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Review

New antimicrobial approaches to gram positive respiratory infections

Adamantia Liapikou^{a, *}, Catia Cilloniz^b, Josep Mensa^c, Antonio Torres^b^a 6th Respiratory Department, Sotiria Chest Diseases Hospital, Athens, Greece^b Department of Pneumology, Institut Clinic del Tòrax, Hospital Clinic, University of Barcelona, Spain^c Department of Infectious Diseases, Hospital Clinic, Spain

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ABSTRACT

Nowadays, we face growing resistance among gram-positive and gram-negative pathogens that cause respiratory infection in the hospital and in the community. The spread of penicillin- and macrolide-resistant *pneumococci*, Community-acquired methicillin-resistant *staphylococcus aureus* (Ca-MRSA), the emergence of glycopeptide-resistant *staphylococci* underline the need for underline the need for therapeutic alternatives. A number of new therapeutic agents, with activity against the above Gram (+) respiratory pathogens, as ceftaroline, ceftopibrole, telavancin, tedizolid have become available, either in clinical trials or have been approved for clinical use. Especially, the development of new oral antibiotics, as nemonoxacin, omadacyclin, cethromycin and solithromycin will give a solution to the lack of oral drugs for outpatient treatment. In the future the clinician needs to optimize the use of old and new antibiotics to treat gram (+) respiratory serious infections.

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1. Introduction

Lower respiratory tract infections (LRTIs) as acute exacerbations of chronic bronchitis, community-acquired pneumonia (CAP) and hospital acquired pneumonia (HAP) are one of the most common diseases in humans and a long-term global public health concern.

Within Europe, CAP is the leading cause of death due to infection [1] with approximately 90% of deaths due to pneumonia occurring in people aged >65 years. Ventilator-associated pneumonia (VAP), representing 80% of HAP, is reported to be the most common hospital-acquired infection among patients requiring mechanical ventilation, carrying an attributable mortality of 33–60%.

Streptococcus pneumoniae, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, Enterobacteriaceae, *Pseudomonas aeruginosa* and *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila* causing atypical pneumonias are the major pathogens implicated in respiratory tract infections.

Nowadays, multi-drug-resistant bacteria have emerged throughout the world with more than one third of the isolates are multidrug-resistant (MDR) [2], and half the deaths from clinical infection in Europe are associated with MDR bacteria [3]. The increasing problem of antibiotic resistance means that community and hospital LRTIs are becoming progressively more difficult to diagnose and treat.

In a recent review Welte et al., analyzing forty-six primary articles of CAP, *S. pneumoniae* was reported as the most frequently pathogen, being isolated in 38% of outpatient cases, 27% of inpatient cases, and 28% of CAP patients admitted in the ICU [4]. In the AWARE Ceftaroline Surveillance Program (2008–2010) showed

* Corresponding author.

E-mail address: mliapikou@yahoo.com (A. Liapikou).

that among 3329 isolates of *S. pneumoniae* in USA, this collection contained up to 21.1% penicillin-resistant strains (using CLSI criteria for penicillin [oral penicillin V]) [5].

Among the Gram-positive respiratory organisms, *S. pneumoniae* resistant to penicillin and macrolides and methicillin-resistant *S. aureus* (MRSA) represent the biggest therapeutic hurdles.

Rates of penicillin resistance of *S. pneumoniae* exceeding 50% occur in certain areas of the world, such as Asia, 25% in some Mediterranean countries but remain low (<5%) in other regions, such as Finland and Sweden [6]. Worldwide, penicillin-resistant strains of pneumococci are usually also resistant to tetracycline, erythromycin and chloramphenicol. Reports from Germany, USA and other European and Asian countries showed a resistance rate of *S. pneumoniae* to macrolides that varies from 18% to 75% [7–8].

S. aureus is the predominant Gram positive pathogen in HAP and VAP. Data from the National Nosocomial Infections Surveillance system of USA suggest that in ICUs the [9] proportion of MRSA has increased to 59.5%–64.4%. MRSA is also commonly isolated in patients with HAP in European ICUs. Koulenti et al. [10] reported that MRSA was isolated in 16% of patients with nosocomial pneumonia (21.4% in HAP and 14.6% in VAP). Coma is the primary risk factor for VAP caused by methicillin sensitive *S. aureus* (MSSA) and risk factors for VAP caused by MRSA include corticosteroid therapy, mechanical ventilation longer than 6 days, >25 yrs of age, prior diagnosis of COPD, and previous use of antibiotics [11].

Another large, prospective study reporting 474 patients with VAP in Spain found that patients with MRSA VAP had significantly higher in-hospital mortality than patients with VAP caused by other microorganisms (59.5% versus 46.8%; *p* 0.02) [12].

Evenmore, the appearance of glycopeptide non-susceptibility among staphylococci, mainly of the vancomycin-intermediate (VISA) and hetero-VISA (hVISA) varieties, makes these infections more difficult to treat [13].

Therefore, new oral and/or parenteral antimicrobial agents with activities against these Gram-positive respiratory pathogens are in demand. To improve our fight against MRSA there are new oxazolidinone (tedizolid) and the extended spectrum cephalosporins, ceftobiprole and ceftaroline treating CAP and HAP. New agents which target protein synthesis and a quinolone are in development for the treatment of moderate to severe respiratory infections: solithromycin, cethromycin and nemonoxacin.

This review is intended to raise awareness of several novel approaches to combating the emergence of Gram (+) positive- especially MDR-respiratory bacteria which are becoming more commonplace in our hospitals and even in our community settings.

2. Approved antimicrobials

A number of new therapeutic agents against Gram (+) respiratory pathogens have been approved for clinical use the last 3 years, including: ceftaroline, ceftobiprole and telavancin (Table 1).

Table 1
New antimicrobials against Gram (+) respiratory infections.

Compound	Formulation	Clinical indication	Stage of development	Side effects
Telavancin	Lipoglycopeptide	cSSSIs in USA HAP in Europe	Approved	Taste disturbance, foamy urine, renal impairment
Ceftaroline	Cefalosporin	cSSSIs and CAP	Approved by FDA and EMA	Hypersensitivity reactions, <i>Clostridium difficile</i> -associated Diarrhea,
Ceftobiprole	Cefalosporin	HAP, excluded VAP	Approved in Europe	Nausea, Vomiting, taste disturbance
Omadacycline	Tetracycline	cSSSIs, CAP	Phase III cSSTI completed	Nausea, elevation of ALT levels
Cethromycin	Ketolide	CAP	Phase III	Diarrhea, dysgeusia, headache
Solithromycin	Ketolide	CAP	Phase III	Diarrhea, headache and nausea
Tedizolid	oxazolidinone	cSSSIs and HAP	Phase III cSSTI & HAP	Nausea, diarrhea, headache, vomiting
Nemonoxacin	Quinolone	CAP	Phase III clinical trial in CAP	Headache, contact dermatitis, pruritus, rash

NDA: new drug application, cSSSIs: complicated skin and skin structure infection, CAP: community acquired pneumonia.

3. Ceftaroline

Ceftaroline fosamil is a new, bactericidal, parental, extended spectrum cephalosporin (Table 2) with activity against Gram positive organisms, including *S. pneumoniae*, *Streptococcus pyogenes*, *S. aureus* (including MRSA and vancomycin-resistant *S. aureus* (VRSA) and hetero-resistant VISA (hVISA), as well as many common Gram-negative organisms, as *Hemophilus influenzae* and *Moraxella catarrhalis*.

Like other b-lactam antibiotics, prevents cell wall formation by binding to the penicillin-binding protein (PBP), especially to PBP – 2a, which confers the methicillin resistance in *S. aureus*. The MIC₉₀ with a range of 0.25–1 against *S. aureus* tends to be low [14] and an MIC of ≤1 µg/mL is considered susceptible.

Ceftaroline is active against *S. pneumoniae*, including penicillin-intermediate and-resistant strains [15]. Ceftaroline exhibits potent *in vitro* activity against *S. pneumoniae* with MIC₉₀ values for penicillin-susceptible, penicillin intermediate and penicillin-resistant strains of 0.015 mg/L, 0.06 mg/L and 0.12 mg/L, respectively [14].

Using single-step and multistep passages, no resistant mutants were selected with ceftaroline in staphylococci, pneumococci, or *H. influenzae* [16].

Ceftaroline has limited protein binding (1–19%) and achieved good lung penetration (40%) in a rabbit model [17]. The major route of elimination is renal excretion with an average *t*_{1/2} is 2.6 h.

Phase III clinical trials have found that ceftaroline is non-inferior to comparator therapy for the treatment of community acquired pneumonia (FOCUS 1 and 2 trials; comparator: ceftriaxone), with cure rates of ceftaroline >82% [18]. Evenmore, in a retrospective integrated analysis of the FOCUS trials clinical response rates associated with the most common pathogens were numerically higher for ceftaroline compared to ceftriaxone (84% vs. 78%, respectively) [19].

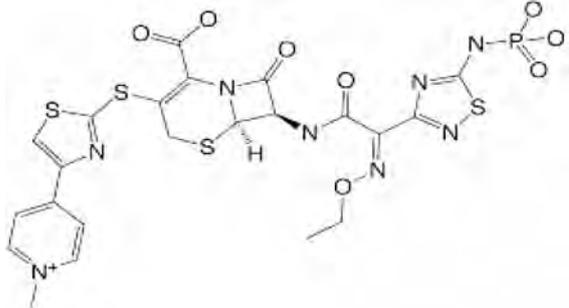
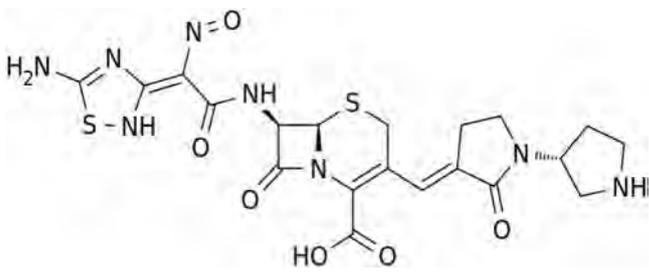
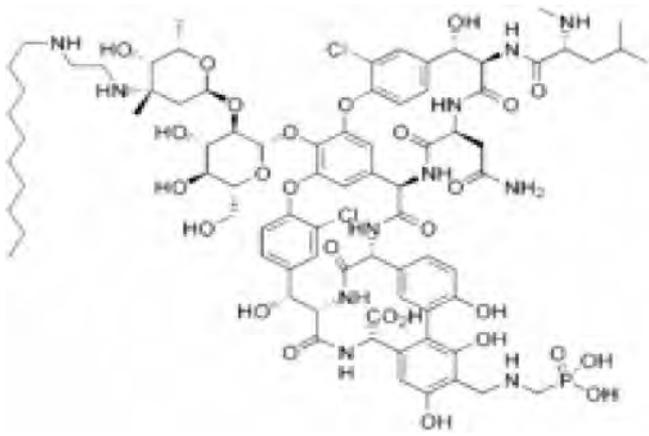
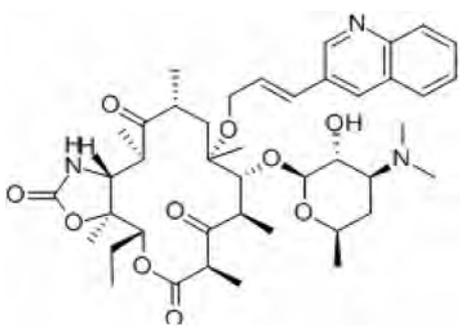
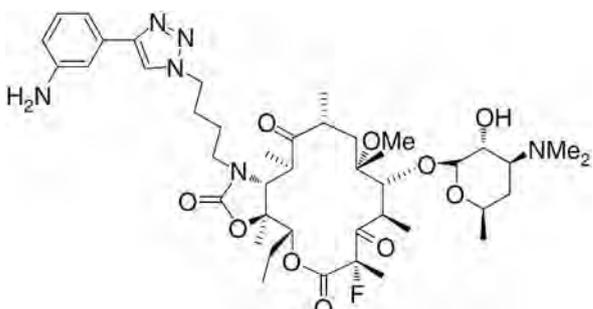
Ceftaroline is usually well tolerated, and in clinical trials only about 3% of subjects discontinued therapy due to adverse effects, most commonly due to allergic reactions. The most common adverse effects were rash, diarrhea, headache, hypokalaemia, insomnia and phlebitis [18].

It has been the only FDA (10/2010) approved cephalosporin for treatment of skin and soft tissue infections (cSSSIs) and CAP, in an i.v. dose of 600 mg/12 h.

The positive attributes of ceftaroline with respect to antimicrobial stewardship programs are: the low potential for resistance development and the favorable safety and tolerability profile in clinical trials.

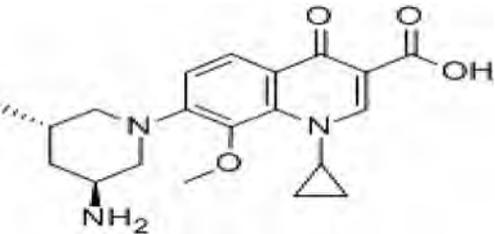
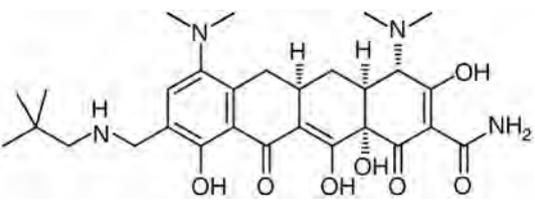
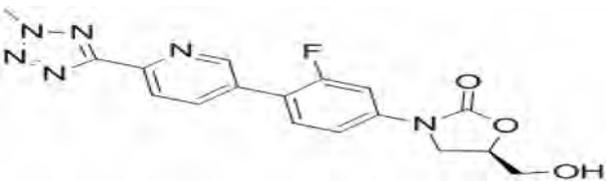
Its limitations are the dosing regimen: three times daily for invasive infections (no data available for continuous infusion), and the absence of an oral formulation.

Table 2
Chemical structures of new antibiotics.

Antibiotics	Chemical figures
1. Ceftaroline	
2. Ceftopibrole	
3. Telavancin	
4. Cethromycin	
5. Solithromycin	

(continued on next page)

Table 2 (continued)

Antibiotics	Chemical figures
6. Nemonoxacin	
7. Omadacycline	
8. Tedizolid	

4. Ceftobiprole

Ceftobiprole is a new member of the pyrrolidone-3-ylidenemethyl cephem series of cephalosporins. It is active against pneumococci, *S. aureus*-including MRSA and vancomycin-intermediate *S. aureus* (VISA), *Enterococcus faecalis* and Gram-negative bacilli-especially has anti-pseudomonal activity similar to cefepime and some anaerobes [20].

Like ceftaroline has strong binding affinity to PBP-2x and PBP-2a resulting in bactericidal activity against resistant *S. pneumoniae* and Ca-MRSA.

MICs for all streptococcal species, except the penicillin-resistant *Streptococcus viridans*, but including penicillin-resistant *S. pneumoniae*, ranged from <or =0.008–2.0 mg/L. Ceftobiprole is active against *E. faecalis* but generally not active against *Enterococcus faecium*. A surveillance study on *S. pneumoniae* called, TRUST 12, showed that ceftobiprole was the most potent cephalosporin tested against *S. pneumoniae* with MIC₅₀ (0.015 µg/mL) and MIC₉₀ (0.5 µg/mL) with values two-fold lower than ceftriaxone [21].

PK/PD studies in humans demonstrate that ceftobiprole has an elimination half-life of about 3 h and predominantly urinary excretion.

In the phase III study published by Nicholson et al. [22], ceftobiprole 500 mg every 8 h was non-inferior to ceftriaxone with or without linezolid for the treatment of CAP patients. Also, for HAP, a phase III clinical trial demonstrates the noninferiority of ceftobiprole plus placebo compared with linezolid plus ceftazidime with respect to the clinical cure (77% for ceftobiprole and 76% for combination therapy). However, ceftobiprole was inferior in the subgroup of patients undergoing mechanical ventilation (VAP) [13].

In a more recent review about ceftobiprole [23], reported that in patients with normal PK and non-VAP, ceftobiprole is effective for the treatment of HAP in the recommended doses, but it is unlikely to achieve the desired PD targets when PK parameters are altered in

VAP (e.g., increased Vd and Cl). That's why it has been approved in Europe for HAP, but not VAP.

It is well tolerated with frequently reported adverse effects included taste disturbances, nausea and vomiting.

5. Telavancin

Telavancin is a vancomycin-derived lipoglycopeptide which is characterized by a broad spectrum of microbiologic activity against Gram-positive bacteria, such as *S. pneumoniae* independent of penicillin susceptibility and staphylococci (including MRSA, hVISA and VISA strains) [24].

Its antibacterial effects are proposed to be achieved through a dual mechanism of action, i.e. inhibition of cell wall peptidoglycan synthesis and depolarization of the cell membrane, resulting in disruption of the functional integrity [25].

The excellent activity of telavancin against *Staphylococcus* spp. represents the main characteristic of this compound. MIC values (MIC₉₀) of tested strains between 0.25 and 1 mg/L have been reported in an over 4500 isolates of MSSA and MRSA worldwide [26]. Against *S. aureus* with reduced susceptibility to glycopeptides, telavancin retains some activity but with elevated MICs [27]. In several studies, telavancin MICs for MRSA ranged from two to eight times lower than those observed for vancomycin, teicoplanin and linezolid.

It is highly protein bound estimated at 93% and has a long half-life (up to 9 h), so that it can be given once a day. Telavancin excreted mainly via the kidneys, so the dose of the drug needs adjustment for patients with moderate renal insufficiency.

Telavancin distributed into lung tissue with epithelial lining fluid concentrations of approximately two- to eightfold above the MIC₉₀ of *S. aureus* for 24 h. Post antibiotic effect of 4–6 h were demonstrated against a variety of Gram-positive bacteria, including MSSA and MRSA [28].

Telavancin has been also evaluated in two studies (ATTAIN 1–2) in the treatment of HAP due to Gram-positive cocci, particularly MRSA. In these studies telavancin was noninferior to vancomycin on the basis of clinical response in the treatment of HAP, especially clinical cure: 82% telavancin. vs. 74% for vancomycin. But in patients with pre-existing moderate/severe renal impairment (CrCl < 50 mL/min) telavancin presented an increased mortality compare to vancomycin [29].

Responding to this result, in a post hoc analysis of data from two Phase 3 ATTAIN trials [30] excluding patients with severe renal impairment (creatinine clearance <30 mL/min, including patients on haemodialysis) and pre-existing acute renal failure, the clinical and safety outcomes were similar in the telavancin and vancomycin treatment groups.

The ATTAIN studies also reported adverse events being gastrointestinal discomfort and taste disturbance, nausea, headache, vomiting, insomnia and foamy urine.

FDA and European Medicines Agency (EMA) accepted telavancin for the treatment for adults with nosocomial pneumonia, including VAP known or suspected to be caused by MRSA, in patients without renal insufficiency [31].

6. Under development antimicrobials

6.1. Cethromycin

Cethromycin is a new fluoroketolide with a reported high potency against Gram-positive, Gram-negative bacteria and atypicals including mycoplasma and ureaplasma. It has also *in vitro* activity against penicillin- and macrolide-resistant Gram-positive organisms, possibly due to a higher affinity for the target site on the ribosomal unit [32].

The SENTRY Antimicrobial Surveillance Program platform has shown that cethromycin was highly active *in vitro* against all Gram-positive organisms (MIC₅₀, 0.015 µg/mL) as compared with telithromycin (MIC₅₀, 0.06 µg/mL), clarithromycin (MIC₅₀, 0.12 µg/mL), and erythromycin (MIC₅₀, 0.25 µg/mL) [33]. Cethromycin had excellent activity against *S. pneumoniae*, including isolates harboring *mef* (A) (MIC₉₀, 0.06 µg/mL), or *erm* (B) (MIC₉₀, 0.25 µg/mL), penicillin-resistant pneumococci (MIC₉₀, 0.12 µg/mL), and serotype 19A pneumococci (MIC₉₀, 0.12 µg/mL) [34].

Cethromycin distributes well into pulmonary compartments and at concentrations higher than plasma, with a daily dose of 150 or 300 mg yielding a C_{max} in the ELF of 0.94 or 2.75 µg/mL in two to four hours and AUC_{0–24} values of 11.4 and 24.15 µg h/mL [35].

There are two comparative CAP studies of cethromycin 300 mg per day to clarithromycin 250 mg twice a day that demonstrating the noninferiority of cethromycin in terms of clinical cure and radiographic improvement [36], in low severity CAP patients. The reported most common adverse events were diarrhea, nausea, dysgeusia and headache.

Cethromycin completed Phase III clinical trials for the treatment of CAP and was deemed to be safe according to the FDA Advisory Committee, after dosing more than 5000 patients in 53 clinical studies for patients with mild or moderate CAP [37]. But more trials will be needed with more severe CAP patients before approval can be granted.

7. Solithromycin

Solithromycin is a novel fluoroketolide with high potency against Gram-positive and Gram-negative bacteria commonly associated with community-LRTIs. Against strains with defined susceptibilities to erythromycin, clindamycin and telithromycin, solithromycin showed potent inhibition against all combinations

(MIC₅₀ = 0.06 µg/mL) except those with non-susceptibility to telithromycin (>2 µg/mL) (MIC₅₀ > 16 µg/mL) [38].

Solithromycin has *in vitro* potency against the major CABP pathogens, *S. pneumoniae* (MIC₉₀, 0.03 g/mL), *Haemophilus influenzae* (MIC₉₀, 2 µg/mL), *Moraxella catarrhalis* (MIC₉₀, 0.06 µg/mL), and MSSA; MIC₉₀, 0.06 µg/mL), including intracellular pathogens *Legionella pneumophila* (MIC₉₀, 0.016 µg/mL), *Chlamydia pneumoniae* (MIC₉₀, 0.25 µg/mL), and *Mycoplasma pneumoniae* (MIC₉₀, 0.000125 µg/mL).

The half-life increased with dose and averaged 5.1–6.5 h for the 400–800 mg dose. A phase 1 study to determine the ELF and alveolar macrophage (AM) levels of solithromycin after five days of oral dosing of 400 mg q24 h found the exposure (AUC_{0–24}) of solithromycin in ELF and AM was >8 times and ≥180 times higher than the total plasma exposure, respectively [39].

A completed Phase 2 study showed comparable efficacy of solithromycin 800 mg on day 1 followed by 400 mg on days 2–5 to levofloxacin 750 mg once daily in adults with PSI-II to PSI-IV CABP [40]. A new global Phase 3 trial of solithromycin in patients with CABP includes a double-blind, placebo-controlled, multicenter study enrolling ~800 CAP patients and randomize them to either oral solithromycin, an 800 mg loading dose followed by 400 mg once daily for 5 days or once-daily oral moxifloxacin 400 mg for 7 days is taken place now and the results are expected with interest [41].

Across all the studies, the most common adverse events of the drug were diarrhea (13%), headache (13%) and nausea (10%), most of which were mild.

8. Nemonoxacin

Nemonoxacin is a novel non-fluorinated quinolone that is a broad-spectrum, once daily oral therapy for cSSSI and CAP.

Nemonoxacin displayed greater activity than the fluoroquinolones (levofloxacin) against MSSA, MSSE, MRSE, *S. pneumoniae*, and *E. faecalis*. Interestingly, nemonoxacin maintained better activity against CA-MRSA than against HA-MRSA. It has also demonstrated a potent antibacterial activity against ciprofloxacin-resistant MRSA, methicillin- and levofloxacin-resistant *Staphylococcus capitis*, penicillin and levofloxacin-resistant *S. pneumoniae* and VRE [42,43].

Oral nemonoxacin (750 mg or 500 mg) administered once daily for seven days showed similar clinical and bacteriological response as levofloxacin (500 mg once daily) in the therapy of CAP [44]. Usual adverse events were diarrhea, dizziness and headache.

It has currently completed one FDA Phase 2 trial specifically for diabetic foot infections and 2 new Phase 3 clinical comparative trials with levofloxacin in patients with CAP [45].

9. Omadacycline

Omadacycline, an aminomethylcycline, is a semisynthetic derivative of minocycline that has *in vitro* potency against Gram-positive and Gram-negative bacteria and atypicals (*L. pneumophila*) causing ASSSIs and CAP.

Like tigecycline, potent activity was observed *in vitro* against resistant Gram-positive bacteria, with MIC₉₀ values ≤0.5 mg/mL. The omadacycline MIC_{90s} for MRSA, VRE, and beta-hemolytic streptococci were 1.0 µg/mL, 0.25 µg/mL, and 0.5 µg/mL, respectively, and for PRSP and *H. influenzae* were 0.25 µg/mL and 2.0 µg/mL, respectively. Omadacycline was active against organisms demonstrating the two major mechanisms of resistance, ribosomal protection and active tetracycline efflux [46].

The *in vitro* activity of omadacycline was also superior to doxycycline, minocycline, clindamycin, linezolid, or vancomycin against enterococcus, including vancomycin-resistant *E. faecalis* or

E. faecium, and *S. pneumoniae* strains including penicillin- and multiresistant strains.

Omadacycline is metabolically stable and has demonstrated low protein binding across all concentrations and species tested [47] and is orally absorbed.

In a Phase 3 study of patients with complicated skin and soft tissue infections (cSSSI), oral and i.v. omadacycline was well tolerated, with efficacy demonstrating comparability with linezolid [48].

The most frequently reported AEs in the IV studies were cannula site reactions and elevated ALT levels ranging from 1.9 to $3.8 \times$ the upper limit of normal (ULN) in 300–600 mg IV doses. Nausea (25%) was observed after oral administration only. All AEs were mild in intensity and resolved by the end of study [48,49].

On January 2013, FDA has designed omadacycline as a Qualified Infectious Disease Product (QIDP) for both IV and oral formulations in the treatment of acute bacterial skin and skin structure infections and bacterial CAP.

10. Oxazolidinones

Tedizolid and radezolid are two new oxazolidinones that are currently under development; both retain activity against MRSA strains that are resistant to linezolid [50].

Tedizolid phosphate, is a new oxazolidinone prodrug that is transformed in the serum into the active drug torezolid. Tedizolid acts by inhibiting protein synthesis and has broad activity against Gram (+) pathogens. The methyl tetrazole D-ring system pick up (Table 2) additional binding site interactions with the ribosome and thus confer increased potency, relative to that of linezolid.

Tedizolid is four to eightfold more active *in vitro* than linezolid against staphylococci, streptococci and enterococci. Close to 80% of linezolid resistant strains were inhibited by tedizolid at a concentration of $\leq 4 \mu\text{g/mL}$ [51].

It is highly potent prodrug with good drug properties, solubility of $\geq 130 \text{ mg/mL}$ in aqueous solutions of $\text{pH} \geq 5.0$, and 91.7% oral bioavailability. The elimination half-life (8–11 h) and volume of distribution for tedizolid were nearly double the values for linezolid. It has an intravenous/oral step-down formulation as well as a 6 day oral dosing regimen [52].

Unlike linezolid, it demonstrate 10-fold accumulation in human macrophages as well intracellular killing of phagocytosed *S. aureus*, *Listeria monocytogenes* and *L. pneumophila*, which contributes to its improved pharmacodynamic properties. Lemaire et al. demonstrated that tedizolid penetrates into macrophages cultured *in vitro* and kills intracellular staphylococci better than linezolid, but that killing is directly related to MIC differential [53].

It shows an improved safety profile that includes decreased haematological effects at the therapeutic dose [54] and the absence of a pressor effect in response to tyramine challenge in an animal model. Unlike linezolid, tedizolid does not inhibit monoamine oxidase *in vivo*, therefore interactions with adrenergic, dopaminergic, and serotonergic drugs are not to be expected.

In a double-blind Phase 2 clinical study, patients with cSSSIs (a vast majority had *S. aureus* and more than 80% had MRSA infection) were given tedizolid once a day oral doses of 200, 300 or 400 mg for 5–7 days. Clinical cure rates in excess of 95% were achieved for MRSA as well as MSSA infections in all three dosage groups [51]. The side effects reported were nausea, stomach discomfort, diarrhea, headache, and dysgeusia.

In December 2013, the FDA designated tedizolid as a Qualified Infectious Disease Product (QIDP), for its potential indication in ABSSSI.

A Phase 3 comparative trial is currently recruiting patients with VAP and Gram (+) bacteremia to compare tedizolid 200 mg IV once daily for 7 days to linezolid 600 mg every 12 h [55].

11. Discussion

Whereas resistant Gram-negative bacteria were a major concern in previous years, over the last few years a dramatic increase in the resistance of Gram-positive bacteria has occurred, these have included MDR staphylococci, penicillin resistant *S. pneumoniae*, and VRE.

Regarding this event we have presented some of the exciting and noteworthy ongoing developments in the field of antibacterials against Gram (+) respiratory pathogens. Our opinion for their clinical use depends according the site of care:

11.1. CAP treatment

The major problem in the management of CAP is the inability to determine the aetiological pathogen. Therefore, it is necessary to carefully consider the various risk factors and epidemiological circumstances and initiate empirical treatment with antibiotics able to effectively treat the most likely pathogens causing the infection.

Among the above mentioned new antibiotics approved or not most appropriate for outpatient treatment will be the two ketolides: cethromycin, solithromycin and the quinolone nemonoxacin. They have oral formulations and are active against the more common respiratory pathogens. The new tetracycline omadacycline needs more studies to evaluate its clinical use.

After the hospital admission we have to think Gram (–) pathogens, so we can use ceftaroline and ceftobiprole but not as monotherapy, because there are not active against atypicals.

11.2. HAP treatment

One of the main challenges in the management of HAP is to overcome the resistance issues. The patients with HAP and especially with VAP, they will have more often a diagnosis, so we can select an intravenous antibiotic with a specific spectrum (f.e. anti-MRSA), as telavancin or tedizolid.

For the Gram (–) microorganisms the dosis of ceftobiprole is not fixed yet and if the etiologic microorganism is *P. aeruginosa* we can choose an antipseudomonal b-lactam or a quinolone. We recommend that companies should, in parallel to the efficacy, develop easy ways to measure blood levels of the new antibiotic especially in these antimicrobial targeting resistant microorganisms.

Apart from the above new antibiotics we need a strategy that promotes research, with more trials regarding PK/PD and safety, into new as well as known but unutilized compounds, allows efficient use, reduces unnecessary overuse, and limits the spread of antibiotic resistance.

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