



**HAL**  
open science

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

Tobias Welte, Mathias W. Pletz

► **To cite this version:**

Tobias Welte, Mathias W. Pletz. Antimicrobial treatment of nosocomial meticillin-resistant (MRSA) pneumonia: current and future options. *International Journal of Antimicrobial Agents*, 2010, 36 (5), pp.391. 10.1016/j.ijantimicag.2010.06.045 . hal-00629958

**HAL Id: hal-00629958**

**<https://hal.science/hal-00629958>**

Submitted on 7 Oct 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## Accepted Manuscript

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

Authors: Tobias Welte, Mathias W. Pletz

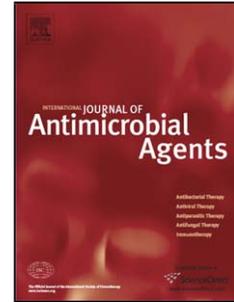
PII: S0924-8579(10)00306-7  
DOI: doi:10.1016/j.ijantimicag.2010.06.045  
Reference: ANTAGE 3381

To appear in: *International Journal of Antimicrobial Agents*

Received date: 22-4-2010  
Revised date: 21-6-2010  
Accepted date: 24-6-2010

Please cite this article as: Welte T, Pletz MW, Antimicrobial treatment of nosocomial meticillin-resistant *Staphylococcus aureus* (MRSA) pneumonia: current and future options, *International Journal of Antimicrobial Agents* (2010), doi:10.1016/j.ijantimicag.2010.06.045

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



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

Tobias Welte \*, Mathias W. Pletz

*Department of Pulmonary Medicine, Hannover Medical School, Carl-Neuberg-  
Strasse 1, 30625 Hannover, Germany*

ARTICLE INFO

*Article history:*

Received 22 April 2010

Accepted 24 June 2010

*Keywords:*

Pneumonia

MRSA

Antimicrobials

\* Corresponding author. Tel.: +49 511 532 x3530.

*E-mail address:* welte.tobias@mh-hannover.de (T. Welte).

## 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.

## 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,

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 ( $\geq 5$  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

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 methicillin-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 methicillin-resistant [16]. In Europe, there is a North to South trend in the proportion of *S. aureus* that is methicillin-resistant, ranging from 0% in

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

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  $\beta$ -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

MIC values [11,12]. *Staphylococcus aureus* strains may also be 'tolerant' to vancomycin, defined as a MIC/minimum bactericidal concentration ratio of  $\geq 32$ . 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  $\beta$ -lactam antimicrobials. In 2002, a class of MRSA strains that developed vancomycin resistance in the presence of  $\beta$ -lactam antibiotics [ $\beta$ -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

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

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].

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

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 doses 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-

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-

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].

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.

#### 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<sub>90</sub> (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%,

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

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  $\gamma$ -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

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  $\beta$ -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  $\beta$ -lactamases but its activity does not cover extended-spectrum  $\beta$ -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%

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

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 ( $\geq 6\%$  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

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.

## 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.

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.

### **Acknowledgment**

Editorial support was provided by Emily Hutchinson, a medical writer at Envision Pharma, funded by Astellas Pharma, Inc.

### **Funding**

None.

### **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.

## References

- [1] American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388–416.
- [2] Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002;165:867–903.
- [3] Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med* 2002;137:791–7.
- [4] Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest* 2005;128:3854–62.
- [5] Masterton RG, Galloway A, French G, Street M, Armstrong J, Brown E, et al. Guidelines for the management of hospital-acquired pneumonia in the UK: report of the Working Party on Hospital-Acquired Pneumonia of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother* 2008;62:5–34.
- [6] Torres A, Ewig S, Lode H, Carlet J. Defining, treating and preventing hospital acquired pneumonia: European perspective. *Intensive Care Med* 2009;35:9–29.

- [7] Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. *Chest* 2002;122:262–8.
- [8] Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 1999;115:462–74.
- [9] Luna CM, Vujacich P, Niederman MS, Vay C, Gherardi C, Matera J, et al. Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. *Chest* 1997;111:676–85.
- [10] Shorr AF, Micek ST, Kollef MH. Inappropriate therapy for methicillin-resistant *Staphylococcus aureus*: resource utilization and cost implications. *Crit Care Med* 2008;36:2335–40.
- [11] Lodise TP, Graves J, Evans A, Graffunder E, Helmecke M, Lomaestro BM, et al. Relationship between vancomycin MIC and failure among patients with methicillin-resistant *Staphylococcus aureus* bacteremia treated with vancomycin. *Antimicrob Agents Chemother* 2008;52:3315–20.
- [12] Soriano A, Marco F, Martínez JA, Pisos E, Almela M, Dimova VP, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2008;46:193–200.
- [13] Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control

- and Prevention, 2006–2007. *Infect Control Hosp Epidemiol* 2008;29:996–1011.
- [14] Styers D, Sheehan DJ, Hogan P, Sahm DF. Laboratory-based surveillance of current antimicrobial resistance patterns and trends among *Staphylococcus aureus*: 2005 status in the United States. *Ann Clin Microbiol Antimicrob* 2006;5:2.
- [15] Klein E, Smith DL, Laxminarayan R. Hospitalizations and deaths caused by methicillin-resistant *Staphylococcus aureus*, United States, 1999–2005. *Emerg Infect Dis* 2007;13:1840–6.
- [16] Klevens RM, Edwards JR, Tenover FC, McDonald LC, Horan T, Gaynes R. Changes in the epidemiology of methicillin-resistant *Staphylococcus aureus* in intensive care units in US hospitals, 1992–2003. *Clin Infect Dis* 2006;42:389–91.
- [17] European Antimicrobial Resistance Surveillance System. EARSS Annual Report 2007. Bilthoven, The Netherlands: EARSS; 2008. [http://www.rivm.nl/earss/Images/EARSS%202007\\_FINAL\\_tcm61-55933.pdf](http://www.rivm.nl/earss/Images/EARSS%202007_FINAL_tcm61-55933.pdf) [accessed 17 March 2010].
- [18] Hidron AI, Low CE, Honig EG, Blumberg HM. Emergence of community-acquired methicillin-resistant *Staphylococcus aureus* strain USA300 as a cause of necrotising community-onset pneumonia. *Lancet Infect Dis* 2009;9:384–92.
- [19] Kollef MH. Limitations of vancomycin in the management of resistant staphylococcal infections. *Clin Infect Dis* 2007;45(Suppl 3):S191–5.
- [20] Chang FY, Peacock JE Jr, Musher DM, Triplett P, MacDonald BB, Mylotte JM, et al. *Staphylococcus aureus* bacteremia: recurrence and the

- impact of antibiotic treatment in a prospective multicenter study. *Medicine* (Baltimore) 2003;82:333–9.
- [21] González C, Rubio M, Romero-Vivas J, González M, Picazo JJ. Bacteremic pneumonia due to *Staphylococcus aureus*: a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. *Clin Infect Dis* 1999;29:1171–7.
- [22] Lodise TP Jr, McKinnon PS, Levine DP, Rybak MJ. Impact of empirical-therapy selection on outcomes of intravenous drug users with infective endocarditis caused by methicillin-susceptible *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2007;51:3731–3.
- [23] Tice AD, Hoaglund PA, Shoultz DA. Risk factors and treatment outcomes in osteomyelitis. *J Antimicrob Chemother* 2003;51:1261–8.
- [24] Cruciani M, Gatti G, Lazzarini L, Furlan G, Broccali G, Malena M, et al. Penetration of vancomycin into human lung tissue. *J Antimicrob Chemother* 1996;38:865–9.
- [25] Scheetz MH, Wunderink RG, Postelnick MJ, Noskin GA. Potential impact of vancomycin pulmonary distribution on treatment outcomes in patients with methicillin-resistant *Staphylococcus aureus* pneumonia. *Pharmacotherapy* 2006;26:539–50.
- [26] Jung YJ, Koh Y, Hong SB, Chung JW, Ho Choi S, Kim NJ, et al. Effect of vancomycin plus rifampicin in the treatment of nosocomial methicillin-resistant *Staphylococcus aureus* pneumonia. *Crit Care Med* 2010;38:175–80.

- [27] Appelbaum PC. The emergence of vancomycin-intermediate and vancomycin-resistant *Staphylococcus aureus*. Clin Microbiol Infect 2006;12(Suppl 1):16–23.
- [28] Hiramatsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover FC. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. J Antimicrob Chemother 1997;40:135–6.
- [29] Steinkraus G, White R, Friedrich L. Vancomycin MIC creep in non-vancomycin-intermediate *Staphylococcus aureus* (VISA), vancomycin-susceptible clinical methicillin-resistant *S. aureus* (MRSA) blood isolates from 2001–05. J Antimicrob Chemother 2007;60:788–94.
- [30] Wang G, Hindler JF, Ward KW, Bruckner DA. Increased vancomycin MICs for *Staphylococcus aureus* clinical isolates from a university hospital during a 5-year period. J Clin Microbiol 2006;44:3883–6.
- [31] May J, Shannon K, King A, French G. Glycopeptide tolerance in *Staphylococcus aureus*. J Antimicrob Chemother 1998;42:189–97.
- [32] Aeschlimann JR, Hershberger E, Rybak MJ. Analysis of vancomycin population susceptibility profiles, killing activity, and postantibiotic effect against vancomycin-intermediate *Staphylococcus aureus*. Antimicrob Agents Chemother 1999;43:1914–8.
- [33] Boyle-Vavra S, Berke SK, Lee JC, Daum RS. Reversion of the glycopeptide resistance phenotype in *Staphylococcus aureus* clinical isolates. Antimicrob Agents Chemother 2000;44:272–7.
- [34] Leclercq R, Derlot E, Duval J, Courvalin P. Plasmid-mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*. N Engl J Med 1988;319:157–61.

- [35] Noble WC, Virani Z, Cree RG. Co-transfer of vancomycin and other resistance genes from *Enterococcus faecalis* NCTC 12201 to *Staphylococcus aureus*. FEMS Microbiol Lett 1992;72:195–8.
- [36] Chang S, Sievert DM, Hageman JC, Boulton ML, Tenover FC, Downes FP, et al. Infection with vancomycin-resistant *Staphylococcus aureus* containing the *vanA* resistance gene. N Engl J Med 2003;348:1342–7.
- [37] Haraga I, Nomura S, Fukamachi S, Ohjimi H, Hanaki H, Hiramatsu K, et al. Emergence of vancomycin resistance during therapy against methicillin-resistant *Staphylococcus aureus* in a burn patient—importance of low-level resistance to vancomycin. Int J Infect Dis 2002;6:302–8.
- [38] Hanaki H, Yamaguchi Y, Barata K, Sakai H, Sunakawa K. Improved method of detection of  $\beta$ -lactam antibiotic-induced VCM-resistant MRSA (BIVR). Int J Antimicrob Agents 2004;23:311–3.
- [39] Takata T, Futo M, Miyazaki M, Hara S, Obata Y, Ngo D, et al. Relationship between heterogeneous vancomycin-intermediate *Staphylococcus aureus* (hVISA),  $\beta$ -lactam induced vancomycin-resistance (BIVR), and outcome in MRSA bacteremia. In: 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 12–15 September 2009; San Francisco, CA. Washington, DC: ASM Press; 2009.
- [40] Levine DP. Vancomycin: a history. Clin Infect Dis 2006;42(Suppl 1):S5–12.
- [41] Kielstein JT, Kretschmer U, Ernst T, Hafer C, Bahr MJ, Haller H, et al. Efficacy and cardiovascular tolerability of extended dialysis in critically ill patients: a randomized controlled study. Am J Kidney Dis 2004;43:342–9.

- [42] Metnitz PG, Krenn CG, Steltzer H, Lang T, Ploder J, Lenz K, et al. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. *Crit Care Med* 2002;30:2051–8.
- [43] Sesso R, Roque A, Vicioso B, Stella S. Prognosis of ARF in hospitalized elderly patients. *Am J Kidney Dis* 2004;44:410–9.
- [44] Vinsonneau C, Camus C, Combes A, Costa de Beauregard MA, Klouche K, Boulain T, et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. *Lancet* 2006;368:379–85.
- [45] Rybak M, Lomaestro B, Rotschafer JC, Moellering R Jr, Craig W, Billeter M, et al. 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. *Am J Health Syst Pharm* 2009;66:82–98.
- [46] Zyvox [package insert]. New York, NY: Pfizer, Inc.; 2008.
- [47] Kollef MH, Rello J, Cammarata SK, Croos-Dabrera RV, Wunderink RG. Clinical cure and survival in Gram-positive ventilator-associated pneumonia: retrospective analysis of two double-blind studies comparing linezolid with vancomycin. *Intensive Care Med* 2004;30:388–94.
- [48] Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest* 2003;124:1789–97.

- [49] Rubinstein E, Cammarata S, Oliphant T, Wunderink R; Linezolid Nosocomial Pneumonia Study Group. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin Infect Dis* 2001;32:402–12.
- [50] Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther* 2003;25:980–92.
- [51] Conte JE Jr, Golden JA, Kipps J, Zurlinden E. Intrapulmonary pharmacokinetics of linezolid. *Antimicrob Agents Chemother* 2002;46:1475–80.
- [52] Powers JH, Lin D, Ross D. FDA evaluation of antimicrobials: subgroup analysis. *Chest* 2005;127:2298–9.
- [53] Powers JH, Ross DB, Lin D, Soreth J. Linezolid and vancomycin for methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: the subtleties of subgroup analyses. *Chest* 2004;126:314–5.
- [54] Wunderink RG, Mendelson MH, Somero MS, Fabian TC, May AK, Bhattacharyya H, et al. Early microbiological response to linezolid vs vancomycin in ventilator-associated pneumonia due to methicillin-resistant *Staphylococcus aureus*. *Chest* 2008;134:1200–7.
- [55] Tsiodras S, Gold HS, Sakoulas G, Eliopoulos GM, Wennersten C, Venkataraman L, et al. Linezolid resistance in a clinical isolate of *Staphylococcus aureus*. *Lancet* 2001;358:207–8.

- [56] Jones RN, Fritsche TR, Sader HS, Ross JE. LEADER surveillance program results for 2006: an activity and spectrum analysis of linezolid using clinical isolates from the United States (50 medical centers). *Diagn Microbiol Infect Dis* 2007;59:309–17.
- [57] Attassi K, Hershberger E, Alam R, Zervos MJ. Thrombocytopenia associated with linezolid therapy. *Clin Infect Dis* 2002;34:695–8.
- [58] Bishop E, Melvani S, Howden BP, Charles PG, Grayson ML. Good clinical outcomes but high rates of adverse reactions during linezolid therapy for serious infections: a proposed protocol for monitoring therapy in complex patients. *Antimicrob Agents Chemother* 2006;50:1599–602.
- [59] Orrick JJ, Johns T, Janelle J, Ramphal R. Thrombocytopenia secondary to linezolid administration: what is the risk? *Clin Infect Dis* 2002;35:348–9.
- [60] Lin YH, Wu VC, Tsai IJ, Ho YL, Hwang JJ, Tsau YK, et al. High frequency of linezolid-associated thrombocytopenia among patients with renal insufficiency. *Int J Antimicrob Agents* 2006;28:345–51.
- [61] De Vriese AS, Coster RV, Smet J, Seneca S, Lovering A, Van Haute LL, et al. Linezolid-induced inhibition of mitochondrial protein synthesis. *Clin Infect Dis* 2006;42:1111–7.
- [62] Azamfirei L, Copotoiu SM, Branzaniuc K, Szederjesi J, Copotoiu R, Berteanu C. Complete blindness after optic neuropathy induced by short-term linezolid treatment in a patient suffering from muscle dystrophy. *Pharmacoepidemiol Drug Saf* 2007;16:402–4.

- [63] Lawrence KR, Adra M, Gillman PK. Serotonin toxicity associated with the use of linezolid: a review of postmarketing data. *Clin Infect Dis* 2006;42:1578–83.
- [64] Wilcox M, Nathwani D, Dryden M. Linezolid compared with teicoplanin for the treatment of suspected or proven Gram-positive infections. *J Antimicrob Chemother* 2004;53:335–44.
- [65] Cepeda JA, Whitehouse T, Cooper B, Hails J, Jones K, Kwaku F, et al. Linezolid versus teicoplanin in the treatment of Gram-positive infections in the critically ill: a randomized, double-blind, multicentre study. *J Antimicrob Chemother* 2004;53:345–55.
- [66] Tascini C, Gemignani G, Doria R, Biancofiore G, Urbani L, Mosca C, et al. Linezolid treatment for Gram-positive infections: a retrospective comparison with teicoplanin. *J Chemother* 2009;21:311–6.
- [67] Drago L, De Vecchi E, Fassina MC, Gismondo MR. Serum and bone concentrations of teicoplanin and vancomycin: study in an animal model. *Drugs Exp Clin Res* 1998;24:185–90.
- [68] Mimoz O, Rolland D, Adoun M, Marchand S, Breilh D, Brumpt I, et al. Steady-state trough serum and epithelial lining fluid concentrations of teicoplanin 12 mg/kg per day in patients with ventilator-associated pneumonia. *Intensive Care Med* 2006;32:775–9.
- [69] Shlaes DM, Shlaes JH. Teicoplanin selects for *Staphylococcus aureus* that is resistant to vancomycin. *Clin Infect Dis* 1995;20:1071–3.
- [70] Svetitsky S, Leibovici L, Paul M. Comparative efficacy and safety of vancomycin versus teicoplanin: systematic review and meta-analysis. *Antimicrob Agents Chemother* 2009;53:4069–79.

- [71] Wood MJ. Comparative safety of teicoplanin and vancomycin. *J Chemother* 2000;12(Suppl 5):21–5.
- [72] Synercid [package insert]. Bristol, TN: Monarch Pharmaceuticals, Inc. and Greenville, NC: DSM Pharmaceuticals, Inc.; 2003.
- [73] Fagon JY, Patrick H, Haas DW, Torres A, Gibert C, Cheadle WG, et al. Treatment of Gram-positive nosocomial pneumonia. Prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. Nosocomial Pneumonia Group. *Am J Respir Crit Care Med* 2000;161:753–62.
- [74] Finberg RW, Moellering RC, Tally FP, Craig WA, Pankey GA, Dellinger EP, et al. The importance of bactericidal drugs: future directions in infectious disease. *Clin Infect Dis* 2004;39:1314–20.
- [75] Pankey GA, Sabath LD. Clinical relevance of bacteriostatic versus bactericidal mechanisms of action in the treatment of Gram-positive bacterial infections. *Clin Infect Dis* 2004;38:864–70.
- [76] Cazzola M, Blasi F, Terzano C, Matera MG, Marsico SA. Delivering antibacterials to the lungs: considerations for optimizing outcomes. *Am J Respir Med* 2002;1:261–72.
- [77] Silverman JA, Mortin LI, Vanpraagh AD, Li T, Alder J. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. *J Infect Dis* 2005;191:2149–52.
- [78] Pertel PE, Bernardo P, Fogarty C, Matthews P, Northland R, Benvenuto M, et al. Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. *Clin Infect Dis* 2008;46:1142–51.

- [79] Tygacil [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; 2009.
- [80] Olson MW, Ruzin A, Feyfant E, Rush TS 3rd, O'Connell J, Bradford PA. Functional, biophysical, and structural bases for antibacterial activity of tigecycline. *Antimicrob Agents Chemother* 2006;50:2156–66.
- [81] Anthony KB, Fishman NO, Linkin DR, Gasink LB, Edelstein PH, Lautenbach E. Clinical and microbiological outcomes of serious infections with multidrug-resistant Gram-negative organisms treated with tigecycline. *Clin Infect Dis* 2008;46:567–70.
- [82] Maroko R, Cooper A, Dukart G, Dartios H. Results of phase 3 study comparing a tigecycline regimen with an imipenem/cilastatin regimen in treatment of patients with hospital acquired pneumonia. In: 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 17–21 September 2007; Chicago, IL. Washington, DC: ASM Press; 2007. Poster L-730.
- [83] Burkhardt O, Rauch K, Kaever V, Hadem J, Kielstein JT, Welte T. Tigecycline possibly underdosed for the treatment of pneumonia: a pharmacokinetic viewpoint. *Int J Antimicrob Agents* 2009;34:101–2.
- [84] Conte JE Jr, Golden JA, Kelly MG, Zurlinden E. Steady-state serum and intrapulmonary pharmacokinetics and pharmacodynamics of tigecycline. *Int J Antimicrob Agents* 2005;25:523–9.
- [85] Higgins DL, Chang R, Debabov DV, Leung J, Wu T, Krause KM, et al. Telavancin, a multifunctional lipoglycopeptide, disrupts both cell wall synthesis and cell membrane integrity in methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2005;49:1127–34.

- [86] King A, Phillips I, Kaniga K. Comparative in vitro activity of telavancin (TD-6424), a rapidly bactericidal, concentration-dependent anti-infective with multiple mechanisms of action against Gram-positive bacteria. *J Antimicrob Chemother* 2004;53:797–803.
- [87] Pace JL, Krause K, Johnston D, Debabov D, Wu T, Farrington L, et al. In vitro activity of TD-6424 against *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2003;47:3602–4.
- [88] Draghi DC, Benton BM, Krause KM, Thornsberry C, Pillar C, Sahm DF. In vitro activity of telavancin against recent Gram-positive clinical isolates: results of the 2004–05 Prospective European Surveillance Initiative. *J Antimicrob Chemother* 2008;62:116–21.
- [89] Gotfried MH, Shaw JP, Benton BM, Krause KM, Goldberg MR, Kitt MM, et al. Intrapulmonary distribution of intravenous telavancin in healthy subjects and effect of pulmonary surfactant on in vitro activities of telavancin and other antibiotics. *Antimicrob Agents Chemother* 2008;52:92–7.
- [90] Lodise TP Jr, Gotfried M, Barriere S, Drusano GL. Telavancin penetration into human epithelial lining fluid determined by population pharmacokinetic modeling and Monte Carlo simulation. *Antimicrob Agents Chemother* 2008;52:2300–4.
- [91] Gander S, Kinnaird A, Finch R. Telavancin: in vitro activity against staphylococci in a biofilm model. *J Antimicrob Chemother* 2005;56:337–43.
- [92] Stryjewski ME, Graham DR, Wilson SE, O'Riordan W, Young D, Lentnek A, et al. Telavancin versus vancomycin for the treatment of

- complicated skin and skin-structure infections caused by Gram-positive organisms. *Clin Infect Dis* 2008;46:1683–93.
- [93] Rubinstein E, Corey GR, Stryjewski ME, Boucher HW, Daly RN, Genter FC, et al. Telavancin for hospital-acquired pneumonia, including ventilator-associated pneumonia: the ATTAIN studies. In: 18th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 19–22 April 2008; Barcelona, Spain. *Clin Infect Dis* 2008;14:S14–5. Abstract O75.
- [94] Hegde SS, Reyes N, Wiens T, Vanasse N, Skinner R, McCullough J, et al. Pharmacodynamics of telavancin (TD-6424), a novel bactericidal agent, against Gram-positive bacteria. *Antimicrob Agents Chemother* 2004;48:3043–50.
- [95] Roecker AM, Pope SD. Dalbavancin: a lipoglycopeptide antibacterial for Gram-positive infections. *Expert Opin Pharmacother* 2008;9:1745–54.
- [96] Jauregui LE, Babazadeh S, Seltzer E, Goldberg L, Krievins D, Frederick M, et al. Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. *Clin Infect Dis* 2005;41:1407–15.
- [97] Domenech O, Francius G, Tulkens PM, Van Bambeke F, Dufrêne Y, Mingeot-Leclercq MP. Interactions of oritavancin, a new lipoglycopeptide derived from vancomycin, with phospholipid bilayers: effect on membrane permeability and nanoscale lipid membrane organization. *Biochim Biophys Acta* 2009;1788:1832–40.

- [98] Kim SJ, Cegelski L, Stueber D, Singh M, Dietrich E, Tanaka KS, et al. Oritavancin exhibits dual mode of action to inhibit cell-wall biosynthesis in *Staphylococcus aureus*. *J Mol Biol* 2008;377:281–93.
- [99] Belley A, Neesham-Grenon E, McKay G, Arhin FF, Harris R, Beveridge T, et al. Oritavancin kills stationary-phase and biofilm *Staphylococcus aureus* cells in vitro. *Antimicrob Agents Chemother* 2009;53:918–25.
- [100] Linden PK. Vancomycin resistance: are there better glycopeptides coming? *Expert Rev Anti Infect Ther* 2008;6:917–28.
- [101] Hebeisen P, Heinze-Krauss I, Angehrn P, Hohl P, Page MG, Then RL. In vitro and in vivo properties of Ro 63-9141, a novel broad-spectrum cephalosporin with activity against methicillin-resistant staphylococci. *Antimicrob Agents Chemother* 2001;45:825–36.
- [102] Walkty A, Decorby M, Nichol K, Karlowsky JA, Hoban DJ, Zhanel GG. In vitro activity of ceftobiprole against clinical isolates of *Pseudomonas aeruginosa* obtained from Canadian intensive care unit (ICU) patients as part of the CAN-ICU Study. *J Antimicrob Chemother* 2008;62:206–8.
- [103] Noel GJ, Bush K, Bagchi P, Ianus J, Strauss RS. A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. *Clin Infect Dis* 2008;46:647–55.
- [104] Noel GJ, Strauss RS, Amsler K, Heep M, Pypstra R, Solomkin JS. Results of a double-blind, randomized trial of ceftobiprole treatment of complicated skin and skin structure infections caused by Gram-positive bacteria. *Antimicrob Agents Chemother* 2008;52:37–44.

- [105] Basilea Pharmaceutica Ltd. Ceftobiprole shows high cure rates in patients hospitalized with community-acquired pneumonia [press release]. 20 May 2008. Basel, Switzerland: Basilea Pharmaceutica Ltd. [http://www.redorbit.com/news/health/1394511/ceftobiprole\\_shows\\_high\\_cure\\_rates\\_in\\_patients\\_hospitalized\\_with\\_communityacquired/index.html](http://www.redorbit.com/news/health/1394511/ceftobiprole_shows_high_cure_rates_in_patients_hospitalized_with_communityacquired/index.html) [accessed 19 March 2010].
- [106] Neuner EA, Ritchie DJ, Micek ST. New antibiotics for healthcare-associated pneumonia. *Semin Respir Crit Care Med* 2009;30:92–101.
- [107] Basilea Pharmaceutica Ltd. Basilea announces positive top-line data from phase III study of ceftobiprole in hospital-acquired pneumonia [press release]. 9 October 2007. Basel, Switzerland: Basilea Pharmaceutica Ltd. <http://www.basilea.com/News-and-Media/Basilea-Announces-Positive-Top-line-Data-from-Phase-III-Study-of-Ceftobiprole-in-Hospital-Acquired-Pneumonia/144> [accessed 19 March 2010].
- [108] Banerjee R, Gretes M, Basuino L, Strynadka N, Chambers HF. In vitro selection and characterization of ceftobiprole-resistant methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2008;52:2089–96.
- [109] Schmitt-Hoffmann A, Roos B, Schleimer M, Sauer J, Man A, Nashed N, et al. Single-dose pharmacokinetics and safety of a novel broad-spectrum cephalosporin (BAL5788) in healthy volunteers. *Antimicrob Agents Chemother* 2004;48:2570–5.
- [110] Schmitt-Hoffmann A, Nyman L, Roos B, Schleimer M, Sauer J, Nashed N, et al. Multiple-dose pharmacokinetics and safety of a novel broad-spectrum cephalosporin (BAL5788) in healthy volunteers. *Antimicrob Agents Chemother* 2004;48:2576–80.

- [111] Fenoll A, Aguilar L, Robledo O, Giménez MJ, Granizo JJ, Biek D, et al. In vitro activity of ceftaroline against *Streptococcus pneumoniae* isolates exhibiting resistance to penicillin, amoxicillin, and cefotaxime. *Antimicrob Agents Chemother* 2008;52:4209–10.
- [112] Ge Y, Biek D, Talbot GH, Sahm DF. In vitro profiling of ceftaroline against a collection of recent bacterial clinical isolates from across the United States. *Antimicrob Agents Chemother* 2008;52:3398–407.
- [113] Kanafani ZA, Corey GR. Ceftaroline: a cephalosporin with expanded Gram-positive activity. *Future Microbiol* 2009;4:25–33.
- [114] Sader HS, Fritsche TR, Jones RN. Antimicrobial activities of ceftaroline and ME1036 tested against clinical strains of community-acquired methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2008;52:1153–5.
- [115] Sader HS, Fritsche TR, Kaniga K, Ge Y, Jones RN. Antimicrobial activity and spectrum of PPI-0903M (T-91825), a novel cephalosporin, tested against a worldwide collection of clinical strains. *Antimicrob Agents Chemother* 2005;49:3501–12.
- [116] Forest Laboratories Inc. Forest Laboratories announces positive results from phase III clinical studies of ceftaroline for the treatment of complicated skin and skin structure infections [press release]. 19 June 2008. New York, NY: Forest Laboratories, Inc. <http://www.frx.com/news/PressRelease.aspx?ID=1167784> [accessed 19 March 2010].
- [117] Forest Laboratories Inc. Forest Laboratories announces positive top-line data from two pivotal phase III trials of ceftaroline for the treatment of

- community-acquired bacterial pneumonia (CABP) requiring hospitalization [press release]. 19 June 2009. New York, NY: Forest Laboratories, Inc. <http://www.frx.com/news/PressRelease.aspx?ID=1300673> [accessed 19 March 2010].
- [118] Talbot GH, Thye D, Das A, Ge Y. Phase 2 study of ceftaroline versus standard therapy in treatment of complicated skin and skin structure infections. *Antimicrob Agents Chemother* 2007;51:3612–6.
- [119] Sader HS, Fritsche TR, Jones RN. Potency and bactericidal activity of iclaprim against recent clinical Gram-positive isolates. *Antimicrob Agents Chemother* 2009;53:2171–5.
- [120] Weiss L, Bihl M, Islam K, Lociuro S, Hawser S. Bactericidal activity of iclaprim against methicillin-sensitive and -resistant *Staphylococcus aureus*. In: 18th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 19–22 April 2008; Barcelona, Spain. *Clin Infect Dis* 2008;14:S140. Poster 588; abstract.
- [121] Entenza JM, Haldimann A, Giddey M, Lociuro S, Hawser S, Moreillon P. Efficacy of iclaprim against wild-type and thymidine kinase-deficient methicillin-resistant *Staphylococcus aureus* isolates in an in vitro fibrin clot model. *Antimicrob Agents Chemother* 2009;53:3635–41.
- [122] Hamilton-Miller JM. Reversal of activity of trimethoprim against Gram-positive cocci by thymidine, thymine and 'folates'. *J Antimicrob Chemother* 1988;22:35–9.
- [123] Proctor RA. Role of folate antagonists in the treatment of methicillin-resistant *Staphylococcus aureus* infection. *Clin Infect Dis* 2008;46:584–93.

- [124] Krievins D, Brandt R, Hawser S, Hadvary P, Islam K. Multicenter, randomized study of the efficacy and safety of intravenous iclaprim in complicated skin and skin structure infections. *Antimicrob Agents Chemother* 2009;53:2834–40.
- [125] Arpida. Pivotal phase III data confirm the efficacy and safety of Arpida's intravenous iclaprim in treating patients with complicated skin and skin structure infections [press release]. 26 October 2008. Reinach, Switzerland: Arpida.  
<http://www.evolva.com/newsroom/2008/10/26/67/pivotal-phase-iii-data-confirm-efficacy-and-safety-arpida%E2%80%99s-intravenous-iclap>  
[accessed 19 March 2010].
- [126] Andrews J, Honeybourne D, Ashby J, Jevons G, Fraise A, Fry P, et al. Concentrations in plasma, epithelial lining fluid, alveolar macrophages and bronchial mucosa after a single intravenous dose of 1.6 mg/kg of iclaprim (AR-100) in healthy men. *J Antimicrob Chemother* 2007;60:677–80.
- [127] ClinicalTrials.gov. Clinical efficacy of intravenous iclaprim versus vancomycin in the treatment of hospital-acquired, ventilator-associated, or health-care-associated pneumonia. ClinicalTrials.gov Identifier NCT00543608. 12 February 2009.  
[http://www.clinicaltrials.gov/ct2/show/NCT00543608?term=iclaprim&rank=](http://www.clinicaltrials.gov/ct2/show/NCT00543608?term=iclaprim&rank=1)  
1 [accessed 19 March 2010].

**Fig. 1.** (A) Sites of action of current and potential antimicrobial agents for the treatment of methicillin-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.

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	<i>Streptococcus pneumoniae</i>	Ceftriaxone
	<i>Haemophilus influenzae</i>	or
	MSSA	levofloxacin, moxifloxacin, ciprofloxacin
	Antibiotic-sensitive enteric	<sup>a</sup>
	Gram-negative bacilli	or ampicillin/sulbactam or ertapenem

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

HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; MDR multidrug resistant; MSSA, methicillin-susceptible *Staphylococcus aureus*; HCAP, healthcare-associated pneumonia; ESBL, extended-spectrum  $\beta$ -lactamase; MRSA, methicillin-resistant *S. aureus*.

- <sup>a</sup> 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.
- <sup>b</sup> 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.
- <sup>c</sup> Combination therapy with fluoroquinolones or aminoglycosides is recommended but remains an issue of debate as clinical data are contradictory.
- <sup>d</sup> If MRSA risk factors are present or there is a high incidence locally.

**Table 2**

Summary of current and potential future agents for the treatment of methicillin-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

---

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

---

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 ( $\geq 10\%$ incidence), diarrhoea, renal impairment. Renal dysfunction appears to be related to the glycopeptide class

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 ( $\geq 8\%$ 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 ( $\geq 2\%$ 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

---

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.

