylococcus aureus*; NHMRC, National Health and Medical Council; NICE, National Institute for Clinical Excellence; SIGN, Scottish Intercollegiate Guideline Network; VRE, vancomycin-resistant Enterococcus.

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1. Introduction

Vancomycin has been in use for over half a century however we still have difficulty prescribing and monitoring this agent [1,2]. Practice recommendations have changed over time [3].To address these changes in practice and promote contemporary clinical guidance, a number of a professional societies from various nations, notably the United States, Japan and recently, China, have published vancomycin guidelines in the medical literature [4–6]. These national guidelines are in addition to the plethora of institutional vancomycin guidelines that been described in a recent systematic review [7]. Significant financial and human resources are invested into the development of transparent evidence-based clinical practice guidelines, however there is very limited information supporting these documents reflecting which implementation strategies best promote the guideline adoption.

To address guideline implementation, organisations involved with knowledge translation and guideline development including the National Institute for Health and Clinical Excellence (NICE), UK, the Scottish Intercollegiate Guideline Network (SIGN), the Australian National Health and Medical Research Council (NHMRC), the United States Institute of Medicine (IOM) and Guidelines International Network (G-I-N) provide general advice on guideline implementation [8–12]. This is important as there are numerous accounts in the literature of poor adoption of guidelines by clinicians [13–16]. Most of the peak organisations advocate for multifaceted interventions when implementing guidelines. Commonly recommended interventions by these organisations are: educational sessions [17], academic detailing [18–20], continuing medical education (CME) [21,22], provision of printed educational material [23], use of opinion leaders to endorse guidelines [24], and engaging target populations who will use the guideline [25]. However, the magnitude of effect from these interventions varies considerably and the impact these interventions have specifically when employed to implement vancomycin guidelines is unknown.

In a pilot study we implemented a vancomycin dosing and monitoring guideline, we elected to use interventions involving face-to-face education and the provision of a pocket guideline as these had limited cost implications. Despite low statistical power, the pilot produce favourable results, increasing prescribing of loading doses from 5 to 65% ($P = \leq 0.001$), adherent first maintenance dosages from 43 to 75% ($P = 0.04$), more concentrations in target range from 27% to 43.8% ($P = 0.04$), and non-significant reductions in potentially toxic concentrations, reduced nephrotoxicity and a trend to more patients attaining target ranger sooner [26]. However, as that pilot was conducted in a single surgical unit, it was unclear if the results of the intervention would be reproducible and sustainable. Thus the objectives of the current study were to determine the effectiveness of a multifaceted intervention to implement a vancomycin dosing and monitoring guideline across multiple units over time.

2. Patients and methods

2.1. Study setting and design

The study was an observational cohort before-and-after interventional design. The study was conducted at Flinders Medical Centre (FMC), a 580 bed government university teaching hospital in Adelaide, Australia. The interventional cohort was all adult patients treated with vancomycin during the months, September to November over three years 2012–2014. This interval is defined as the follow-up period. A pre-implementation comparator group included all patients treated with vancomycin during the months August to December over two years 2010–2011. Ethical approval for the study granted by the Southern Adelaide Clinical Human Research Ethics Committee, Australia (approval number 123.12).

2.2. Patients

Admitted patients ≥18 years receiving vancomycin who had ≥1 vancomycin concentration result were included in the study. Patients were identified from the daily therapeutic drug monitoring report generated by the biochemistry department. Patients were excluded if they commenced treatment in the intensive and critical care unit (ICCU), receiving hemo- or peritoneal dialysis, this was due to both units having dedicated vancomycin dosing protocols.

2.3. Serum creatinine measurement and creatinine clearance calculation

Serum creatinine (S_{Cr}) concentrations were measured using Roche (Basel, Switzerland) C702 enzymatic method. Calculation of creatinine clearance (CrCl) was performed using the Cockcroft-Gault equation,

$$\text{CrCl (mL/min)} = \{[(140 - \text{age years}) \times \text{body weight kg}] / (72 \times S_{Cr}\ \text{mg/dL})\} \times 0.85\ \text{(if female)}$$ [27].

2.4. Vancomycin guideline

The vancomycin dosing and monitoring guideline for adults used in this study was based on a guideline developed for a single unit pilot study in our institution [26], later used in a broader proof of concept study across medical and surgical units [28]. The guideline largely reflected the North American consensus recommendations adapted with Australian Therapeutic Guidelines content on vancomycin [29,30]. The current study guideline was endorsed with input from institutional leaders in infectious diseases, clinical pharmacology and pharmacy, refined in early 2012 and uploaded to the institutions intranet in August 2012. *Key prescribing features were*: a loading dose of 25 mg/kg at discretion of prescriber and maintenance dosing determined by CrCl (>90 mL/min 1.5 g 12-hourly; 60–90 mL/min 1 g 12-hourly; 20–59 mL/min 1 g 24-hourly; <20 mL/min 1 g every 2–7 days with vancomycin TDM 48-hourly). *Key monitoring features were*: timing of initial trough blood sample for concentration measurement was determined by CrCl (>60 mL/min required blood to be taken prior to the fourth dose; 20–59 mL/min before the third dose and <20 mL every 48-hourly until target (15–20 mg/L) attainment) (Supplementary file 1). In the pre-implementation period there was no institutional guidance on vancomycin dosing and monitoring except for a comment on pathology result record or electronic report of a target range 15–20 mg/L. This comment remained in effect for the follow-up period.

2.5. Target audience

The principal target audience of the implementation strategy was junior medical officers (postgraduate years 1 and 2) as they perform the majority of prescribing and pathology test ordering in our and many other institutions [31]. However, all medical, pharmacy and nursing staff were potential end-users of the guideline.

2.6. Interventions

There were four components to the multifaceted intervention to support the release of the guideline: 1) educational session, 2) an online continuing education module on vancomycin with knowledge assessment, 3) dissemination of printed material and 4) email reminder alert.

Education session: Learning objectives for the session were for JMOs to become familiar with the guideline and be able to dose and monitor vancomycin effectively for patients. Three identical 60-minute face-to-face educational sessions were provided to JMOs periodically through the year. The session was provided in a dedicated university teaching room in the hospital, located in close proximity to patient wards, facilitating ease of attendance. Attendance was voluntary and no incentives were offered other than lunch. The session contained information on pharmacology and indications, local audit data on vancomycin prescribing and monitoring, and MRSA prevalence. Issues of reduced susceptibility to vancomycin and minimising the development of resistance, limiting nephrotoxicity and the pharmacoeconomics of comparative agents was presented. Importantly the session included a clinical vignette with practical advice on how to dose and monitor vancomycin. The sessions were delivered by CJP a pharmacist educator who is an experienced facilitator, has expertise in clinical education, pharmacotherapy of infectious diseases and therapeutic drug monitoring. Fidelity of the content and delivery of the educational sessions was assured by CJP providing all sessions over 2012–14. One variance to this was the addition of the Infectious Diseases registrar as a co-presented at sessions in 2012.

Online continuing education: was provided to JMOs in the latter half of the hospital training year over 2012–14. The CME document was formally emailed via the Trainee Medical Officer Unit. The CME contained background information on vancomycin and how to dose and monitor vancomycin and a clinical vignette and questions. The details of this intervention have been provided in detail elsewhere [32]. An electronic copy of the guideline was also provided with the CME.

Dissemination of printed material (pocket guideline): A small pocket size version of the guideline (6 cm × 10 cm) compatible for attaching to hospital identification badges was provided to all JMOs. The pocket guideline was disseminated at all vancomycin educational sessions and from the Trainee Medical Officer Unit for those unable to attend. The pocket guideline was also provided to all pharmacy staff in their clinical induction.

Email alert: The Director of Medical Services sent a reminder email to all medical staff soon after the guideline was uploaded to the intranet (August 2012). The email advised staff where to locate the guideline and requested staff adherence to the guideline.

2.7. Outcome measures/process measure

Outcomes measures for vancomycin prescribing: loading doses, first maintenance dose adherent to guideline and appropriate dosage adjustment in response to concentrations outside target range, i.e. if a vancomycin concentration returned below target, was the next dose increased? Conversely, if the vancomycin concentration result was above target range, was the next dose reduced? Monitoring outcomes were proportion of vancomycin initial concentrations taken at steady-state concentration, proportion of appropriate pre-dose trough concentrations, attainment of trough concentrations in therapeutic range (15–20 mg/L) and time to achieve therapeutic range, and potentially nephrotoxic trough concentrations (>20 mg/L). Nephrotoxicity was included as a safety outcome, defined as a rise in serum creatinine of ≥50% or 50 mg/dL from baseline on two or more consecutive days of vancomycin therapy in the absence of an alternative explanation [33]. A process measure was the frequency of intranet access of the vancomycin guideline.

2.8. Power calculation and statistical analysis

The study was powered to detect similar differences in the proportion of patients within target range between pre and post intervention periods to those observed in the pilot study where we observed a 16.9% increase from 26.9% to 43.8% [26]. Assuming a similar proportion of 26.9% at baseline, a sample size of 125 subjects in both the pre and post intervention groups (n = 250 total) would be required to have 80% power to detect the same increase at a two-sided Type 1 error rate of $P < 0.05$. The study had more than 90% power to detect a reduction in the median time to target range from 5 days to 3 days, similar to the changes observed in a pilot study. Differences in clinical characteristics of subjects between the pre and post-implementation phases was assessed using an independent *t*-test for normally distributed continuous variables and a Mann-Whitney *U* test for non-normally distributed data. Differences in proportions and categorical variables were assessed using 2-sample tests of proportions and chi-squared tests of association respectively. Differences in the time to reach therapeutic range since commencing vancomycin between subjects was assessed using Kaplan-Meier plots and log-rank statistics. Subjects that did not reach the therapeutic range were censored at the end of their follow-up period. All analysis was performed using Stata version 14.1 (StataCorp, Texas, USA).

3. Results

3.1. Patient characteristics

There were 258 subjects in the study. The interventional cohort consisted of 133 patients receiving vancomycin treatment in hospital and the pre-implementation cohort included 125 patients. Patient characteristics between the two groups were similar with exceptions in the pre-implementation group which had a longer median stay, more patients coming from residential aged care facilities, higher vancomycin-resistant Enterococcus (VRE) colonisation and more patients managed by surgical teams. More patients in the post-implementation group had comorbidity with malignancy and congestive heart failure (Table 1). There were no differences between groups for infection site or microbiological data (Table 2).

3.2. Outcomes measures

In the post-implementation group, there were significant increases in guideline-adherent prescribing of loading and first maintenance doses. The median time with interquartile range (IQR) of the first concentration attained in therapeutic target range reduced significantly from 6 (4–9) to 4 (3–6) days in the post-implementation group ($P = <0.001$) (Table 3). The time taken to reach target for all patients that had a measured concentration was significantly reduced from 25 to 13 days post-implementation ($P = <0.001$) (Fig. 1). The overall duration of vancomycin therapy decreased from a median of 9 days (IQR 5–13) to 5 days (4–9) for those in the post implementation group ($P = <0.001$).

The proportion of initial concentrations drawn at the correct times (i.e. vancomycin reached steady-state concentration in the serum) improved from 43.2% to 51.9% in the post-implementation group ($P = 0.01$). A significantly greater number of patients post-implementation attained target trough range (15–20 mg/L) 32.6% vs 44.1% ($P = <0.001$), and fewer reached potentially nephrotoxic trough concentrations (>20 mg/L) with a decrease from 30.7% to 20.9% post-implementation ($P = <0.001$). The safety outcome of nephrotoxicity post-implementation was also significantly decreased from 10.4% to 6.8% ($P = <0.001$) (Table 3).

A sub-analysis was performed on those patients that attained their initial concentration within target range (n = 9 pre-implementation and n = 32 post-implementation) and whether

Table 1
Baseline characteristics of patients receiving vancomycin treatment.

	Pre-implementation 2010–11 $n = 125$ (%)[b]	Post-implementation 2012–14 $n = 133$ (%)[b]	P[a]
Characteristic			
Age, years mean (SD)	64.4 (19.2)	63.7 (19.5)	0.77
Male sex	74 (59.2)	79 (59.4)	0.54
Residence in RACF	64 (51.2)	26 (19.5)	<0.001
Prior admission to hospital ≤12 months	95 (76%)	89 (66.9)	0.07
Prior colonisation with MRO in ≤12 months			
MRSA	49 (39.2)	37 (27.8)	0.05
VRE	26 (20.8)	14 (10.5)	0.02
CrCL, mL/min mean (SD)	102.7 (60.8)	93.5 (52.5)	0.19
Weight, kg mean (SD)	81.2 (21.9)	78.1 (22.7)	0.27
Comorbidities			
Diabetes	36 (28.8)	37 (29.3)	0.86
Malignancy	15 (12)	30 (22.6)	0.03
Valvular disease	12 (9.6)	7 (5.2)	0.18
Congestive heart failure	4 (3.2)	17 (12.8)	0.005
Medication/allergic status			
Aminoglycoside	23 (18.4)	32 (24.1)	0.27
Penicillin/β-lactam allergy	39 (31.2)	34 (25.6)	0.32
Treating team			
Medical	43 (34.4)	62 (46.6)	0.04
Surgical	82 (65.6)	71 (53.4)	0.04
Days of admission; median (IQR)	10 (3–17)	13 (7.8–24.3)	0.02

[a] Using a 2-sample test of proportions.
[b] Unless otherwise stated: CrCL, creatinine clearance; IQR, interquartile range; RACF, residential aged care facility; MRO, multi-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; SD, standard deviation; VRE, vancomycin-resistant *Enterococcus*.

they were prescribed recommended loading and initial maintenance doses. Pre-implementation only 3 patients of the 9 (3/9) 33.3% received recommended prescribing compared to 12/32 (37.5%) post-implementation ($P = 0.82$). A sub-analysis was also performed on those patients that acquired nephrotoxicity (n = 13 pre-implementation and n = 9 post-implementation) and whether they received an appropriate initial maintenance dose. Pre-implementation 6 patients (9/13) 43.2% were prescribed appropriate initial maintenance doses compared to 5/9 (55.5%) post-implementation ($P = 0.66$).

The effect changes observed for prescribing, monitoring and duration of treatment for the post implementation group were largely sustained or improved when examined by individual year for 2012, 2013 and 2014 (Table 4). A notable variant was nephrotoxicity, which had a lower incidence in 2012 and 2013 compared to pre-implementation data, however 2014 data was unchanged from pre-implementation data.

3.3. Process measure

The vancomycin guideline accessed from the hospital intranet was recorded monthly from upload in August 2012 until December 2014. The guideline was consistently accessed with a mean and standard deviation (±SD) 88.6 ± 21.8 times per month over the follow-up period.

4. Discussion

In this study we demonstrated that a multifaceted intervention improved guideline-adherent vancomycin prescribing, resulting in

Table 2
Infection site requiring vancomycin treatment and microbiological data.

	Pre-implementation 2010–11 $n = 125$ (%)[b]	Post-implementation 2012–14 $n = 133$ (%)[b]	P[a]
Infection site			
Bacteraemia/cardiac	29 (23.2)	29 (21.8)	0.89
Synovial/prosthetic	23 (18.4)	9 (6.8)	0.41
CNS/cranial	11 (8.8)	2 (1.5)	0.74
Skin & soft tissue infection	39 (31.2)	44 (30.1)	0.91
Osteomyelitis	11 (8.8)	10 (7.5)	0.91
Respiratory	9 (7.2)	8 (6)	0.92
GI/abdominal infection	13 (10.4)	8 (6)	0.73
Pyrexia of unknown origin	12 (9.6)	20 (15)	0.66
Organism[c]			
MRSA	40 (32)	35 (26.6)	0.61
Enterococcus spp	16 (12.8)	14 (10.5)	0.85
CoNS	5 (4)	8 (6)	0.87
Staphylococcus epidermidis	10 (8)	10 (7.5)	0.97
MSSA	12 (9.6)	15 (11.3)	0.89
Other	15 (12)	15 (11.3)	0.95
No growth detected	24 (19.2)	36 (27.1)	0.48
No specimen collected	3 (2.4)	0	0.11

[a] Using a 2-sample test of proportions.
[b] Unless otherwise stated: CNS, central nervous system; GI, gastrointestinal; Spp, bacterial species; MRSA, methicillin-resistant *Staphylococcus aureus*; CoNS, coagulate negative *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.
[c] Note some patients had infection with more than one organism.

Table 3
Outcomes measurements of vancomycin prescribing and monitoring.

	Pre-implementation 2010–11 $n = 125$ (%)[b]	Post-implementation 2012–14 $n = 133$ (%)[b]	P[a]
Prescribing			
Loading dose prescribed	12 (10.4)	58 (43.6)	<0.001
First maintenance dose adherent	55 (44)	91 (68.4)	0.04
First dose adjustment correct[c]	51/96 (53.1)	60/82 (72.2)	0.009
Days of vanco treatment; median (IQR)	9 (5–13)	5 (4–9)	<0.001
Monitoring			
Total number of conc. per treatment days	506/977 = 0.52	408/1061 = 0.38	0.12
Css. adherent timing of initial conc.	54 (43.2)	69 (51.9)	0.01
Days until first conc. in target; median (IQR)	6 (4–9)	4 (3–6)	<0.001
Potentially subtherapeutic conc. <10 mg/L	48 (15)	34 (12.1)	0.71
Conc. in target range 15–20 mg/L	104 (32.6)	124 (44.1)	0.001
Potentially nephrotoxic conc.>20 mg/L	98 (30.7)	59 (20.9)	<0.001
Nephrotoxicity	13 (10.4)	9 (6.8)	<0.001

[a] Using *t*-test for normally distributed data, Mann-Whitney *U* test for non-normally distributed data, and chi-squared tests for categorical data.
[b] Unless otherwise stated: Conc, concentration; Css, concentration steady-state achieved; IQR, interquartile range; vanco, vancomycin.
[c] first dose adjustment correct where vancomycin continuing and not in target range.

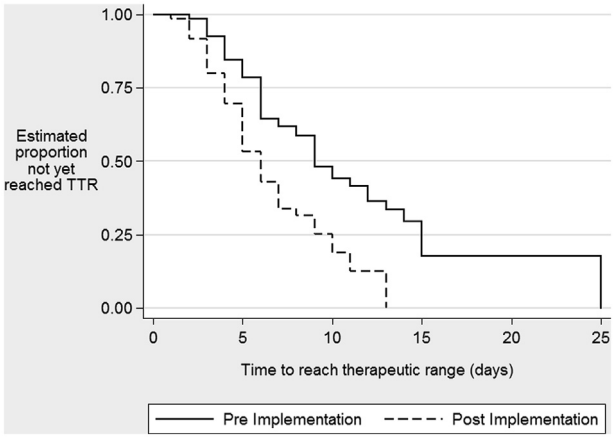

Fig. 1. Kaplan Meier plot – time to reach therapeutic range.

hospital inpatients more rapidly attaining target concentrations, which have been associated with improved clinical outcomes and reduced risk of nephrotoxicity [34,35]. The findings observed in the current study were generally consistent with our pilot [26], and we showed meaningful reductions in the duration of vancomycin treatment and nephrotoxicity. We have been explicit in reporting our methodology and study design which has recently been identified as a priority when seeking to change behaviour regarding the use of antibiotics in hospitals [36], and specifically for guideline dissemination and implementation [37]. Furthermore, we have quantified the effect of our multifaceted intervention, which comprises commonly recommended strategies, specifically for the purpose of implementing a vancomycin guideline.

A major review on the effectiveness of guideline dissemination and implementation strategies found that the majority of multifaceted interventions had a median absolute improvement in care of 14.1% for reminders and 8.1% for dissemination of educational material [38]. Our study used education, dissemination of educational material and reminder email. We observed more than a four-fold increase in prescribing of loading doses, a fifty-percent rise in appropriate maintenance dosing and a thirty-percent rise in attainment of target range. We used face-to-face educational sessions as a key pillar of our implementation strategy. A Cochrane review on educational meetings and workshops in healthcare found from 30 trials, the median (IQR) difference in compliance for practice measures was a modest 6% (1.8%–15.9%) where education was a component of an intervention compared to no intervention. Mixed interactive and didactic educational meetings had a difference median of 13.6%. The median (IQR) difference observed on

Table 4
Temporal outcome measures for all years of vancomycin prescribing and monitoring.

	Pre-implementation	Post-implementation		
	2010–11	2012	2013	2014
	$n = 125$*	$n = 39$*	$n = 48$*	$n = 46$*
Prescribing				
Loading dose prescribed	12 (10.4)	10 (25.6)	28 (58.3)	20 (43.5)
First maintenance dose adherent	55 (44)	25 (64.1)	32 (66.7)	34 (73.9)
First dose adjustment correct[a]	51/96 (53.1)	18/28 (64.3)	30/48 (62.5)	21/24 (87.5)
Days of vanco treatment; Median (IQR)	9 (5–13)	4 (4–11.5)	6 (4–10.8)	5 (3–7)
Monitoring				
Total number of conc. per treatment days	506/977 = 0.52	132/345 = 0.38	155/411 = 0.38	121/305 = 0.40
Adherent pre-dose trough conc.	319/506 (63)	98/132 (74.2)	96/155 (61.9)	87/121 (71.9)
Css adherent timing of initial conc.	54 (43.2)	21 (53.8)	25 (50.1)	23 (50)
Days until first conc. in target; median (IQR)	6 (4–9)	4 (3–6)	5 (3.5–6)	3 (2.3–5)
Potentially subtherapeutic conc. <10 mg/L	48 (15)	16 (16.3)	8 (8.3)	10 (11.5)
Conc. in target range 15–20 mg/L	104 (32.6)	41 (41.8)	45 (46.9)	38 (43.7)
Potentially nephrotoxic conc. >20 mg/L	98 (30.7)	18 (18.4)	23 (24)	18 (20.7)
Nephrotoxicity	13 (10.4)	3 (7.7)	1 (2.1)	5 (10.9)

*n, (%) Unless otherwise stated: Conc, concentration; Css, concentration steady-state; IQR, interquartile range; vanco; vancomycin.
[a] First dose adjustment correct where vancomycin continuing and not in target range.

patient outcomes was only 3% (0.1%–4.0%) [17]. A Cochrane review on providing educational material to physicians when compared to no intervention showed a median (IQR) effect increase for categorical measures of 2% (0%–11%) and a mean (range) effect increase of 13% (16%–36%) when followed-up to 6 and 9 months respectively [39]. We provided an electronic CME on vancomycin and a printed pocket guideline to junior doctors. The magnitude of effect for each of our interventions is unclear, however the changes in our outcome measures are considerable in excess of those reported above.

Although our study demonstrated significant improvements for most outcomes measures, that fact remains that less than half of all vancomycin concentrations were within the target range and there is still considerable room for improvement. This study focused on building prescribers knowledge of the clinical use vancomycin, and awareness of consequences to patients if vancomycin is not prescribed appropriately. The reasons why some doctors did not use the guideline are not clear. It has been reported in the literature that some doctors may lack agreement with guidelines, have a distrain for rigid medicine and guidelines may be seen as encroaching on professional autonomy and a disbelief that following the guideline will achieve the desired outcomes [15]. Furthermore, insufficient time to use guidelines, lack of peer or superiors support, have also been identified as factors influencing adherence to guidelines [16]. It is important these attitudinal factors are given greater consideration when designing implementation strategies to improve the ongoing use of vancomycin.

A strength of this study was that the implementation strategy was executed consistently and with fidelity, providing confidence in the results. The sustained effect observed over three years provides further confidence as many other studies measuring the effect of vancomycin guidelines are much shorter in duration. The finding from this study are corroborated with the process measure of intranet access of the guidelines over the same time period demonstrating a consistency of electronic access to the guideline. Considerable rigour has gone into reporting the details of our interventions, in particular the educational component to enable others to reproduce our work. We assessed our description of the educational component of the intervention against a recently published guidance for the reporting of evidence-based educational interventions in health and found 13 of the 17 criteria were met [40]. Our study had some limitations. The study was conducted at a single centre and data was collected retrospectively. There were some significant differences in baseline characteristics that may have impacted on the results. Notably pre-implementation there were more patients from residential aged care facilities with higher rates of VRE colonisation, suggesting these patients may have been more complex and frail. This in turn may have made attainment of appropriate vancomycin target concentrations more difficult. However, post-implementation more patients having malignancy and congestive heart failure may have also adversely impacted monitoring outcomes. Cancer has been reported to alter clearance of vancomycin [41], and congestive heart failure is known to decrease vancomycin clearance [42]. Potentially both these factors may have resulted in more patients failing to attain target concentration. Furthermore the longer median duration of admission post-implementation can be attributable to an unusually complex patient with a surgical site infection that was admitted for 107 days.

Whilst provider or facilitator fatigue did not feature in this study, it is possible that this may be a variable which could bias results. Future elements to add to this multifaceted intervention, could be the incorporation of guideline content into electronic prescribing as has been suggested by the IOM [8]. In recent times much has been made of pharmacokinetic/pharmacodynamic monitoring of vancomycin using area-under-the-curve (AUC)/minimum inhibitory concentration (MIC) originally derived by Moise et al. [43], and MRSA isolates with elevated MIC [44]. We elected not to promulgate AUC/MIC monitoring in our guideline nor sought to record it as an outcome measure, as a recently published study on MRSA clinical isolates from our institution found all MRSA isolates had an MIC $\leq$1 mg/L when determined by broth microdilution [45].

These data confirm the efficacy over time of a systematic implementation strategy to improve the dosing and monitoring of vancomycin which is likely to be similarly applicable to other antimicrobial agents and as well as to improving prescribing more broadly. Our findings provide some guidance to those tasked with allocation of resources for local guideline implementation, enabling clinicians to make informed decision when treating their patients with vancomycin.

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Conflict of interest

All authors report no conflict of interest in relation to this work.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jiac.2017.09.010.

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Chapter 8: Discussion, conclusions and future directions

8.1 Use of theory in identifying barriers and designing interventions

Implementing evidenced-based recommendations into clinical practice is challenging. (171) The role of using a theoretical framework (Chapter 3) to assess the barriers and enablers in designing our interventions to improve the prescribing and monitoring of vancomycin was important, as this led to interventions which were tailored to our setting. We identified barriers spanning domains of knowledge, skills, beliefs about consequences, environmental context and resources, memory and attention to decision processes. A recent Australian study examining factors influencing appropriate vancomycin prescribing found that specific assessment of barriers needs to be undertaken, prior to interventions targeting those barriers can be employed. (145) Authors have been calling for more detail in the use of theory in studies using interventions to change the practice of clinicians, including designing interventions seeking to improve the use of antibiotics. (115) Furthermore, a systematic review identifying studies employing interventions targeting practitioners' behaviour in healthcare found interventions are likely to be more effective when theory is used in designing the interventions. (172)

8.2 Interventions

A majority of studies in the medical literature employing multifaceted interventions to improve antibiotic use have focused on reducing the usage (quantity) of antibiotics, rather than optimising appropriate prescribing and monitoring. After identifying our barriers, we determined which interventions would be suitable. We identified interventions that had been used to implement other clinical practice guidelines and care initiatives and then used a theoretical framework to determine which interventions would be best suited in our tertiary care setting. We elected to employ a multifaceted intervention including implementation of clinical practice guidelines, face-to-face education, CPD modules, provision of a pocket

guideline, use of email communication and reminders to target the prescribing and monitoring of vancomycin. Furthermore, we tailored our educational intervention to our target audience, as proposed in a recent systematic review of educational interventions to change prescribing behaviour in hospital. (125) In our systematic review and meta-analysis (Chapter 2), we found that studies employing multifaceted interventions were more effective than single intervention studies. The effect of the multifaceted intervention was successful in improving prescribing monitoring and safety outcomes described below, however from our data it is not possible to identify which components(s) if the interventions were most effective.

In this thesis I describe the implementation of clinical practice guidelines for dosing and monitoring of vancomycin. Whilst there are numerous vancomycin guidelines in the grey literature (42), there are only three countries (USA, Japan and China) where professional societies have published 'national' guidelines. (41, 141, 173) Only the protocol for the guideline from the Chinese Pharmacological Society makes any reference to how the guideline will be implemented or how to evaluate implementation. (174) No analysis has been published to date post implementation of the Chinese guideline. Our work adds to the literature on this topic regarding how to implement vancomycin dosing and monitoring guidelines and how to evaluate the implementation.

8.3 Prescribing, monitoring and nephrotoxicity

Through the work undertaken in this thesis, we found that prescribing and monitoring of vancomycin was improved and nephrotoxicity reduced with implementation of a multifaceted intervention bundle. Our systematic review (Chapter 2) contributed to broader understanding of this topic by synthesising the literature, and found that prior to our study assessing the effect of interventions over time (Chapter 7) (104), the published works on this topic generally had

small sample sizes, were conducted over short durations, and were a mix of multifaceted and singular interventions. Studies had a greater emphasis on vancomycin monitoring rather than dosing. The methodological quality of these studies was rated as having a moderate or serious risk of bias. In the literature some have debated about whether multifaceted interventions produce any better effects than single interventions. (175) We found studies with only a single intervention had no effect on measured outcomes (106), while studies with two intervention had larger effects. (107, 108) Overall greatest effects on outcomes were seen in studies with three or more interventions, involving introduction of guideline, face-to-face education, and provision of pocket dosing and monitoring cards. (104, 109)

8.3.1 Prescribing

We found that our multifaceted intervention targeting vancomycin dosing and monitoring increased doctors' prescribing appropriate loading doses, absolute effect size 34% (p=<0.001) compared to other studies employing two interventions with non-significant absolute effect differences compared to usual care -1%; (p=N/R)(108), and 2.4% (p=0.68). (107) Loading doses have been found to facilitate rapid attainment of therapeutic target range. (176) Improvement in appropriate initial maintenance dosing after our multifaceted interventions produced an absolute effect size of 24.4% (p=<0.001) (104), which was similar to another study with three interventions which had an absolute effect size of 27% (p=<0.0001) (109), providing some confidence in the effect sizes suggesting these results maybe reproducible with those interventions.

8.3.2 Monitoring

Regarding monitoring of vancomycin, our multifaceted intervention demonstrated a 10% (p=<0.012) absolute effect change in the number of patients attaining therapeutic target. In

contrast another study which did not include any dissemination of educational materials showed an absolute effect change of -3% (p=N/R). (108) We also achieved reductions in the time taken to achieve therapeutic target post-intervention from 6 (IQR 4-9) to 4 (IQR 3-6) days. Our multifaceted intervention showed an absolute reduction in the proportion of patients with subtherapeutic vancomycin levels (<10mg/L) by 9.8% (p=<0.001) contrasted against a prior study which produced a 3% (p=N/R) absolute reduction by employing only two interventions and no dissemination of educational materials. (108) Meaningful reductions in the proportion of subtherapeutic vancomycin levels are important, as low vancomycin levels (<10mg/L) have been associated with the emergence of *S. aureus* isolates which have reduced susceptibility or resistance to vancomycin. (24)

8.3.3 Nephrotoxicity

Our multifaceted intervention resulted in an absolute decrease 3.6% (10.4% - 6.8%; p=<0.001) in rates of nephrotoxity. (141) This effect was larger than another study comprised of two interventions that did not include dissemination of educational materials 2.4% (16.7% - 14.3%; p=0.197). (107)

8.3.4 Outcomes maintained

We found that the prescribing, monitoring and safety outcomes were maintained three years after implementing the multifaceted intervention (Chapter 7). This is meaningful as our study had the longest follow-up of any study evaluating the effect of interventions targeting vancomycin prescribing and monitoring. Other studies included in our systematic review evaluated interventions over only short durations (<12 months) (105-109). Additionally our study provided much greater detail of interventions and fidelity of implementation than any other study to our knowledge targeting vancomycin prescribing and monitoring, which is

important as it permits others to replicate our work.

8.5 Confidence and Knowledge

We undertook studies on the impact of face-to-face education, continuing professional development (CPD) modules and provision of a pocket guideline on knowledge scores and clinician preparedness to use vancomycin (Chapter 5).

8.3.5 Preparedness

Prior to any intervention, pharmacists reported self-confidence (agreement they were prepared) to provide advice on all areas of vancomycin management except managing an infusion related reaction. When comparing junior doctors' confidence from the start to the end of their training year, those that underwent face-to-face education were more confident for only three of the 10 domains; knowing when to first measure vancomycin levels, knowing how often to measure levels and how to interpret levels to inform dosing compared to those that did not attend the education. At the end of their training year, junior doctors that were in possession of a pocket guideline reported significantly higher self-confidence to; treat patients with vancomycin, choose a maintenance dose and manage an infusion related reaction.

8.5.6 Knowledge

Pharmacists who completed an electronic CPD module had very high scores >94% for eight of 10 questions which was similar to junior doctors who scored >88% for seven of 10 questions. Questions were similar although not identical for each group. Interestingly, both professional groups obtained lowest scores for managing the infusion related reaction 'red man syndrome' with pharmacists scoring 77% and junior doctors 61%. Both CPD modules contained advice on how to manage an infusion related reaction, however greater content and increased use in

clinical vignettes may have improved the score for managing this adverse drug reaction. When knowledge scores were evaluated for junior doctors that attended face-to-face education or were in possession of a pocket guideline, the intervention showed no effect on knowledge scores. This finding was counter intuitive and surprising. However, a study published after our work, undertook a similar approach assessing knowledge scores attained by hospital staff after completion of a vancomycin e-learning module. (177) Those authors also found no change in knowledge scores for pharmacists or doctors post completion of their e-learning module, however there was an improvement in knowledge scores of nursing staff.

Whilst face-to-face education and possession of a pocket guideline did improve preparedness (self-reported confidence) for some areas of vancomycin use, these interventions did not translate into improved knowledge scores. Based on these findings, we are unable to recommended face-to-face education, undertaking a CPD module or provision of a pocket guideline to improve knowledge scores. Small sample sizes in these studies (Chapter 5) with different groups over multiple time periods may have limited our ability to detect any effect on knowledge scores.

A 2019 qualitative study exploring perceptions of healthcare educators experienced with delivering education on vancomycin, and recipients of education on vancomycin provides some interesting reflections. (178) Both educators and recipients held views that nurses respond to in-services or e-learning modules, senior doctors needed 'convincing' of the merits of the education and 'if convinced', case based learning or academic detailing would be useful for seniors doctors, while e-learning and problem-based learning would be effective for junior doctors. These views on the best methods of delivering education on vancomycin in this study were not supported by reference to any data.

Whilst our educational work did not include nursing staff, or directly educate senior doctors, we did engage senior medical opinion leaders in the development of our vancomycin guideline and educational program including the CPD module. The CPD module contained problem-based learning and was completed online. Larger scale studies employing more tailored educational strategies to specific disciplines or subsets of disciplines may offer opportunity for future research.

8.4 Guidance on minimum inhibitory concentration determination and selection of vancomycin for therapy

Elevated vancomycin MICs of MRSA isolates within the susceptible range have been associated with poorer clinical outcomes. (48, 179) This has increased our need to better understand MIC results and methodologies used. In our antibiotic susceptibility work (Chapter 6), we studied vancomycin MICs of MRSA clinical isolates sourced from a diagnostic laboratory by three different methodologies, E-test®, VITEK2® and BMD. Previous work comparing these methodologies has shown varying results. (54, 55, 180) An MIC obtained from one method may be 0.5-1.5 dilutions higher when compared to a result from BMD from the same isolate. (181, 182) Whilst we found the level of agreement between the MIC methods to be relatively weak, we used this data to develop novel guidance to help clinicians to interpret the results of E-test® and VITEK2® against the gold stand standard BMD. We calculated the optimal cut-points for sensitivity and specificity for detection of a MIC ≥1mg/L by BMD for E-test® and VITEK2®. (183) This is important as clinicians have struggled to make sense of theses differing MIC results, in light of the fact diagnostic laboratories will rarely preform BMD (51).

When performing vancomycin pharmacokinetic / pharmacodynamic (PK/PD) monitoring, the

index found to be optimal for monitoring vancomycin is the area under concentration time curve (0-24hr) divided by the MIC of the MRSA isolate. This index AUC/MIC value is 400 which is reported to equate to a vancomycin trough level of 15mg/L. (63, 184) In using MIC results to inform dosing, authors have recently articulated the need to consider bias in MIC determination from automated methods compared to the standard BMD. (66) Our novel work providing guidance on MIC is important, as the draft 2019 Revised Therapeutic Monitoring of Vancomycin Consensus Guidelines of the Infectious Diseases Society of America, is recommending AUC/MIC vancomycin monitoring for all serious MRSA infections. (185) Examining the diagnostic accuracy and optimising the interpretation of MIC results may limit unnecessary escalation to another antibiotic when vancomycin will be effective to treat the infection.

8.5 Conclusions

This thesis and the work contained within, has systematically reviewed the literature on interventions targeting the prescribing and monitoring of vancomycin. Multifaceted interventions were more effective than use of any single intervention. A theoretical framework used to determine barriers to improving vancomycin use is described and our evidence-based intervention selected. We designed a multifaceted intervention comprised of development and implementation of clinical practice guidelines, face-to-face education, continuing professional development modules with assessment, dissemination of a pocket guideline and email communication and reminders. We found improved outcomes of dosing and monitoring of vancomycin, and reduced nephrotoxicity. Furthermore, these results were maintained over three years. Based on these findings we can recommend the multifaceted intervention to improve vancomycin dosing and monitoring.

When face-to-face education, continuing professional development module and the provision of a pocket guideline were evaluated for effect on knowledge outcomes of junior doctors and pharmacists, they had no measurable effect. However, they did increase preparedness for some areas of vancomycin clinical use by junior doctors and pharmacists. Thus, we are unable to recommend these interventions to improve vancomycin knowledge scores, however we can provide a moderate recommendation for use to increase clinician preparedness to use vancomycin.

We also established a method to provide practical guidance on how vancomycin susceptibility determination can be interpreted with multiple test results from routine diagnostic laboratories, compared against the gold standard broth-microdilution to inform treatment decision to use vancomycin. This novel work requires further exploration in a larger dataset.

The reduction in nephrotoxicity is a defined patient outcome. The question arises as to whether the multifaceted intervention that improved dosing and monitoring of vancomycin translates into other tangible patient outcomes. A study published after this work was completed, assessed the impact of implementing an antimicrobial stewardship interventional bundle on 30-day mortality rates in US veterans treated with vancomycin. (186) The authors of that study found that the multifaceted intervention including monthly education to junior doctors, audit and feedback, and antibiotic restriction, did decrease mortality in patients treated with vancomycin. However, others have criticised the statistical methods used to analyses this data. (187)

Questions from this work requiring further investigation are; what is the effect of each intervention? What is the role of electronic versus face-to-face education? How much should educational content be adapted for the discipline (pharmacy, medical, nursing) or cohort

(junior/senior) and what frequency of delivery is optimal? What is the most effective participant size for educational sessions? Is one-on-one academic detailing akin to practices employed by the pharmaceutical industry more effective (188), and what other models can be developed to facilitate education in the busy schedule of a clinician? Lastly, other interventions which may be employed to target vancomycin prescribing and monitoring should be explored.

8.6 Future directions

There are a number of interventions which offer potential benefit in targeting the prescribing and monitoring of vancomycin. These interventions are discussed below.

8.6.1 Information systems

Artificial intelligence

Information technology potentially offers opportunities to improve the prescribing and monitoring of vancomycin. Artificial intelligence (AI) and machine learning are currently being explored to combat infection and antimicrobial resistance. (189, 190) Whilst there is no published work canvasing AI to optimise the clinical use of vancomycin, researchers have discussed the utility of AI in regard providing decision support and prescribing antibiotics. (191) Concerns have been raised however about the inability of current technological systems to contextualise patient information and clinical scenarios. (192)

Smartphones

Smartphones have been used in many areas of healthcare, research and clinical education. (193-195) Smartphones have been shown to have a role as an interface for guidelines in the clinical setting providing support for prescribing antibiotics including vancomycin. (196) However, evaluation of smartphones as tools to improve antibiotic knowledge of junior doctors has been

underwhelming to date. (197) The ubiquitous availability of smartphones is likely to result in additional developments in apps and software with the potential to improve the prescribing and monitoring of vancomycin.

Computer physician order entry systems

Several studies employing an intervention utilising computer physician order entry (CPOE) systems have shown some promise in improving vancomycin prescribing and monitoring. This intervention requires the use of an electronic health record (EHR). One study implemented an order set (assessment of body weight and renal function for determining vancomycin dose) on physicians generating a vancomycin order. That study evaluated 522 vancomycin doses and found that there was an improvement in the number of appropriate doses from 99/279 (36%) to 114/243 (47%); p=0.008 post implementation. (198) A more recent study evaluating an order set for vancomycin dosing in an emergency department found appropriate dosing increased from 100/220 (45%) to 254/377 (67.4%); p=<0.05 post implementation. (199) A study assessing the impact of CPOE on vancomycin TDM found that blood was collected at an appropriate time for measurement of the first vancomycin level 52 (52%) to 70 (70%); p=0.01 post implementation. (200) Not all interventions employing automation in EHRs to optimize vancomycin dosing and monitoring have been successful. One very recent study found an increase in the frequency of monitoring but no change in the appropriateness of timing of those trough levels. (201) Use of CPOE interventions was not an option when we commenced our work targeting vancomycin dosing and monitoring as our institution did not have an EHR. As EHRs are increasingly adopted around the world, this presents opportunities for refinement of CPOEs and to improve vancomycin dosing and monitoring.

8.6.2 Increased understanding of barriers to appropriate vancomycin use

A recent Australian study undertook a qualitative approach to examine factors that hinder appropriate prescribing and monitoring of vancomycin. (145) This study canvased views of junior and senior clinicians, finding poor coordination between phlebotomy services and individual wards to ensure blood samples were taken at appropriate times to permit useful interpretation of vancomycin levels. Communication after-hours and patients transferred within hospital had implications on TDM being missed or delayed. Time constraints were identified, with clinicians reporting "not enough hours in the day", also leading to TDM being postponed. Clearly the area of phlebotomy, has an impact on the appropriateness of sample timing in relation to dosing, thus designing interventions which can overcome the traditional 'ward by ward approach' irrespective of timing of phlebotomy services will be helpful for TDM and subsequently informing clinicians to prescribe appropriate doses.

8.6.3 Economic modelling of interventions

The implementation of guidelines can have favorable outcomes to reduce waste of healthcare resources. (202) However, many large developers of guidelines do not necessarily provide information on resource use and cost (RUC) of recommendations to support the use of guidelines, let alone RUC on interventions to implement guidelines. (203, 204) It is important to understand the cost consequences of an intervention (single or multifaceted) before it can seriously be considered for implementation. (99) Costing the management of nephrotoxicity and its resultant sequelae from inappropriate (or appropriate) vancomycin dosing is complex (205), but worthy of further investigation to compared to the cost of interventions to reduce these adverse outcomes. A study assessing the health economics of patients treated for nosocomial MRSA pneumonia reported that patients receiving vancomycin (n=226) who developed nephrotoxicity (n=34) during their treatment incurred an additional USD $10, 361

in costs. (206) This figure is significant and warrants economic modelling against the costs of delivering the interventions described in this thesis.

8.6.4 Behavioural influences on antibiotic prescribing

There is increasing literature assessing the social and cultural forces influencing antibiotic prescribing behaviour. (207) Designing studies implementing interventions based on sound understanding of these factors will be more likely to be effectual. (208) Interventions addressing prescribing etiquette and clinical leadership with antibiotics offer further opportunities to target vancomycin prescribing and monitoring. (209, 210)

8.7 Closing remarks

If the interventions described above, or elements of them can be harnessed, this may translate into improved vancomycin prescribing and monitoring outcomes and limit the unnecessary escalation from vancomycin to broader spectrum antibiotics, and potentially prolonging the utility of this essential antibiotic.

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Appendices

Appendix 1: Clinical practice guideline: vancomycin dosing and monitoring for adults

Appendix 2: Vancomycin dosing and monitoring continuing medical education module with assessment

Appendix 3: Pocket guideline for vancomycin dosing and monitoring

Appendix 1

Vancomycin Dosing and Monitoring Guideline for Adults

Note: not to be used for meningitis. Alternative dosing recommended, consult Infectious Diseases Team

Creatinine Clearance (mL/min)		CrCL > 90 mL/min	CrCL = 60-90 mL/min	CrCL = 20-59 mL/min	CrCL < 20 mL/min (patient should be discussed with ID)
Loading dose		25mg/kg (actual bodyweight: maximum dose 2g) # For unwell patients or for rapid attainment of target conc.			
Maintenance Dosing (IV)		1.5g 12-hourly (or 15mg/kg ≤50kg)	1g 12-hourly	1g 24-hourly	1g 2-7 days (Re-dose when trough <20mg/L)
Monitoring Trough conc. (approx. 1 hr pre-dose)		Check initial trough concentration before fourth dose		Check initial trough concentration before third dose	Check initial trough concentration at 48 hours
Frequency of Subsequent Monitoring		Repeat trough concentration every 48 hours until stable, then repeat **twice** weekly			
Target range 15-20 mg/L		Therapeutic Range: trough (pre-dose) concentration of 15–20 mg/L For patients on continuous infusion at FMC or H@H target steady-state concentration of 20-25 mg/L			
Dosage Adjustment (Intermittent infusions)	Conc. < 10 mg/L	Convert to 1g 6-hourly (total daily dose 4g) Seek ID advice	Increase each dose by 500mg	Convert to 750mg 12-hourly	Re-dose when trough <20mg/L
	Conc. 10-14.9 mg/L	Convert to 1.25g 8-hourly	Increase each dose by 250mg	Convert to 500-750mg 12-hourly	
	Conc. 15-20 mg/L	No change required			
	Conc. 20.1 – 24.9 mg/L	Reduce each dose by 250mg			
	Conc. 25-30mg/L	Reduce each dose by 500mg	Reduce each dose by 250mg	Reduce dose by 250mg	
	Conc. > 30mg/L	Hold dose, re-check conc. after 24 hours & re-commence at reduced dose. Review renal function			
Administration		Vancomycin should be administered as an infusion over a period of at least 1 hour (to minimise infusion related red man syndrome). For higher dosage (>1g) the infusion time should be extended to 1.5-2 hours.			

#Round each dose to the nearest 250mg

- Total daily dose > 3g are best administered as 6-8 hourly
- Calculate CrCL via link or formula below http://rghapps.rgh.sa.gov.au/apps/gfr/gfrPlusFMC.aspx
- CrCL mL/minute = $\frac{(140 - \text{age}) \times (\text{weight in Kg})}{\textbf{0.815 x serum creatinine (}\mu\text{ mol/L)}}$ x (0.85 for females).

Contact unit clinical pharmacist or ID Registrar DECT phone (clinical 67709 or lab 67719) if further advice required

Vancomycin Dosing & Monitoring Guideline version 2.0. C. Phillips, D. Gordon & M. Martinello, June 2012 Document CC1.1380 Adapted from Vancomycin dosing & monitoring guidelines Royal Adelaide Hospital, Antibiotic Expert Group, Therapeutic guidelines: antibiotic. Version 14, 2010 and Rybak et al. Therapeutic monitoring of vancomycin in adult patients: a consensus view of the American Society of Health-System Pharmacists, the Infectious Disease Society of North America, and the Society of Infectious Disease Pharmacists. Am J Health-Sys Pharm 2009; 66:82-98. Please check SALAHN intranet to ensure current version. Due for revision June 2014

Approval: Vancomycin may require Infectious Diseases approval (see FMC Reserved Anti-Infective Protocol)

Loading dose: is not required for all patients however it will facilitate rapid attainment of target concentration when indicated.

Dosing: Calculate CrCL then select the appropriate maintenance dose from the table. Do not use eGFR for dosing.

Collection & labeling of blood vancomycin samples:

1. Blood to be collected in a green-top (lithium heparin) or white-top tube
2. Annotated on pathology request form:
   - Time of sample collection → this is essential for accurate interpretation of result
   - Time of last dose
   - Dosage regimen i.e. 1g q12h
3. Dose should not be withheld pending trough concentration result.

Monitoring: Confirm the blood vancomycin sample was taken at the right time to indicate a trough concentration.

Patients for Hospital at Home (H@H) administration of vancomycin:

- Patients to receive vancomycin via H@H administration will preferably have two consecutive vancomycin concentrations within target range prior to discharge.
- Please ensure treating team to provide H@H staff with appropriate signed pathology request forms (i.e. tick the rule 3 exemption to allow for continued use).
- A vancomycin concentration is to be taken 24 hours post-commencement of continuous infusion (target range 20-25mg/L). Monitoring of vancomycin concentrations and urea & creatinine will be required twice weekly until stable then weekly for patients receiving vancomycin via H@H.
- Infectious Diseases H@H registrar (page 48051) is responsible for amending vancomycin dosage and determining frequency of monitoring for patients being administered vancomycin by H@H.

Red man syndrome:

Red man syndrome is a non-immunological reaction which can occur during or shortly after an infusion of vancomycin, which is related to the rate of infusion. The reaction is mediated by histamine release, which can result in pruritus, flushing, erythematous rash (face, neck and upper thorax predominantly), fever, chills and in severe cases angioedema and hypotension. True IgE-mediated allergy can occur but is rare.

If a patient experiences an infusion related reaction to vancomycin:

1. Cease infusion
2. Administer antihistamine (fexofenadine 180mg PO)
3. Consider adrenaline if hypotensive (SBP<90mmHg)
4. Consult clinical pharmacist or Infectious Diseases team for advice on recommencement of vancomycin at a slower rate of infusion.

Vancomycin Dosing & Monitoring Guideline version 2.0. C. Phillips, D. Gordon & M. Martinello, June 2012 Document CC1.1380 Adapted from Vancomycin dosing & monitoring guidelines Royal Adelaide Hospital, Antibiotic Expert Group, Therapeutic guidelines: antibiotic. Version 14, 2010 and Rybak et al. Therapeutic monitoring of vancomycin in adult patients: a consensus view of the American Society of Health-System Pharmacists, the Infectious Disease Society of North America, and the Society of Infectious Disease Pharmacists. Am J Health-Sys Pharm 2009; 66:82-98. Please check SALAHN intranet to ensure current version. Due for revision June 2014

Appendix

Vancomycin Dosing & Monitoring Continuing Medical Education with Assessment

FMC, RGH & NHS: Southern Adelaide Local Health Network

Authored by: Cameron Phillips BPharm, MClinPharm, NHMRC Translating Research into Practice Fellow
Clinical Educator SA Pharmacy, Flinders Medical Centre

Vancomycin Dosing & Monitoring Continuing Medical Education

Learning objectives

1. Become familiar with the SALHN Vancomycin Dosing & Monitoring Guidelines for Adults.
2. To understand why it is important to appropriately dose and monitor vancomycin
3. To be able to accurately use the guideline to appropriately dose, monitor and manage patients' vancomycin therapy that are within the care of the SALHN.

Background

The *Vancomycin Dosing and Monitoring Guideline for Adults* has now been approved for use at all sites across the Southern Adelaide Local Health Network (FMC, RGH and NHS). (1) The purpose of this CPD is to provide trainee medical officers with an opportunity to understand some of the reasons for recommendations in the vancomycin guideline and to use the guideline to assist typical scenarios that may present in the management of patients receiving vancomycin while admitted at the SALHN.

The guideline was developed with input from FMC; Infectious Diseases & Microbiology, Clinical Pharmacology, Immunology, Pharmacy and Hospital in the Home (H@H) after review of the literature and review of Therapeutic Guidelines: antibiotic version 14 and the document, Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. (2, 3)

Vancomycin has been in use since the 1950s and yet we are still learning how to use it properly. (4) Vancomycin use increased significantly since methicillin (of the penicillin family) resistance to *Staphylococcus aureus* (MRSA) emerged. Vancomycin remains an important antibiotic and is the treatment of choice for serious MRSA infections and for the treatment of infection caused by coagulase-negative staphylococci, in addition vancomycin also has a role in the treatment of infection with *Staphylococcus aureus* when there is a serious allergy to penicillin. (5)

Efficacy, safety & resistance

To use vancomycin safely and with therapeutic effect, appropriate dosing and therapeutic drug monitoring (TDM) are required. As reports of vancomycin treatment failure continue to increase, appropriate dosing and TDM is becoming even more important, as vancomycin trough levels <10mg/L are associated with the development of resistant bacteria. (6)

Pharmaceutical products

SA Pharmacy departments have available 500mg and 1g vials of vancomycin for injection. Vancomycin 125mg oral capsules are also available for treatment of severe *Clostridium difficile* infection (not the subject of this CME).

Infectious Diseases (ID) approval
At FMC vancomycin is a restricted antibiotic requiring ID. The TMO staff member should seek ID approval prior to prescribing vancomycin. Details of the restrictions and exemption for vancomycin use are available in the *FMC Anti-infective reserved protocol* on the SALHN intranet.

Dosing & Administration

Loading dose
In recent years loading doses have demonstrated to safely shorten the time it takes to attain therapeutic target levels. (7, 8, 9) A key US recommendation supports a loading dose of 25mg/kg based on actual body weight capped at 2g maximum, which is the loading dose chosen for the SALHN Vancomycin Dosing and Monitoring Guideline for Adults. (3) A loading dose is not required to be used in all patients however it will be appropriate for a great majority of patients. If a patient has a serious infection then a loading dose is advisable. In any dose calculation, round the dose to the nearest 250mg to assist nursing staff with preparation of the infusion.

Maintenance doses
The first maintenance dose is determined by creatinine clearance (CrCl) and subsequent maintenance doses are determined by TDM and CrCl. For example if a patient has a CrCl >90mL/min, a dose of 1.5g 12 hourly is recommended (except in patients ≤60kg where 25mg/kg is recommended). Maintenance dosing for other CrCl ranges are listed below in Table 1. While some medical staff are keen to use the estimated glomerular filtration rate (eGFR) to choose the dose, please be aware that the maximum eGFR reported in Oacis is >60mL/min. With a reported eGFR >60mL/min you are unable to determine which dosing category the patients will be in; i.e. 60-90mL/min or >90mL/min. Always calculate CrCl, a hyperlink to the Therapeutic Guideline (eTG) CrCl calculator is embedded in the SALHN vancomycin guidelines. You will need to be using an SA Health computer for the hyperlink to work.

Table 1

CrCl (mL/min)	Dose
>90	1.5g 12 hourly (if ≤60kg give 25mg/kg 12 hourly)
60-90	1g 12 hourly
20-59	1g 24 hourly
<20	1g & then check vancomycin level at 48 hours

Dosing interval
If the total daily vancomycin dose is >3g, it is recommend the dosing interval be changed to 8 or 6 hourly. This change in dosing interval will significantly reduce the fluctuations in vancomycin levels that can occur in patients with high renal clearance i.e. CrCl >90mL/min.

Red man syndrome

Red man-syndrome is a non-immunological reaction which can occur shortly after or during an infusion of vancomycin, which is related to the rate of infusion (i.e. the drug is infused too quickly). The reaction is mediated via histamine release with typical patient presentation of puritis, flushing, erythematous rash (face, neck and upper thorax predominately), fever, chills and in severe cases angioedema and hypotension.

Management of red man syndrome

In the event that one of your patients develops red man syndrome the key considerations are;

1. Cease the infusion
2. Administer an antihistamine such as oral fexofenadine 180mg SR stat
3. Consider adrenaline stat if the patient is hypotension i.e. systolic blood pressure is <90mmHg
4. If your team wishes to continue with vancomycin, recommence the infusion at a slower rate i.e. double the original infusion duration that caused the initial reaction and monitor.

Monitoring

Vancomycin levels

Vancomycin levels should always be taken as a trough level i.e. approximately 1 hour pre-dose. (10) Peak levels are no longer considered useful. (11)

What is the Current therapeutic range for vancomycin?

In 2010 SA Pathology increased the therapeutic range to 15-20mg/L for intermittent intravenous infusions which is the range chosen for the SALHN Vancomycin Dosing & Monitoring Guideline for Adults. This is consistent with numerous recommendations, with the therapeutic range being increased due to increasing vancomycin minimum inhibitory concentrations (MIC) of *Staphylococcus aureus* and more treatment failure being reported when vancomycin is use for treatment of MRSA infection.

When to take the first vancomycin level?

This is determined by the half-life of the drug and the renal clearance of the patient. For patients with CrCl ≥60mL/min, taking the level before the fourth dose is recommended. If a patient has a CrCl of 20-59mL/min, taking the first vancomycin level is recommend before the third dose is recommended, and if CrCl <20mL/min, the guideline recommends taking the level at 48 hours. The loading dose should be considered the first dose when counting doses to determine when the level should be taken.

When should subsequent vancomycin levels be measured?

Trough levels should be taken every 48 hours until the patient is within therapeutic range (15-20mg/L) then repeated twice weekly. Serum creatinine should also be measured with the same frequency.

Interpretation of vancomycin levels

Always check the time the last dose was given on the medication chart (not just the time it was originally charted for). Vancomycin levels can be used to inform dosage adjustment.

Dose adjustment
There is a dosage adjustment table in the SALHN Vancomycin Dosing & Monitoring Guideline. When a patient's trough level becomes available it can be matched with the level range specified in the table with their current CrCl to identify if a dosage adjustment is required

More information
For more information or questions on vancomycin dosing and monitoring, please directed them to the Infectious Disease registrars, clinical pharmacists or Cameron Phillips NHMRC Fellow.

Acknowledgements
Thank you to Professor David Gordon, Head of Infectious Diseases and Microbiology FMC, Dr. Matt Doogue, Dept. Clinical Pharmacology FMC and Vaughn Eaton, Director of Pharmacy FMC & NHS for their review of this CME and associated questions. Special thanks also to Greg Roberts, Research Pharmacist RGH for incorporating the new vancomycin dosing and monitoring recommendations into the application GFR+ (dosing calculator) which is available on the SALHN intranet.

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Questions

To complete the questions you **MUST** answer them in the Survey Monkey link provided in the email that contained this CME. Please select the **MOST** appropriate answer. You may consult the SALHN Vancomycin Dosing & Monitoring Guideline for Adults & use a creatinine calculator while completing the questions as you would in normal practice. If you wish to receive feedback please enter your email address. Your individual results will remain confidential.

Question 1: What site are you currently working at? (FMC, RGH, NHS)

Question 2: What is your email address? (optional - this will be used to inform you of your confidential results)

Question 3: Did you attended an education session on vancomycin this earlier this year?

Case

Mr. AB is a 55 year old man with type 2 diabetes who is systemically unwell with fever and suspected sepsis/infection in the Acute Medical Unit. After 24 hours his blood culture result is positive (Gram-positive cocci). At 10:00am your treating decides to commence vancomycin, ID approval has been granted. What loading dose of vancomycin should be charted for Mr. AB?

Mr. AB's is 76kg & 176cm. His serum creatinine is 70 micromoles/L
Current medications: metformin 850mg q12 hourly, gliclazide MR 60mg mane & perindopril 5mg mane.
You will need to calculate the patients CrCl.

Q4: What loading dose of vancomycin would you chart?

A) 500mg
B) 1g
C) 1.5g
D) 2g

Q5: What subsequent maintenance dose of vancomycin will you chart for Mr. AB?

A) 500mg 12 hourly
B) 1g daily
C) 1g 12 hourly
D) 1.5g 12 hourly

Q6: Before which dose would you take the first vancomycin level?

A) Before the second dose
B) Before the third dose
C) Before the fourth dose
D) Before the fifth dose

Q7: If Mr. AB had a creatinine clearance of 30mL/min, before which dose would you take the initial vancomycin level?

A) Before the first dose
B) Before the second dose
C) Before the third dose
D) Before the sixth dose

Q8: What is the therapeutic range for vancomycin (for intermittent intravenous infusion) recommended by SA Pathology?
A) 5-15mg/L
B) 10-25mg/L
C) 15-20mg/L
D) <20mg/L

Q9: Mr. ABs initial vancomycin trough level is reported as 23.2mg/L. What dosage regimen will you chart?
A) 1g 12 hourly
B) 1.25g 12 hourly
C) Continue current dose
D) Withhold the next dose

Q10: When should Mr. ABs next vancomycin trough level be checked?
A) 24 hours
B) 48 hours
C) 72 hours
D) Further checking of level is not required

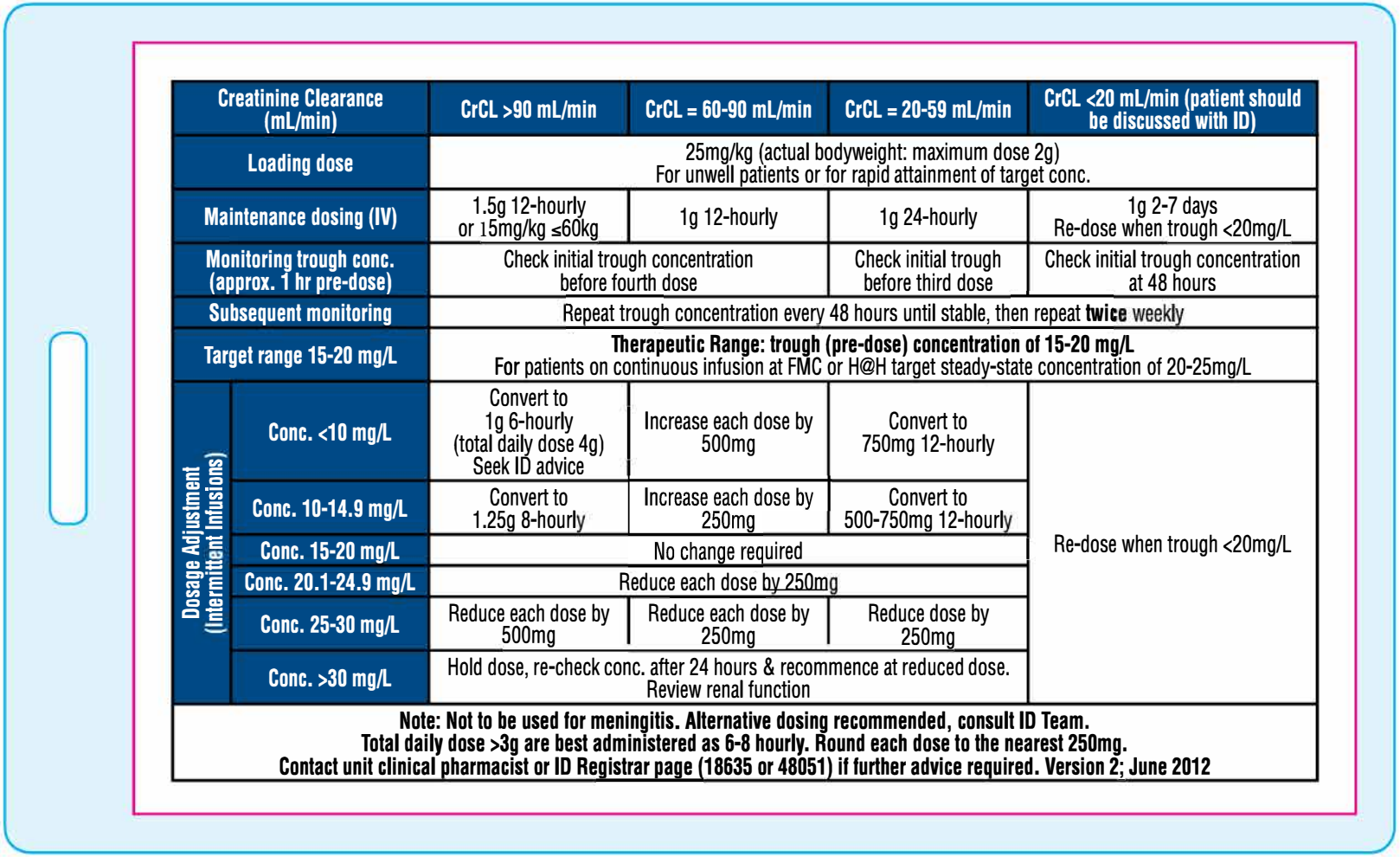
Q11: How often should a vancomycin level be taken once Mr. ABs vancomycin level is in target range (provided his renal function is stable)?
A) Every day
B) Twice weekly
C) Once a week
D) Once a fortnight

After one week of therapy (ID have recommended his course be 4 weeks in total, for MRSA bacteraemia) Mr. AB develops a red neck during his 0800 infusion of vancomycin (his medications are otherwise unchanged). You think it looks like 'red man syndrome' from what you know. Mr. ABs blood pressure is 135/80mmHg (consistent with his usual readings). Your registrar colleague discusses Mr. ABs presentation with immunology who advises that the reaction is likely to be red man syndrome and **NOT** a true IgE mediated drug reaction.

Q12: In addition to charting an antihistamine what will you do?
A) Continue the vancomycin infusion at half the previous rate
B) Cease the vancomycin infusion, resume in 3 hours at the previous rate
C) Cease the vancomycin infusion, resume in 3 hours at a slower rate
D) Cease the infusion, and recommend another antibiotic

Q13: How many consecutive vancomycin levels within target range will Mr. AB require PRIOR to him leaving the ward and Hospital at Home (H@)H) administering the remainder of his vancomycin therapy at home?
A) One level
B) Two levels
C) Three levels
D) Four levels

Appendix 3



Creatinine Clearance (mL/min)		CrCL >90 mL/min	CrCL = 60-90 mL/min	CrCL = 20-59 mL/min	CrCL <20 mL/min (patient should be discussed with ID)
Loading dose		25mg/kg (actual bodyweight: maximum dose 2g) For unwell patients or for rapid attainment of target conc.			
Maintenance dosing (IV)		1.5g 12-hourly or 15mg/kg ≤60kg	1g 12-hourly	1g 24-hourly	1g 2-7 days Re-dose when trough <20mg/L
Monitoring trough conc. (approx. 1 hr pre-dose)		Check initial trough concentration before fourth dose		Check initial trough before third dose	Check initial trough concentration at 48 hours
Subsequent monitoring		Repeat trough concentration every 48 hours until stable, then repeat **twice** weekly			
Target range 15-20 mg/L		**Therapeutic Range: trough (pre-dose) concentration of 15-20 mg/L** For patients on continuous infusion at FMC or H@H target steady-state concentration of 20-25mg/L			
Dosage Adjustment (Intermittent Infusions)	Conc. <10 mg/L	Convert to 1g 6-hourly (total daily dose 4g) Seek ID advice	Increase each dose by 500mg	Convert to 750mg 12-hourly	Re-dose when trough <20mg/L
	Conc. 10-14.9 mg/L	Convert to 1.25g 8-hourly	Increase each dose by 250mg	Convert to 500-750mg 12-hourly	
	Conc. 15-20 mg/L	No change required			
	Conc. 20.1-24.9 mg/L	Reduce each dose by 250mg			
	Conc. 25-30 mg/L	Reduce each dose by 500mg	Reduce each dose by 250mg	Reduce dose by 250mg	
	Conc. >30 mg/L	Hold dose, re-check conc. after 24 hours & recommence at reduced dose. Review renal function			

Note: Not to be used for meningitis. Alternative dosing recommended, consult ID Team.
Total daily dose >3g are best administered as 6-8 hourly. Round each dose to the nearest 250mg.
Contact unit clinical pharmacist or ID Registrar page (18635 or 48051) if further advice required. Version 2; June 2012