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Review

New antimicrobial approaches to gram positive respiratory infections

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Cethromycin (Pubmed CID: 447451)
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Omadacycline (Pubmed CID:54697325)
Ceftopibrole (Pubmed CID: 6918430)
Nemonoxacin (Pubmed CID: 11993740)
Tedizolid phosphate (Pubmed CID: 11476460)

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 nemonaxacin, 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.

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*, Enterobacteriacea, *Pseudomonas aeruginosa* and *Mycoplasma pneumoniae*, *Chlamydophila 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

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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 methacillin 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).

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 catarrhallis.*

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 MIC_{90} 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 MIC_{90} 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 $t½$ 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, 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. dosis 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 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, *Clostridium difficile*-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.