New therapeutic options for respiratory tract infections

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Purpose of review
The progressive increase of respiratory tract infections caused by multidrug-resistant organisms (MDROs) has been associated with delays in the prescription of an adequate antibiotic treatment and increased mortality, representing a major concern in both community and hospital settings. When infections because of methicillin-resistant Staphylococcus aureus (MRSA) are suspected, vancomycin still represents the first choice, although its efficacy has been recently questioned in favor of new drugs, reported to provide better clinical outcomes. Moreover, few therapeutic options are currently available for the treatment of severe infections caused by Multidrug-resistant (MDR) Gram-negative pathogens, which are frequently resistant to all the available β-lactams, including carbapenems. We have reviewed the therapeutic options for the treatment of respiratory tract infections that have recently become available with promising implications for clinical practice, including ceftaroline, ceftrRobipro, tedizolid, telavancin, delafloxacin, eravacycline, and new β-lactams/β-lactamase inhibitors.

Recent findings
A number of new antimicrobials with activity against MDROs have been recently approved for the treatment of respiratory tract infections, and other agents are under investigation. Recent developments, with a specific focus on the possible advantages of new drugs for the management of respiratory tract infections caused by MDROs in everyday clinical practice are discussed.

Summary
Newly approved and investigational drugs for the treatment of respiratory tract infections are expected to offer many advantages for the management of patients with suspected or confirmed infections caused by MDROs. Most promising features among new compounds include the broad spectrum of activity against both MRSA and MDR Gram-negative bacteria, a limited risk of antimicrobial resistance, the availability of oral formulations, and a promising safety profile.

Keywords
methicillin-resistant Staphylococcus aureus, multidrug resistance, new antimicrobials, respiratory tract infections

INTRODUCTION
The progressive increase of respiratory tract infections caused by multidrug-resistant organisms (MDROs) represents a major concern, particularly among critically ill patients in whom 60% of the cases of pneumonia are caused by MDROs [1]. Infections because of MDROs in the community are common among patients presenting specific risk factors (i.e., recent antimicrobial use or hospitalization, admission from a nursing home or long-term care facilities, use of prosthetic devices) [2,3]. In clinical practice, the isolation of MDROs frequently leads to delays in the prescription of an adequate antimicrobial treatment, with significant increases in the length of stay, crude and attributable mortality, and healthcare costs [1,4]. Methicillin-resistant Staphylococcus aureus (MRSA) is the most frequently isolated MDRO both in the community and in hospital settings [5,6], and is responsible for up to 20–30% of cases of hospital-acquired pneumonia (HAP), even if a wide variability is present among different areas [7,8]. Although vancomycin can still be considered the first-line treatment for...
MRSA pneumonia, its efficacy has been recently questioned because of a limited intrapulmonary penetration [9], a suboptimal clinical response for strains showing minimum inhibitory concentration (MIC) greater than 1 mg/l [10], and the need for therapeutic drug monitoring in order to achieve adequate plasma concentrations [11]. Linezolid, the first member of the oxazolidinone family, was found to be superior than vancomycin for the treatment of hospital-acquired MRSA pneumonia in a recent phase IV, randomized, controlled trial [12]. Multidrug-resistant (MDR) Gram-negative bacteria, mainly represented by *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Enterobacteriaceae*, also represent a frequent cause of pneumonia, particularly in the nosocomial setting [2,13]. In recent years, the overuse of broad-spectrum antimicrobials, such as piperacillin/tazobactam and carbapenems, resulted in a vicious circle of further increase in antimicrobial resistance; as a result, pathogens carrying carbapenemases are nowadays commonly encountered in clinical practice. Because of the paucity of new antimicrobials, combination therapies including old drugs such as colistin, fosfomycin, and aminoglycosides have been widely used against carbapenemase-producing Gram-negative bacteria, but the results were not satisfactory [14].

Here we review the characteristics of the new therapeutic options for the treatment of respiratory tract infections caused by MDR pathogens, with a specific focus on the potential role of these drugs in everyday clinical practice. Specifically, ceftaroline, ceftobiprole, tedizolid, telavancin, delafloxacin, eravacycline, and new \(\beta\)-lactams/\(\beta\)-lactamase inhibitors were included in the review. Table 1 summarizes the drug spectrum of activity, indications, and current developmental stage for the use in respiratory tract infections. Table 2 reports the expected advantages and disadvantages associated with antimicrobial use.

**CEPHALOSPORINS: CEFTAROLINE AND CEFTOBIROLE**

Ceftaroline and ceftobiprole belong to the new fifth-generation cephalosporin group and are characterized by a unique activity against MRSA, because of the high binding affinity for the penicillin-binding protein (PBP)-2a [15]. Both ceftaroline and ceftobiprole provide an attractive broad spectrum, showing bactericidal activity against Gram-positive (including MRSA with reduced susceptibility to vancomycin and penicillin-resistant *Streptococcus pneumoniae*) and Gram-negative bacteria, with the exception of extended-spectrum \(\beta\)-lactamase (ESBL)-producing and carbapenemase-producing *Enterobacteriaceae* [16–18]. Ceftobiprole is also active against *Enterococcus faecalis* (but not *Enterococcus faecium*) and exerts an activity against *P. aeruginosa* superior to that of cefepime [18].

Ceftaroline has been approved by the U.S. Food and Drug Administration (FDA) and European Medical Agency (EMA) for the treatment of acute bacterial skin and soft tissue infections (ABSSSIs) and community-acquired pneumonia (CAP). The efficacy of ceftaroline for the treatment of CAP has been evaluated in two double-blinded, randomized, noninferiority trials (FOCUS 1 and FOCUS 2), comparing ceftaroline (600 mg every 12 h) with ceftriaxone (1 g every 24 h) [19,20]. Ceftaroline provided clinical cure rates in up to 80% of cases and was well tolerated, with mild adverse events mainly represented by diarrhea, headache, and insomnia [21]. A recent analysis of data coming from the FOCUS trials showed that ceftaroline was associated with a shorter time for clinical response compared with ceftixime [22]. Recent findings suggest that in patients with normal renal function, the administration of higher doses of ceftaroline (600 mg every 8 h) may provide better clinical outcomes in MRSA infections [23].

Ceftobiprole medocaril has been investigated for the treatment of both CAP requiring...
hospitalization and HAP [including ventilator-associated pneumonia (VAP)] [24,25*]. Ceftobiprole (500 mg every 8 h, intravenously) was found as effective as the comparator both in CAP (ceftriaxone with or without linezolid) and in HAP (ceftazidime and linezolid), providing cure rates of 86.6% and 59.6%, respectively. Further investigation, however, is needed before recommending the use of ceftobiprole in VAP, as reported cure rates were only 23.1% in this subset of patients [24,25*]. Ceftobiprole is currently approved for clinical use in Europe.

| Drug               | Spectrum of activity                                                                 | Route of administration | Dose               | Current clinical indications | Development phase for the use in respiratory tract infections |
|--------------------|--------------------------------------------------------------------------------------|--------------------------|--------------------|-----------------------------|---------------------------------------------------------------|
| Ceftaroline        | Gram positives (no enterococci) and Gram negatives (no ESBL and P. aeruginosa)       | IV                       | 600 mg every 12 h  | ABSSSIs, CAP                | Approved by FDA and EMA                                       |
| Ceftobiprole       | Gram positives (including E. faecalis) and Gram negatives (including P. aeruginosa; no ESBL) | IV                       | 500 mg every 8 h   | CAP, HAP                    | Approved in Europe                                            |
| Telavancin         | Gram positives, including MRSA and S. pneumoniae                                     | IV                       | 10 mg/kg every 24 h | HAP                         | Approved by FDA and EMA                                       |
| Cefazidime/avibactam | Similar to cefazidime, with an extended activity against class A (including KPCs), class B (Amp-C cephalosporinase) and some class D (OXA-48) \(\beta\)-lactamase-producing pathogens | IV                       | 2.5 g every 8 h    | cIAIs, cUTIs               | Phase III (in progress)                                       |
| Ceftrazolin/ tazobactam | Similar to cefazidime, with enhanced activity against P. aeruginosa; inhibits the majority of ESBL-producing pathogens | IV                       | 1.5 g every 8 h    | cIAIs, cUTIs               | Phase III (in progress)                                       |
| Tedizolid          | Gram-positive pathogens (including MRSA and VRE)                                     | IV and oral              | 200 mg every 24 h  | ABSSSIs                     | Phase I                                                       |
| Delafloxacin       | Gram positives (including MRSA, streptococci and enterococci) and Gram negatives (including fluoroquinolone-susceptible P. aeruginosa) | IV and oral              | –                  | –                           | Phase II                                                      |
| Eravacycline       | Gram positives (including MRSA) and Gram negatives (including ESBL and carbapenemase-producing Enterobacteriaceae and A. baumannii; not effective against P. aeruginosa) | IV                       | –                  | –                           | Phase I                                                       |

**Table 1. Characteristics of new therapeutic options for respiratory tract infections**

ABSSSIs, acute bacterial skin and soft tissue infections; CAP, community-acquired pneumonia; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; EMA, European Medical Agency; ESBL, extended-spectrum \(\beta\)-lactamases; FDA, Food and Drug Administration; HAP, hospital-acquired pneumonia; IV, intravenous; MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant strain.
LIPOGLYCOPEPTIDES: TELAVANCIN

Telavancin, together with oritavancin and dalbavancin, belongs to the class of new lipoglycopeptides, exerting a rapid, concentration-dependent, bactericidal activity against a broad-spectrum of Gram-positive pathogens, including MRSA and S. pneumoniae [26,27]. The drug is characterized by the presence of a lipophilic side chain which attaches to the bacterial membrane showing increased affinity compared with old glycopeptides. Telavancin displays two different mechanisms of action: inhibition of bacterial wall synthesis (transglycosylation and transpeptidation) and disruption of bacterial membrane function [28]. Telavancin achieves good levels into the epithelial lining fluid (ELF) in healthy volunteers, supporting the role of this molecule for the treatment of respiratory tract infections [29]. The noninferiority of telavancin (10 mg/kg every 24 h) versus vancomycin (1 g every 12 h) for the treatment of HAP has been demonstrated in two phase III, randomized, double-blinded studies [assessment of telavancin for treatment of hospital-acquired pneumonia (ATTAIN)] [30]. A pooled analysis of data coming from SSSIs and HAP studies on telavancin, however, showed a higher risk of nephrotoxicity and serious adverse events among telavancin-treated patients compared to vancomycin [31]. Overall, an increased mortality was reported in patients with HAP and moderate-to-severe renal impairment treated with telavancin compared to vancomycin [32]. Further data from the ATTAIN studies demonstrated that, in the subset of patients without severe renal impairment or preexisting acute renal failure, clinical and safety outcomes were similar in the telavancin and vancomycin treatment groups [33*].

Telavancin is currently approved for the treatment of adult patients with HAP (including VAP) only when the infection is known or believed to be caused by MRSA and other alternative treatments are not suitable. Moreover, it is strongly suggested to restrict the use of telavancin only to patients with normal renal function [34].

### Table 2. Expected advantages and disadvantages of new antimicrobials for respiratory tract infections

| Drug | Pros | Cons |
|------|------|------|
| Ceftaroline | Broad-spectrum activity, including MRSA<br>Good tolerability profile | Only intravenous |
| Ceftobiprole | Broad-spectrum activity, including MRSA and P. aeruginosa<br>Good tolerability profile | Only intravenous |
| Telavancin | High ELF penetration | Potential nephrotoxicity<br>Spectrum limited to Gram-positives<br>Only intravenous |
| Ceftazidime/avibactam | Broad-spectrum activity against MDR Gram negatives<br>Good tolerability profile | Potential resistance development<br>Only intravenous |
| Ceftolozane/tazobactam | Broad-spectrum activity (including ESBL-producing Enterobacteriaceae)<br>High efficacy against P. aeruginosa | Only intravenous |
| Tedizolid | Oral formulation, potentially allowing treatment of outpatients/early oral shift and discharge<br>Once-daily administration<br>High ELF penetration<br>Low drug interactions<br>Low myelotoxicity | Bacteriostatic<br>Spectrum limited to Gram positives |
| Delafloxacin | Oral formulation available<br>Broad-spectrum activity<br>Low risk of resistance selection | Dose-dependent diarrhea |
| Eravacycline | Broad-spectrum activity including MRSA, VRE, and ESBL-producing and carbapenemase-producing Enterobacteriaceae and A. baumanii | No activity against P. aeruginosa |

ELF, epithelial lining fluid; ESBL, extended-spectrum β-lactamases; MDR, multidrug resistant; MRSA, meticillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant strain.
**β-LACTAMS/β-LACTAMASE INHIBITOR COMBINATIONS: CEFTAZIDIME/AVIBACTAM AND CEFTOLOZANE/TAZOBACTAM**

Ceftazidime/avibactam combination has been recently approved by the U.S. FDA for the treatment of complicated intra-abdominal infections (in combination with metronidazole) and complicated urinary tract infections including pyelonephritis, when no alternative treatment is available. Avibactam is a new-generation β-lactamase inhibitor characterized by high affinity against class A (including KPC), class C, and some class D β-lactamases, but not against metallo-β-lactamase enzymes [35*]. Thus, avibactam extends the antibacterial activity of ceftazidime toward most ceftazidime-resistant Gram-negative pathogens, including ESBL, carbapenemase-producing *Klebsiella pneumoniae* (KPC), and AmpC-producing strains through the inhibition of avibactam-sensitive β-lactamases [36*37]. Moreover, ceftazidime/avibactam has shown some *in vivo* activity also against New Delhi metallo-β-lactamase-producing *Enterobacteriaceae* [38]. Phase I studies demonstrated that ceftazidime/avibactam is usually well tolerated, and no QT prolongation have been observed, even at supratherapeutic plasma concentrations [39–41]. A potential threat is represented by the risk of resistance development in *Enterobacteriaceae* and *P. aeruginosa* [42,43]. Nevertheless, because of its attractive bactericidal broad-spectrum activity, linear pharmacokinetics with high lung penetration, and low risk of serious adverse events, ceftazidime/avibactam represents a promising option for the treatment of pneumonia caused by MDR Gram-negative pathogens, especially when carbapenem resistance is suspected. However, few studies have assessed the efficacy of ceftazidime/avibactam in this setting so far. In-vitro data demonstrated that ceftazidime/avibactam MICs toward ESBL are not affected by the presence of pulmonary surfactant [44]. Moreover, in a murine model of *P. aeruginosa* pneumonia ceftazidime/avibactam achieved significant concentrations in lungs producing reductions above 1 log10 CFU for MICs at least 32 μg/ml [45]. A phase III study assessing the efficacy, safety, and tolerability of ceftazidime/avibactam compared with meropenem for the treatment of HAP (including VAP) is expected to be completed in February 2016.

Ceftolozane/tazobactam is the association of a new antipseudomonal cephalosporin with tazobactam, a well-established β-lactamase inhibitor that inhibits most class A and some class C β-lactamases. The most impressive characteristic of ceftolozane is the intrinsic potent antipseudomonal activity, because of a modified side chain conferring a greater affinity for all essential PBPs. Furthermore, ceftolozane is not affected by changes in porin permeability and upregulation of efflux pumps, typical *P. aeruginosa* antimicrobial resistance mechanisms [46]. In a recent study by Farrell et al. [47*], ceftolozane/tazobactam was found to be active against ceftazidime, meropenem, and piperacillin/tazobactam-nonsusceptible *P. aeruginosa* isolates, including MDR pathogens. However, as well as other cephalosporins, ceftolozane is susceptible to enzymatic degradation by ESBL and carbapenemases; the association with tazobactam broadens the spectrum of activity of ceftolozane to the majority of ESBL-producing *Enterobacteriaceae* [48]. Ceftolozane/tazobactam is currently approved in the United States for the treatment of complicated urinary tract infections and complicated intra-abdominal infections at the dose of 1.5 g every 8 h.

In a phase I trial on healthy volunteers, ceftolozane tazobactam displayed a good penetration into the ELF after parenteral administration, suggesting a potential role for the treatment of lung infections [49]. However, pharmacokinetic/pharmacodynamic (PK/PD) studies suggest that an increased dosage (3 g every 8 h) might be necessary for the treatment of pneumonia in patients with normal renal function in order to achieve a more than 90% probability of target attainment [50*]. A phase III trial to assess the safety and efficacy of ceftolozane/tazobactam (3 g every 8 h) compared with meropenem (1 g every 8 h) for the treatment of VAP sustained by *P. aeruginosa* is expected to be completed in 2018 [51].

**OXAZOLIDINONES: TEDIZOLID**

Tedizolid (formerly known as TR700) is a new oxazolidinone approved by the U.S. FDA in July 2014 and by the EMA in January 2015 for the treatment of acute bacterial SSTI. The role of tedizolid for the treatment of MRSA respiratory tract infections is only investigational so far, but it might represent an interesting option because of many advantages over linezolid, including: lower risk of myelotoxicity [52,53]; lower risk of drug–drug interactions with selective serotonin reuptake inhibitors (SSRIs) and other compounds with serotonergic activity, and adrenergic agents, because of a weak and reversible *in vitro* inhibition of the monoamine oxidase pathway [54]; high bioavailability (>80%), with *in vivo* half-life value approximately twofold greater compared with linezolide, allowing once daily administration [55]; higher ELF penetration [56]. A recent study found that tedizolid exhibits a twofold to fourfold higher *in vitro* activity compared with linezolid against a variety of Gram-positive...
NEW FLUOROQUINOLONES: DELAFOXACIN

Delafloxacin is an investigational fluoroquinolone antibiotic showing a potent anti-MRSA activity and a reduced probability for the selection of resistant mutants in vitro, because of its unique dual mechanism of DNA target inhibition (DNA gyrase and topoisomerase IV) [61]. Moreover, it is effective against a broad spectrum of Gram-positive (including penicillin-sensitive, penicillin-resistant, and levofloxacin-resistant Staphylococcus pneumoniae, Streptococcus pyogenes and Enterococci) and Gram-negative pathogens (Escherichia coli, Klebsiella spp., Haemophilus influenzae, Moraxella catharralis, and quinolone-susceptible P. aeruginosa) [62,63]. Only two studies assessing the potential role of delafloxacin for the treatment of respiratory tract infections are available so far. In a double-blinded, randomized, phase-II study, 309 outpatients affected by CAP have been treated with once-daily oral administration of delafloxacin at different dosages (100, 200, and 400 mg) for 7 days. Clinical and bacteriological cure rates were 87 and 88%, respectively, both in the 200 and 400 mg groups, and slightly lower in the 100 mg group (80 and 79%, respectively), but the difference was not statistically significant. Pathogen eradication rates were higher than 90% for H. influenzae, H. parainfluenzae and atypicals, and achieved 100% for S. aureus and S. pneumoniae [64]. The second study investigated the safety and efficacy of delafloxacin in patients with acute bacterial exacerbation of chronic bronchitis. Four different regimens were tested (100, 200, 400, and 500 mg, given orally every 24 h); clinical response was similar in the four treatment groups, with clinical and microbiological cure rates higher than 70% [65]. In both studies delafloxacin was generally well tolerated, and diarrhea, headache, and nausea were the most commonly reported adverse events; diarrhea occurred more frequently in patients treated with high-dose delafloxacin (200 and 400 mg) compared with lower doses (100 mg) [64,65]. Data coming from studies on the use of delafloxacin for the treatment of SSSIs demonstrate that delafloxacin at the dose of 300 mg every 12 h is well tolerated. In healthy volunteers doses up to 900 mg were found to be well-tolerated, without any effect on QTc prolongation [66,67].

Because of the broad spectrum of activity, including the pathogens most commonly involved in CAP and in HAP, the availability of an oral formulation, the reduced probability for resistance selection and the good tolerability profile, delafloxacin could represent a promising option for the treatment of respiratory tract infections.

NEW TETRACYCLINES: ERAVACYCLINE

Eravacycline is a novel fluorocycline that is not subjected to the mechanisms that are responsible for tetracycline resistance, such as efflux pumps and ribosomal protection proteins [68]. The most attractive characteristic of eravacycline is the broad-spectrum activity, including both Gram-positive and Gram-negative resistant pathogens. Eravacycline exerts a potent activity against staphylococci (including MRSA), enterococci [both E. faecalis and E. faecium, including vancomycin-resistant strains (VRE)] and streptococci (including penicillin-resistant and macrolide-resistant S. pneumoniae) [69]. Moreover, eravacycline is active against a wide spectrum of MDR Gram-negative pathogens, including Enterobacteriaceae expressing resistance genes from different classes of ESBL and carbapenemases [69] and A. baumannii, with a fourfold higher activity compared with tigecycline [70*]. Similar to tigecycline, eravacycline is not effective against P. aeruginosa [69]. One of the most attractive features of eravacycline is the availability of both oral and intravenous formulations, thus representing a possible option for early oral shift and sequential therapy also in patients with infections sustained by MDR Gram-negative bacteria [71].

A recent phase I study conducted on 20 healthy volunteers evaluated the pulmonary distribution of...
eravacycline given at the dose of 1 mg/kg intravenously every 12 h, for a total of seven doses over 4 days. Eravacycline was found to achieve concentrations sixfold and 50-fold higher in ELF and in alveolar macrophages than in plasma, respectively, supporting a potential role of the drug for the treatment of respiratory infections. Moreover, the drug was well tolerated and nausea, vomiting, infusion-related irritation, and headache were the most frequent adverse events [72]. No studies assessed eravacycline efficacy for the treatment of respiratory infections in humans so far, but promising results come from murine models. In a recent study by Grossman et al. [73], eravacycline was found to be as effective as linezolid and more effective than vancomycin in MRSA mouse lung infection models; moreover, eravacycline was more effective than linezolid in lung infections due to tetracycline-resistant S. pneumoniae. In one randomized clinical trial, however, eravacycline failed the noninferiority criterion in the treatment of UTI, suggesting that more data on oral formulation efficacy and bioavailability are necessary [74].

These data, together with the broad spectrum of activity and the availability of an oral formulation, make eravacycline an attractive option for the treatment of respiratory tract infections, particularly when ESBL-producing Enterobacteriaceae or A. baumannii are involved.

CONCLUSION

New approved and investigational agents for the treatment of respiratory tract infections represent promising options to preserve and enhance our antibiotic armamentarium. The most attractive characteristic of new drugs is the broad-spectrum activity against MDRs, particularly Gram-negatives, which still represent a major challenge in clinical practice because of the lack of new therapeutic options. However, studies assessing the efficacy of these agents in real-life are needed, particularly regarding the potential opportunity for a monotherapy in patients with infections sustained by MDR Gram-negative pathogens. The cost-efficacy of new agents with anti-MRSA activity needs to be evaluated and compared with older agents, in order to optimize the use of healthcare resources and patients’ outcomes.

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