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Short Communication
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Vancomycin: an overview on current alternative antibiotic therapy to vanquish

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Abstract

Objectives For more than 60 years, vancomycin has continued to be in clinical use despite drug resistance. Therefore, finding alternative antibiotics to vancomycin is of great need and urgency. The main objective was to provide robust evidence for the clinical pros and cons of these alternatives.
Methods A rigorous literature search was conducted for studies involving vancomycin and suitable alternatives such as teicoplanin, linezolid, tedizolid, dalbavancin, telavancin, daptomycin, tigecycline, quinupristin/dalfopristin (streptogramins) and ceftobiprole/ceftaroline (cephalosporins).
Key findings This review explored the limitations associated with the clinical utility of vancomycin in day-to-day clinical practice. New remedies such as ceftaroline, ceftobiprole, tedizolid, dalbavancin and oritavancin with specific clinical utility are becoming available and offer enhanced tolerability profile, effective cure rate and minimum rates of resistance. However, these alternatives are not without limitations.
Conclusions We objectively provide suitable alternatives to vancomycin that could be included in hospital formularies and guidelines. However, caution must be undertaken when utilizing these alternatives, given their limitations.

Keywords: Vancomycin; toxicity; resistance; antibiotics; alternatives; *Staphylococcus aureus*

Introduction

For several decades, vancomycin has continued to be in clinical use despite the enormous reported concerns of versatile resistance. The rampant clinical utility of vancomycin has been associated with vancomycin-resistant *Staphylococcus aureus* (VRSA), vancomycin-resistant enterococci (VRE), nephrotoxic effects, patient discomfort, lengthy nursing time and the need for therapeutic drug monitoring. Furthermore, management of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia, which causes osteomyelitis, septic arthritis and infective endocarditis, via vancomycin treatment is not optimal. Furthermore, the rising of vancomycin-resistant bacteria such as vancomycin-intermediate sensitive staph (VISA), heterogeneous vancomycin-intermediate *Staphylococcus aureus* (hVISA), VRSA and VRE has been well reported and hence dictates an immediate action concerning vancomycin clinical utility.

Numerous recent medications have been recently licensed for the management of MRSA, VRE, VRSA and hVISA. These newly found drugs could be alternative therapies to vancomycin. The main objective is to provide robust evidence for the clinical benefits and limitations of these alternatives.

Methods

A robust literature search was conducted in databases such as Cinhal and Cochrane library, EBSCO, Embase, Google Scholar, Medline, PubMed and Scopus for vancomycin studies and suitable alternatives. The search criteria were defined as the following MeSH terms: Ceftaroline/ Ceftobiprole (5th generation cephalosporins), dalbavancin, daptomycin, linezolid, oritavancin, quinupristin/dalfopristin (streptogramins), teicoplanin, telavancin, tedizolid, tigecycline, vancomycin, vancomycin and MRSA, vancomycin and

Table 1 Milestones in vancomycin alternatives drugs and the year of FDA approval

Antibiotic	Year of approval
Vancomycin	1958
Teicoplanin	Not FDA approved. Only in the UK and some other countries. EMA with disagreement.
Quinupristin/dalfopristin	2001
Linezolid	2001
Daptomycin	2003
Tigacycline	2005
Telavancin	2009
Ceftaroline	2010
Ceftobiprole	2012
Dalbavancin	2014
Oritavancin	2014
Tedizolid	2014
Delafloxacin	2017
Teixobactin	2015 to 2019 (animal studies, preclinical development)
Iclaprim	2019 Novel antibiotic, New Drug Application (NDA)

VRE, VISA, vancomycin and resistance, vancomycin and therapeutic drug monitoring, vancomycin toxicity and vancomycin-resistant *Enterococcus faecium/faecalis* (VREFm/s).

Results and Discussion

Tedizolid may provide an effective alternative to vancomycin in treating MRSA in acute bacterial skin and skin structure infections (ABSSSI). In a network meta-analysis study that evaluated the efficacy, safety and cost-effectiveness, linezolid (bacteriostatic) and tedizolid showed superiority in treating MRSA causing complicated ABSSSI. Despite the current clinical practice of using vancomycin as a first-line treatment of MRSA, it was not cost-effective in the pharmacoeconomic evaluation.[1]

Alternative remedies such as lipoglycopeptides antibiotics, dalbavancin, oritavancin and telavancin are becoming available and offer enhanced tolerability profile, infrequent dosing requirements, effective cure rate and minimum rates of resistance than vancomycin. Dalbavancin once-weekly dosing may be an alternative option to vancomycin against hVISA and VISA, isolates with decreased susceptibility to daptomycin and VREF without any emerging resistances.[2] Oritavancin, a one-dose treatment option for ABSSSI caused by resistant Gram-positive bacteria can be a suitable alternative to vancomycin. In phase III trials, one 1200-mg dose of oritavancin demonstrated non-inferiority to a 7- to 10-day course of vancomycin. Telavancin is FDA labelled and indicated for hospital-acquired pneumonia (including ventilator-associated pneumonia) caused by susceptible isolates of *Staphylococcus aureus* and complicated ABSSSI.

The fifth-generation cephalosporin, such as ceftobiprole medocaril, is a candidate for monotherapy of complicated bacterial skin and skin structure infections and also for pneumonia that required combination therapy in the past. It has been approved for the treatment of adult patients with hospital-acquired pneumonia (excluding ventilator-acquired pneumonia) and community-acquired pneumonia (CAP) in 12 European countries by the European Medicines Agency (EMA). The drug is highly safe and provides a suitable alternative to vancomycin for VISA treatment.[3] Ceftaroline fosamil is another fifth-generation cephalosporin that is FDA labelled for CAP (not caused by MRSA) and ABSSSI in adults and children above 2 months of age. Previously, a systematic review and meta-analysis of experimental and observational studies have demonstrated the high efficacy and safety of ceftaroline fosamil in patients with pneumonia (even against multi-drug-resistant strains).[4]

A combination of the streptogramins, quinupristin and dalfopristin, is an effective alternative to vancomycin in persistent cases of MRSA bacteraemia or vancomycin/linezolid clinical failure. In addition, the combination was effective against VISA and VRSA isolates. Furthermore, the combined quinupristin/dalfopristin drug is one of only three antibiotics effective in treating VRE. However, in 2010, it lost its FDA approval for the treatment of endocarditis caused by VRE strains.[5, 6] The infectious Disease Society of America (IDSA) guidelines recommend quinupristin/dalfopristin (or ampicillin) for methicillin-resistant coagulase-negative staphylococci and VRE *faecium* treatment.

On the other hand, the vancomycin alternatives have limitations. Teicoplanin is a classical alternative to vancomycin. Compared with linezolid, it was less effective in treating MRSA, and its safety profile was not superior. In addition, there are concerns about the lack of evidence regarding its pharmacokinetics and clinical pharmacodynamics. Although EMA has approved teicoplanin, it was not by FDA. Furthermore, the dose and duration of teicoplanin therapy are to be reduced in any degree of renal impairment (Table S1).

Another alternative is the FDA-approved bacteriostatic tigecycline, which is used for CAP and complicated skin and skin structure infections. However, tigecycline bears a black box warning from the FDA for all-cause mortality, mortality imbalance and lower cure rates for ventilator-associated pneumonia and pancreatitis. It is better for use in situations when alternative treatments are not suitable (Table S1).

Linezolid induces serious adverse drug reactions, such as thrombocytopenia, optic neuropathy, peripheral neuropathy and lactic acidosis, and potential drug interactions, such as monoamine oxidase inhibition. Tedizolid single dosing improves patient adherence. However, the drug has adverse effects such as thrombocytopenia, leucopoenia, anaemia, peripheral neuropathy and optic neuritis (Table S1).

Daptomycin is the only drug approved by the FDA to treat *S. aureus* bacteraemia (SAB) and right-sided native valve endocarditis. It offers a better alternative to vancomycin for SAB treatment, with once-daily dosing (6 mg/kg/d).[7] However, it cannot substitute vancomycin for pneumonia treatment. The drug is associated with elevated creatine kinase and rhabdomyolysis (Table S1).

Dalbavancin and oritavancin effectiveness in bacteraemia, pneumonia, bone, joint infections and prosthetic infections was not established. Additionally, a higher occurrence of osteomyelitis was reported in clinical studies with oritavancin. Telavancin poses the risk of nephrotoxicity and has a low safety profile (Table S1).

The newer fifth-generation cephalosporin, ceftobiprole, is suitable for ABSSSI and CAP treatment due to severe MRSA infections. However, it is not FDA approved. Significant concerns of ceftobiprole include the development of agranulocytosis and increased risk of leukopenia, which warrants close monitoring of patients. The other fifth-generation cephalosporin, ceftaroline, offers a suitable alternative to vancomycin in ABSSSI. [8]

The streptogramins (quinupristin/dalfopristin) exhibited the side effects such as infusion-site inflammation, rash, thrombophlebitis, pain, nausea, diarrhoea, vomiting, oedema, arthralgia, myalgia (Table S1) and potential drug interactions with CYP3A4 inhibitors.

The devastating bacteraemia poses a significant threat, resulting in mortality within 3 months post-infection. The presence of the above-mentioned versatile alternatives to vancomycin deserves more reflection. The potential alternatives to vancomycin in the developing phases include teixobactin and its analogues, malacidins, FabI inhibitors, iclaprim, pleuromutilins and mycoredoxin-1. The milestones in vancomycin alternative drugs and their years of FDA approvals were depicted in Table 1.

Conclusions

Currently, vancomycin has enormous limitations for its clinical utility. Recently, numerous drugs licensed for the management of MRSA, VRE, VRSA and hVISA. The newer agents such as tedizolid were approved in the treatment of MRSA ABSSSI. Dalbavancin and oritavancin demonstrated efficacy and safety and also resulted in cost savings for the treatment of complicated skin and soft tissue infections. Ceftobiprole and ceftaroline provide a safe alternative to vancomycin in MRSA infections such as ABSSSI. Quinapristin/dalfopristin is one of only three antibiotics effective in the treatment of VRE. However, whether the benefits of vancomycin alternatives outweigh their risks warrants further exploration. The current review raises the vigilance of clinicians and provides a guide for the possible selection of the available vancomycin alternatives in the day-to-day real clinical practice.

Supplementary Material

Supplementary data are available at *Journal of Pharmaceutical Health Services Research* online.

Author Contributions

A.A.E. and A.R. were responsible for the study concept, design, acquisition and analysis of observed data and have also contributed equally to the preparation of whole manuscript, literature review, development and proofreading. A.A.E. and A.R. have approved the manuscript and its submission to the journal.

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Conflicts of Interest

All authors declare no conflict of interest. The authors have not published or submitted any related papers from the same study. This article is not under consideration or submission for any other journals.

Data availability

No new data were generated or analysed.

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