PROTOCOL

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

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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 (PIKO)

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).
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 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].
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 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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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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