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Antimicrobial treatment of nosocomial meticillin-resistant *Staphylococcus aureus* (MRSA) pneumonia: current and future options

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ABSTRACT

Meticillin-resistant *Staphylococcus aureus* (MRSA) is a frequent cause of nosocomial pneumonia. Inadequate or inappropriate antimicrobial therapy, often caused by antimicrobial resistance, is associated with increased mortality for these infections. Agents currently recommended for the treatment of MRSA pneumonia include vancomycin and linezolid in the USA, and vancomycin, linezolid, teicoplanin and quinupristin/dalfopristin in Europe. Antimicrobials such as tigecycline and daptomycin, although approved for the treatment of some MRSA infections, have not demonstrated efficacy equivalent to the approved agents for MRSA pneumonia. Further agents lack data from randomised controlled trials (e.g. fosfomycin, fusidic acid or rifampicin in combination with vancomycin). Antimicrobial agents that have recently been approved or are being investigated as treatments for MRSA infections include the lipoglycopeptides telavancin (approved for the treatment of complicated skin and skin-structure infections in the USA and Canada), dalbavancin and oritavancin, the cephalosporins ceftobiprole and ceftaroline, and the dihydrofolate reductase inhibitor iclaprim. To be an effective treatment for MRSA pneumonia, antimicrobial agents must have activity against antimicrobial-resistant *S. aureus*, penetrate well into the lung, have a low potential for resistance development and have a good safety profile. Here, the available data for current and potential future MRSA pneumonia antimicrobials are reviewed and discussed.

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1. Introduction

Pneumonia is a common infection in communities and healthcare facilities, with mortality rates as high as 76% reported under some circumstances in ventilated patients [1,2]. Currently accepted categories of pneumonia include community-acquired pneumonia (CAP) and nosocomial pneumonia, the latter encompassing healthcare-associated pneumonia (HCAP), hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). CAP is defined as pneumonia occurring outside of the hospital or within 48 h of hospital admission in patients with no prior contact with the healthcare system. HCAP is defined as pneumonia acquired outside of the hospital by patients with certain risk factors for infection with pathogens of nosocomial origin [3,4]. Patients are required to have at least one of the following risk factors for a diagnosis of HCAP: hospitalisation for >2 days in the previous 90 days in an acute care facility; residence in a nursing home or other long-term care facility; previous antibiotic therapy, chemotherapy or wound care in the previous 30 days; haemodialysis in a hospital or clinic; home infusion therapy or wound care; or a family member infected with a multidrug-resistant (MDR) pathogen [1]. HAP is defined as pneumonia occurring after 48 h following hospital admission and, similarly, VAP is defined as pneumonia occurring at least 48 h after endotracheal intubation [1].

Nosocomial pneumonia is associated with increased disease severity, mortality, length of hospital stay and hospital costs compared with CAP [4]. HCAP is more similar to HAP and VAP in terms of causative organisms,

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treatment requirements and prognosis than it is to CAP [4]. A distinction can also be made between early-onset and late-onset nosocomial pneumonia, with late-onset infections (≥5 days of current hospitalisation) more likely to be caused by MDR pathogens [1]. Additional risk factors for infection with MDR pathogens are antimicrobial therapy in the previous 90 days, current hospitalisation of at least 5 days, high frequency of antibiotic resistance in the community or hospital unit, presence of risk factors for HCAP, or immunosuppressive disease and/or therapy [1].

Potential pathogens and recommended empirical antimicrobial therapies for nosocomial pneumonia, according to the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) 2005 guidelines [1], are shown in Table 1. Other more recent guidance includes the 2008 UK HAP treatment guidelines [5] and the wider European perspective of HAP published in 2009 [6]. As the ATS/IDSA guidelines are the most widely accepted worldwide, these guidelines have been selected as the basis for further discussion. An update of the ATS/IDSA 2005 guidelines is expected in 2010. As the causative pathogen is rarely identified before antimicrobial therapy is initiated, the relevance of the categorisation of pneumonia is to guide prompt administration of an appropriate (pathogen is susceptible) and adequate (high enough level of drug at the site of infection) empirical antimicrobial treatment [1].

Inadequate (insufficient level of agent at the site of infection), inappropriate (pathogen resistant to agent) or delayed antimicrobial therapy is associated

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with increased pneumonia mortality [7–9] as well as increased length of hospital stay and costs [10]. Antimicrobial resistance is thought to be an important determinant of inadequate or inappropriate antimicrobial administration. Kollef et al. [8] demonstrated by multiple logistic regression analysis that inappropriate antimicrobial therapy was independently associated with prior administration of antibiotics (thought to result in subsequent infection with drug-resistant pathogens) in Intensive Care Unit (ICU) patients. Furthermore, this same study demonstrated that patients infected with meticillin-resistant *Staphylococcus aureus* (MRSA) were more likely to receive inappropriate antimicrobial therapy [8]. Similarly, increasing vancomycin minimum inhibitory concentrations (MICs) have been associated with administration of inadequate antimicrobial therapy and increased mortality due to MRSA bacteraemia [11,12].

Staphylococcus aureus is a major cause of HCAP, HAP and VAP, and increasingly CAP in some countries, particularly the USA [13]. *Staphylococcus aureus* is uniquely problematic due to its ubiquity, expression of virulence factors and high frequency of resistance to many antimicrobial agents [14]. *Staphylococcus aureus* was the only pathogen that correlated with mortality in a multiple logistic regression analysis carried out in a large retrospective cohort study of inpatients with culture-positive pneumonia in the USA [4]. MRSA is growing in prevalence and is now endemic in many healthcare facilities and communities [15]. In 2003, >60% of *S. aureus* isolates from US ICUs were meticillin-resistant [16]. In Europe, there is a North to South trend in the proportion of *S. aureus* that is meticillin-resistant, ranging from 0% in

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northern European countries to >50% in more southern countries [17]. Some

strains of MRSA, particularly those of community origin [community-acquired

MRSA (CA-MRSA)], produce the Panton–Valentine leukocidin (PVL) toxin,

which is associated with necrotizing infections, often in previously healthy

individuals [18]. PVL-producing strains may become of increasing importance

if CA-MRSA strains continue to invade the hospital setting but they will not be

discussed further in this article in order to maintain a focus on nosocomial

pneumonia in which PVL-producing strains are much less prevalent.

A summary of the antimicrobial agents currently approved for the treatment of

MRSA pneumonia in the USA and Europe as well as those that may provide

treatment options in the future can be found in Table 2 and are discussed

further hereafter.

2. Antimicrobial agents approved for the treatment of MRSA pneumonia

Only vancomycin and linezolid are currently approved in the USA for the

treatment of MRSA pneumonia. In some European countries, teicoplanin and

quinupristin/dalfopristin (Q/D) are available in addition to vancomycin and

linezolid for this indication.

2.1. Vancomycin

Vancomycin is a glycopeptide antibiotic that disrupts cell wall synthesis in

Gram-positive bacteria by inhibiting peptidoglycan biosynthesis (Fig. 1). It is

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generally considered slowly bactericidal. Although currently the treatment of choice, there are limitations of vancomycin for the treatment of pneumonia and other serious infections caused by MRSA [19]. Vancomycin has been shown to be less effective than β-lactams for the treatment of meticillin-susceptible *S. aureus* infections [20–23]. In addition, vancomycin penetrates poorly into the lung at therapeutic doses, which is associated with pneumonia treatment failure despite in vitro susceptibility of the bacterial isolates [21,24,25].

Combining vancomycin with rifampicin, fusidic acid or fosfomycin is theoretically effective for the treatment of MRSA pneumonia although data from randomised controlled (RCTs) trials are lacking. A recent study of 93 patients in South Korea demonstrated that vancomycin plus rifampicin was more effective in the treatment of MRSA nosocomial pneumonia than vancomycin alone [26]. Further clinical data are required to assess whether such therapy has clinical utility.

Vancomycin resistance is currently uncommon but seems likely to increase as use of this agent for the treatment of ever more frequent MRSA infections becomes more commonplace [27]. Since the first documented clinical infection with vancomycin-intermediate *S. aureus* (VISA) in 1996 in Japan (Mu50) [28], clinical isolates have been observed throughout the world. Vancomycin MICs have been observed to be increasing over time ('MIC creep') [29,30], with increased rates of mortality and treatment failure seen in patients with bacteraemia caused by *S. aureus* with increased vancomycin

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MIC values [11,12]. *Staphylococcus aureus* strains may also be 'tolerant' to vancomycin, defined as a MIC/minimum bactericidal concentration ratio of ≥32. This takes into account susceptible strains that show increased resistance to killing, potentially resulting in treatment failures [31].

Susceptibility to vancomycin decreases under persistent exposure and improves upon removal of the selection pressure [32,33], such that increased use of vancomycin to treat escalating MRSA infections will intuitively lead to more resistance.

Complete resistance to vancomycin is conferred by the *vanA* determinant, first detected in 1988 in a vancomycin-resistant enterococci (VRE) isolate [34]. In vitro studies have shown that *vanA* has the capacity to be transferred from VRE to *S. aureus* by naturally occurring horizontal gene transfer, thus creating a vancomycin-resistant *S. aureus* (VRSA) [35]. In 2002, the first *vanA*-containing VRSA was isolated from a dialysis patient in Michigan, USA [36]; such isolates have since been detected throughout the world although the incidence remains low.

Vancomycin is frequently combined with β-lactam antimicrobials. In 2002, a class of MRSA strains that developed vancomycin resistance in the presence of β-lactam antibiotics [β-lactam-induced vancomycin-resistant meticillin-resistant *S. aureus* (BIVR)] were reported in Japan [37]. Although defined phenotypically, the mechanism of this acquired resistance is not yet understood. Up to 20% of MRSA strains in a further Japanese study exhibited

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the BIVR phenotype [38]. Recent results indicate that BIVR may be associated with increased mortality in patients with MRSA bacteraemia [39].

Vancomycin is associated with nephrotoxicity and ototoxicity, although the frequency of these adverse reactions was higher in early reports and is attributed to the low purity of early formulations [40]. Nephrotoxicity due to vancomycin is of great concern owing to the contribution of acute kidney injury to poor clinical outcome in critically ill patients in the ICU, a population particularly vulnerable to MRSA infection [41–44]. Concurrent aminoglycosides and other known nephrotoxic agents are thought to increase the risk of nephrotoxicity during vancomycin therapy, in addition to medical conditions including sepsis, liver disease, obstructive uropathy and pancreatitis [45]. Monitoring of trough serum vancomycin concentrations is recommended to reduce vancomycin nephrotoxicity in patients with unstable renal function or in those receiving aggressive or prolonged vancomycin therapy or concomitant nephrotoxic agents [45].

2.2. Linezolid

Linezolid is approved for the treatment of nosocomial pneumonia in the USA and Europe, including cases caused by MRSA. In the USA it represents the only alternative to vancomycin for this indication. Linezolid is a synthetic oxazolidinone that prevents binding of the 30S and 50S ribosomal subunits, thus inhibiting the initiation of protein synthesis (Fig. 1) [46]. Linezolid has activity against Gram-positive pathogens, including bacteriostatic in vitro

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activity for staphylococci, but has limited activity against Gram-negative bacteria [46].

Two retrospective subgroup analyses of ventilated and non-ventilated patients with MRSA [47,48] from nosocomial pneumonia clinical trials [49,50] showed that linezolid-treated patients had higher survival and clinical cure rates than vancomycin-treated patients. It has been suggested that this may be due to the favourable intrapulmonary distribution of linezolid [51]. However, the viability and validity of these subset analyses has been questioned [52,53] such that further trials are required before linezolid can be recommended to be used preferentially over vancomycin for the treatment of MRSA pneumonia. A recent trial of patients with MRSA VAP failed to show statistical superiority of linezolid over vancomycin, although linezolid-treated patients had numerically better values compared with vancomycin-treated patients with respect to microbiological eradication (56.5% and 47.4%, respectively), clinical cure (66.7% and 52.9%, respectively), survival rate (86.7% and 70.0%, respectively), length of hospitalisation (18.8 days and 20.1 days, respectively), duration of ventilation (10.4 days and 14.3 days, respectively) and length of ICU stay (12.2 and 16.2 days, respectively) [54].

Resistance was first observed in a clinical *S. aureus* isolate in 2001 [55], although the LEADER surveillance programme has shown that 99.55% of isolates remained susceptible to linezolid in the USA in 2006 [56].

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Thrombocytopenia is a commonly observed adverse reaction to linezolid therapy, with occurrence rates of ca. 30% [57–59], a rate much higher than that reported in phase 3 trials [46]. Thrombocytopenia is more common following prolonged treatment (>14 days) and in patients with renal insufficiency [58,60]. The inhibition of mitochondrial protein synthesis by linezolid can result in potentially severe clinical effects, including optic/peripheral neuropathy and lactic acidosis [61]. These events are not frequently observed and are mostly reversible following termination of linezolid treatment, but there are reports of severe irreversible effects such as permanent blindness in patients treated for only a short time [62]. As a reversible, non-selective monoamine oxidase inhibitor, linezolid in combination with serotonergic agents has been associated with serotonin syndrome [63]. The linezolid licence recommends that treatment be restricted to a maximum of 28 days [46].

2.3. Teicoplanin

Teicoplanin is a glycopeptide with bactericidal activity against many Gram-positive pathogens, including MRSA. It is approved for the treatment of lower respiratory tract infections, including those caused by MRSA, in some parts of Europe but not in the USA.

Linezolid was shown to be superior to teicoplanin for the treatment of suspected or confirmed Gram-positive infections (skin infections, pneumonia and bacteraemia) [64] and equivalently effective for the treatment of Gram-positive infections in the critically ill [65]. A retrospective analysis comparing

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the two drugs also indicated the clinical superiority of linezolid over teicoplanin, with numerically better response to therapy (although not statistically significant) for *S. aureus* infections, including MRSA [66].

Although there is evidence to suggest that the tissue penetration of teicoplanin may be better than that of vancomycin [67], lung penetration may be suboptimal. A study in critically ill patients with VAP indicated that high teicoplanin doses are required to reach adequate trough concentrations in the lung [68]. In addition, owing to a common target in the bacterial cell wall, reduced susceptibility to teicoplanin in *S. aureus* manifests in the same way as that of vancomycin, and a general term for strains with reduced susceptibility to either agent is glycopeptide-intermediate *S. aureus* (GISA) [69].

Teicoplanin is generally considered to have a favourable safety profile compared with vancomycin, with lower risk of nephrotoxicity and reactions resulting from histamine release (such as red man syndrome). However, thrombocytopenia is more commonly observed during teicoplanin than vancomycin therapy, especially when administered at does higher than those normally recommended [70,71].

2.4. Quinupristin/dalfopristin

Q/D consists of two streptogramin components; quinupristin inhibits late-stage protein synthesis whilst dalfopristin inhibits early-stage protein synthesis (Fig. 1) [72]. Q/D has demonstrated good in vitro activity against many Gram-

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negative and Gram-positive pathogens, including *S. aureus* resistant to meticillin and vancomycin [72]. Q/D is approved for the treatment of MRSA pneumonia in some European countries but not in the USA [72]. The ATS/IDSA nosocomial pneumonia guidelines do not recommend Q/D for the treatment of MRSA pneumonia owing to clinical cure rates being lower than those of vancomycin in clinical trials (30.9% for Q/D vs. 44.4% for vancomycin in the bacteriologically evaluable population, and 19.4% vs. 40%, respectively, in the all-treated population with a baseline pathogen) [1,73].

3. What drug attributes should antimicrobials for MRSA pneumonia possess?

New agents are urgently needed to expand the limited repertoire of available agents approved for the treatment of MRSA pneumonia. To be a useful agent to treat MRSA pneumonia, several characteristics are important. Activity against key pneumonia pathogens, including MRSA and other resistant strains, is essential (Table 1). Bactericidal activity would be preferable, as the rapid resolution of serious infections has many benefits. However, the importance of bactericidal versus bacteriostatic activity is still a matter of debate [74,75]. The clinical outcome of respiratory infections is dependent on sustained antimicrobial concentrations at the site of infection [76], therefore it is important that the agent reaches microbiologically active concentrations in the relevant parts of the lung and is not inactivated by pulmonary surfactant. Low nephrotoxicity is also important; many patients with MRSA pneumonia are critically ill in the ICU with multiple organ dysfunction. Antimicrobial-

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induced nephrotoxicity resulting in acute kidney injury may contribute to poor clinical outcome in this population [41–44]. As the use of agents with activity against MRSA looks certain to increase in the future, an agent with low potential for resistance development would be ideal.

4. Approved anti-MRSA agents not currently indicated for the treatment of MRSA pneumonia

Agents approved in some countries for the treatment of MRSA infections other than pneumonia that have potential utility for the treatment of MRSA pneumonia include tigecycline and telavancin. Daptomycin will not be discussed as although this agent has demonstrated good activity against MRSA it is inactivated by pulmonary surfactant in animal models [77] and did not achieve non-inferiority to vancomycin in clinical trials of pneumonia [78]. It is thus unlikely that daptomycin has clinical utility for the treatment of MRSA pneumonia.

4.1. Tigecycline

Tigecycline is a semisynthetic glycycline with antimicrobial activity (generally bacteriostatic) against a broad range of Gram-positive, Gram-negative and anaerobic pathogens, although it is ineffective against *Pseudomonas aeruginosa* [79]. Like the tetracyclines, tigecycline inhibits protein translation by binding the 30S ribosomal subunit, preventing peptide elongation (Fig. 1) [80].

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Tigecycline is approved in the USA and some European countries for the treatment of complicated skin and skin-structure infections (cSSSIs) and complicated intra-abdominal infections as well as for the treatment of CAP (not including infections caused by MRSA) in the USA.

Early clinical experiences with tigecycline for the treatment of VAP and/or bacteraemia caused by MDR *Acinetobacter baumannii* were positive. However, development of resistance in MDR Gram-negative bacilli and subsequent poor outcome has been observed in patients with infections treated with tigecycline [81]. Furthermore, in a phase 3 study, tigecycline (plus ceftazidime and aminoglycoside for *P. aeruginosa* coverage, if required) did not achieve non-inferiority to imipenem (plus an aminoglycoside and vancomycin for MRSA coverage, if required) for the treatment of HAP [82]. This reflected the lower clinical cure rates for the subgroup of patients with VAP [47.9% for tigecycline vs. 70.1% for imipenem (per-protocol analysis) and 46.5% for tigecycline vs. 57.8% for imipenem (intent-to-treat analysis)] [82].

Pharmacokinetic/pharmacodynamic studies in humans indicate that tigecycline has good penetration into alveolar cells but achieves only low levels in epithelial lining fluid (ELF) [83,84]. Such results indicate that tigecycline may potentially be underdosed for the treatment of pneumonia [83]; effectiveness at higher doses is being investigated in ongoing trials, although the impact of such doses on tolerability needs to be carefully evaluated.

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4.2. Telavancin

Telavancin is a bactericidal lipoglycopeptide derivative of vancomycin with a multifunctional mechanism of action, disrupting bacterial cell wall synthesis and membrane integrity (Fig. 1) [85]. Telavancin has displayed good activity against clinically important Gram-positive pathogens, including MRSA, and has displayed rapid concentration-dependent bactericidal activity against *S. aureus* in time–kill studies [86,87]. As with other similar agents, telavancin does not have activity against Gram-negative pathogens and is less active against *vanA*-expressing strains of VRE [88]. Telavancin has demonstrated good penetration into human ELF and alveolar macrophages, being present at concentrations greater than the MIC_{90} (MIC for 90% of the organisms) for MRSA (0.5 μg/mL) for the entire dosing interval, and Monte Carlo simulation has indicated that the levels of telavancin in ELF are ca. 75% of those in plasma [89,90]. In a staphylococcal biofilm model, telavancin was more effective than vancomycin and teicoplanin, displaying bactericidal activity [91].

In phase 3 trials, telavancin demonstrated non-inferiority to vancomycin for the treatment of Gram-positive cSSSI [92] and is approved in the USA and Canada for this indication. Preliminary data from phase 3 trials of Gram-positive nosocomial pneumonia showed that clinical cure rates in clinically evaluable patients at test-of-cure visit were comparable for telavancin and vancomycin [82.7% and 80.9%, respectively; 95% confidence interval (CI) of difference in clinical cure rate −4.1 to 7.7] and were higher for telavancin than vancomycin in patients with MRSA pneumonia (81.8% and 74.1%,

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respectively; 95% CI of difference −3.5 to 19.3) and VAP (80.3% and 67.6%,

respectively; 95% CI of difference −1.8 to 26.8) [93].

Telavancin has displayed low potential for resistance development in vitro and

in vivo, potentially due to its unique dual mechanism of action [87,94]. The

most common side effects reported for telavancin in the phase 3 cSSSI trials

(>10% incidence) were taste disturbance, nausea, headache, vomiting and

foamy urine, and in the phase 3 HAP trials (>8% incidence) were diarrhoea,

renal impairment, anaemia, constipation and hypokalaemia [92,93]. Renal

dysfunction was observed in 3% of telavancin-treated patients and 1% of

vancomycin-treated patients in the cSSSI trials [92] and in 10% of telavancin-

treated patients and 8% of vancomycin-treated patients in the HAP trials [93].

5. Potential new agents for the treatment of MRSA pneumonia

Agents with activity against MRSA that are currently at various stages of

development and investigation for the treatment of pneumonia (and are thus

not approved at present) include the lipoglycopeptides dalbavancin and

oritavancin, the cephalosporins ceftobiprole and ceftaroline, and the

dihydrofolate reductase (DHFR) inhibitor iclaprim.

5.1. Lipoglycopeptides: dalbavancin and oritavancin

Dalbavancin is a lipoglycopeptide derived from teicoplanin with Gram-positive

activity [95]. Dalbavancin has the same mechanism of action as vancomycin

(Fig. 1) but has a uniquely long half-life (5–7 days), which allows once-weekly

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intravenous dosing as part of a two-dose regimen [95]. In vitro studies demonstrated that dalbavancin was bactericidal against *S. aureus*, including strains resistant to meticillin and strains with reduced susceptibility to vancomycin, although dalbavancin is inactive against pathogens possessing the *vanA* gene [95].

Dalbavancin demonstrated non-inferiority to linezolid for the treatment of cSSSI in phase 3 trials [96]. In these trials, the type and severity of adverse events were similar between the treatment groups, with the most frequent dalbavancin-associated adverse events being nausea, diarrhoea, elevated blood lactate dehydrogenase or γ-glutamyltransferase level, headache and vomiting [96].

There are no trials currently underway for dalbavancin for the treatment of pneumonia such that further data are required to assess the usefulness of dalbavancin for this indication.

Oritavancin is a semisynthetic lipoglycopeptide derivative of vancomycin. Like telavancin, oritavancin is thought to have a dual mechanism of action involving disruption of cell wall synthesis and membrane permeability (Fig. 1) [97,98]. Oritavancin has demonstrated bactericidal activity against stationary-phase and biofilm *S. aureus* in vitro [99]. Drug concentrations in ELF indicate that oritavancin may need to be dosed more aggressively for the treatment of pneumonia [100]. In phase 3 studies investigating oritavancin for the treatment of cSSSI, oritavancin demonstrated comparable efficacy to

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vancomycin as well as a favourable safety profile. There are no pneumonia trials currently underway; further data are required to assess the usefulness of oritavancin in the treatment of pneumonia.

5.2. Cephalosporins: ceftobiprole and ceftaroline

Cephalosporins inhibit bacterial cell wall formation by binding penicillin-binding proteins (PBPs) and preventing peptidoglycan cross-linking in the cell wall (Fig. 1).

Ceftobiprole is a fifth-generation cephalosporin with activity against Gram-positive and Gram-negative organisms. As ceftobiprole is structurally engineered to bind to PBP2a, as encoded by the *mecA* gene of β-lactam-resistant MRSA, it has bactericidal activity against MRSA [101]. Ceftobiprole has similar activity to cefepime against *P. aeruginosa* [102]. Ceftobiprole is thought to be stable against staphylococcal β-lactamases but its activity does not cover extended-spectrum β-lactamase (ESBL)-producing bacteria [101].

Ceftobiprole demonstrated non-inferiority to vancomycin for the treatment of cSSSI in two phase 3 trials [103,104]. Ceftobiprole has also demonstrated non-inferiority to ceftriaxone, with or without linezolid, for the treatment of CAP requiring hospitalisation in phase 3 trials, with cure rates of 87% for ceftobiprole and 88% for the comparator agents [105,106]. In a further phase 3 trial, ceftobiprole achieved non-inferiority for the treatment of HAP compared with ceftazidime plus linezolid (clinical cure in clinically evaluable patients 77%

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for ceftobiprole and 76% for combination therapy), but was inferior for the treatment of ventilated patients; further analysis of this subset of patients is ongoing [106,107].

In serial-passage studies of ceftobiprole against MRSA, PBP2a-mediated resistance has been observed, with high-level resistance also observed in a *mecA*-negative MRSA strain, suggesting that multiple mechanisms of resistance development may be possible [108]. The clinical relevance of this in vitro resistance is unresolved.

Ceftobiprole is generally well tolerated. In single-dose [109] and multiple-dose [110] pharmacokinetic evaluations in healthy volunteers, no serious adverse events were reported and most events were mild. In phase 3 trials of cSSSI, the overall incidence of adverse events was similar between ceftobiprole- and vancomycin-treated patients [103,104]. In phase 3 and pharmacokinetic studies, nausea, dysgeusia, vomiting and headache were the most common adverse events [103,104,109,110].

Ceftaroline has demonstrated a greater range of Gram-positive activity than other members of the cephalosporin class, including activity against *S. aureus* strains that are resistant to meticillin, linezolid and daptomycin [111–115]. Ceftaroline also has activity against some Gram-negative organisms but is not active against *P. aeruginosa* and its activity is reduced against ESBL-producing bacteria. Ceftaroline achieved non-inferiority to vancomycin plus aztreonam in phase 3 trials for cSSSI [113,116]. In two phase 3 trials for

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bacterial CAP requiring hospitalisation, ceftaroline demonstrated non-inferiority to ceftriaxone [117].

Although the broad spectrum of ceftaroline can be considered a favourable attribute, some believe that its use for the treatment of MRSA infections may result in the emergence of resistant Gram-negative isolates, although this is yet to be investigated [113]. This may be of particular concern given that ceftaroline is not active against *P. aeruginosa*, a common VAP pathogen.

In a phase 2 study of ceftaroline for the treatment of cSSSI, the overall incidence of adverse events was similar between ceftaroline and standard cSSSI treatment [118]. The most common treatment-related adverse events (≥6% frequency) for ceftaroline were crystalluria, headache, insomnia, nausea and elevated levels of blood creatine phosphokinase, alanine aminotransferase or aspartate aminotransferase. Safety data from the CAP trials have not yet been published.

5.3. Dihydrofolate reductase inhibitors: iclaprim

Iclaprim is a synthetic diaminopyrimidine that functions by inhibiting the microbial DHFR enzyme, which depletes the bacterial cell of thymidine monophosphate and thus affects RNA, DNA and protein synthesis (Fig. 1) [106]. Iclaprim is bactericidal against clinically important Gram-positive pathogens, including MRSA [119,120]. Iclaprim appears to have a lower potential for resistance development than trimethoprim. Additionally, resistance is less likely to develop as a result of the use of other MRSA

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antimicrobials, as iclaprim has a different mechanism of action than many of the agents that are currently available or in development. However, the antibacterial effect of DHFR inhibitors can be antagonised in vitro by supplementing thymidine owing to bacterial uptake of exogenous thymidine and its subsequent conversion into thymidine monophosphate by thymidine kinase, bypassing the DHFR inhibition [121,122]. Because thymidine is found in large concentrations in human pus, some believe that iclaprim and other DHFR inhibitors are less effective in purulent infections [123].

In a phase 2 trial comparing iclaprim with vancomycin for the treatment of cSSSI, clinical cure was similarly high for patients treated twice daily with iclaprim 0.8 mg/kg, iclaprim 1.6 mg/kg or vancomycin 1 g (92.9%, 90.3% and 92.9%, respectively) [124]. Iclaprim was well tolerated during this investigation. Of 32 patients who received iclaprim 1.6 mg/kg, 2 patients experienced pruritus and erythema that was deemed related to the study drug, whereas no patients who received iclaprim 0.8 mg/kg reported any adverse event. Two phase 3 studies demonstrated the non-inferiority of iclaprim to linezolid for the treatment of cSSSI while indicating a favourable safety profile [125].

Iclaprim showed good pulmonary distribution in healthy human subjects [126]. A phase 2 trial comparing iclaprim with vancomycin for the treatment of non-CAP pneumonia has been terminated for non-clinical reasons [127]. Further data from pneumonia trials are required to assess the potential usefulness of this agent in the treatment of drug-resistant pneumonia.

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6. Conclusions

MRSA has become an important pneumonia pathogen with high morbidity, mortality and healthcare costs and with relatively few agents approved for the treatment of MRSA pneumonia. Vancomycin exhibits poor penetration into lung tissue, and increasing MIC values for *S. aureus* are associated with treatment failure and poor microbiological eradication. Older agents such as fosfomycin, fusidic acid and rifampicin in combination with vancomycin are theoretically effective; however, clinical data from RCTs are lacking. Linezolid has exhibited better performance than vancomycin in post hoc analyses from clinical studies with regard to mortality and pathogen eradication. However, in the only RCT (which was considered underpowered) there was no advantage of linezolid with regard to survival, only in respect to secondary end-points. Studies have indicated that teicoplanin may not be as effective as linezolid for the treatment of Gram-positive infections, and Q/D has demonstrated lower efficacy than vancomycin for the treatment of MRSA pneumonia.

Some RCTs of novel MRSA antibiotics for nosocomial pneumonia have produced disappointing results. Of the newer drugs discussed in this article, thus far only telavancin has achieved comparable clinical cure rates to vancomycin for the treatment of nosocomial pneumonia in phase 3 trials, although it is currently not approved for this indication. Whether any of the agents discussed here will provide a viable alternative for the treatment of MRSA pneumonia will be revealed in the future.

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In summary, there is an urgent need for new antimicrobials that have good safety profiles, adequate lung penetration, low potential for resistance development and clinical efficacy for the treatment of MRSA pneumonia.

Competing interests

MWP has received fees for lectures from Pfizer and Wyeth and is a member of the international advisory board of Wyeth. TW has received fees for lectures from Pfizer and Johnson & Johnson and is a member of the international advisory board of Astellas, Johnson & Johnson, and Cerexa.

Ethical approval

Not required.

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Fig. 1. (A) Sites of action of current and potential antimicrobial agents for the treatment of meticillin-resistant *Staphylococcus aureus* (MRSA) pneumonia. (B) Cell wall synthesis inhibitors prevent peptidoglycan polymerisation and cross-linking, catalysed by penicillin-binding proteins (PBPs), by binding PBPs or their D-Ala-D-Ala target.

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ACCEPTED MANUSCRIPT

Table 1

Potential pathogens and recommended empirical antimicrobial therapy for the treatment of nosocomial pneumonia according to

the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines [1]

	Potential pathogens	Recommended therapy
HAP and VAP in patients with no known risk factors for MDR pathogens, early onset (until Day 4) and any disease severity	*Streptococcus pneumoniae* *Haemophilus influenzae* MSSA Antibiotic-sensitive enteric Gram-negative bacilli	Ceftriaxone or levofloxacin, moxifloxacin, ciprofloxacin [a] or ampicillin/sulbactam or ertapenem

1

HAP, VAP and HCAP in patients with late-onset disease or risk factors for MDR pathogens and all disease severity	Pathogens as above, plus: *Pseudomonas aeruginosa* ESBL-positive *Klebsiella pneumoniae* [b] *Acinetobacter* spp. [b] MRSA *Legionella pneumophila* [b]	Antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam/β-lactamase inhibitor (piperacillin/tazobactam) plus [c] antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin or tobramycin) plus linezolid or vancomycin [d]

HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; MDR multidrug resistant; MSSA, meticillin-susceptible

Staphylococcus aureus; HCAP, healthcare-associated pneumonia; ESBL, extended-spectrum β-lactamase; MRSA, meticillin-

resistant *S. aureus*.

2

[a] The frequency of penicillin-resistant *S. pneumoniae* and MDR *S. pneumoniae* is increasing; levofloxacin or moxifloxacin are preferred to ciprofloxacin. In the authors' opinion, ciprofloxacin as empirical antimicrobial therapy for early-onset HAP is insufficient owing to limited activity against pneumococci, which occur frequently in early-onset pneumonia.

[b] If an ESBL-positive strain, such as *K. pneumoniae*, or an *Acinetobacter* spp. is suspected, a carbapenem is a reliable choice. If *L. pneumophila* is suspected, the combination antibiotic regimen should include a macrolide (e.g. azithromycin), or a fluoroquinolone (e.g. ciprofloxacin or levofloxacin) should be used rather than an aminoglycoside.

[c] Combination therapy with fluoroquinolones or aminoglycosides is recommended but remains an issue of debate as clinical data are contradictory.

[d] If MRSA risk factors are present or there is a high incidence locally.

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Table 2

Summary of current and potential future agents for the treatment of meticillin-resistant *Staphylococcus aureus* (MRSA) pneumonia

	Class	Current MRSA indications	Pneumonia data	Significant clinical side effects
Vancomycin	Glycopeptide	Vancomycin-susceptible MRSA infections	Approved for the treatment of pneumonia caused by MRSA	Nephrotoxicity, ototoxicity
Linezolid	Oxazolidinone	Nosocomial pneumonia, cSSSI	Approved for the treatment of pneumonia caused by MRSA	Myelosuppression (particularly thrombocytopenia), lactic acidosis, optical/peripheral neuropathy, serotonin syndrome
Daptomycin	Lipopeptide	cSSSI, bacteraemia, right-sided infective endocarditis	Inferior to vancomycin in phase 3 trials (inactivated by pulmonary surfactant)	Myopathy, peripheral neuropathy

1

Teicoplanin	Glycopeptide	Not USA: potentially serious Gram-positive infections	Approved in some European countries. Potentially not as effective as linezolid for the treatment of HAP	Myelosuppression (particularly thrombocytopenia)
Quinupristin/dalfopristin	Streptogramin ×2	Not USA: cSSSI, nosocomial pneumonia and VRE infections when there is documentation such that no other agent is suitable	Approved in some European countries. Lower cure rates than vancomycin in phase 3 HAP trials	Myelosuppression, myalgia/arthralgia, hyperbilirubinaemia

2

Tigecycline	Glycylcycline	cSSSI, cIAI	Approved for CAP indication (non-MRSA); inferior to imipenem for nosocomial pneumonia in phase 3 trials	Hepatic dysfunction, pancreatitis
Telavancin	Lipoglycopeptide	Approved for cSSSI in USA and Canada. Under review in the USA for nosocomial pneumonia and in Europe for cSSSI and nosocomial pneumonia	Non-inferior to vancomycin for Gram-positive nosocomial pneumonia in phase 3 trials	Adverse events in phase 3 trials: cSSSI (>10% incidence), taste disturbance, nausea, headache, vomiting, foamy urine; HAP (≥10% incidence), diarrhoea, renal impairment. Renal dysfunction appears to be related to the glycopeptide class

3

Ceftobiprole	Cephalosporin	Investigational, approved in the USA for cSSSI pending investigation of study conduct issues	Non-inferior to linezolid ± ceftriaxone for CAP and HAP; inferior for VAP in phase 3 trials	Adverse events in phase 3 cSSSI trials (≥8% incidence): nausea, infusion-site reaction, dysgeusia, diarrhoea, headache
Ceftaroline	Cephalosporin	Investigational, NDA expected to be filed for cSSSI and CAP in 2009	Phase 3 CAP trials ongoing	Full phase 3 results not yet published
Dalbavancin	Lipoglycopeptide	Investigational, all marketing applications currently withdrawn pending new phase 3 cSSSI trials	No pneumonia trials underway	Adverse events in phase 3 cSSSI trials (≥2% incidence): nausea, diarrhoea. Renal dysfunction appears to be related to the glycopeptide class
Oritavancin	Lipoglycopeptide	Investigational, the FDA has requested further data for cSSSI indication	No pneumonia trials underway	Full phase 3 results not yet published. Renal dysfunction appears to be related to the glycopeptide class

4

| Iclaprim | Dihydrofolate reductase inhibitor | Investigational, the FDA has requested further data for cSSSI indication | No pneumonia trials underway | Full phase 3 results not yet published |

cSSSI, complicated skin and skin-structure infection; HAP, hospital-acquired pneumonia; VRE, vancomycin-resistant enterococci; cIAI, complicated intra-abdominal infection; CAP, community-acquired pneumonia; VAP, ventilator-associated pneumonia; NDA, new drug application; FDA, US Food and Drug Administration.

5

A

Inhibition of cell wall synthesis
Vancomycin
Teicoplanin
Telavancin*
Dalbavancin
Oritavancin*
Ceftobiprole
Ceftaroline

Inhibition of folic acid metabolism
Iclaprim

Ribosome

50S

30S

Dihydrofolic acid

Dihydrofolate reductase

Tetrahydrofolic acid

Thymine

Inhibition of protein synthesis
Linezolid
Tigecycline
Quinupristin-dalfopristin

Cell membrane disruption
Telavancin*
Oritavancin*

*Agents with multiple mechanisms of action

B

Polymerization

Cross-linking

Lipid II

Lipid II

D-Ala
D-Ala

PBP

PBP

Vancomycin
Telavancin
Dalbavancin
Oritavancin

Ceftobiprole
Ceftaroline