Review

New Antibiotics for Hospital-acquired pneumonia

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ABSTRACT

INTRODUCTION: Hospital-acquired pneumonia is the most common life-threatening hospital-acquired infection, and the majority of cases (80%) are associated with mechanical ventilation. Once pneumonia develops, the appropriateness of the initial antibiotic regimen is a vital determinant of outcome. **AREAS COVERED:** In this review we summarize the actual situation of new antibiotics for treatment of HAP and VAP. This article covers medical literature published in English language since 2000 until February 2019, on "hospital pneumonia", identified using PubMed and www.clinicaltrial.gov. The search terms used were "ventilator associated pneumonia", "resistance", "therapy" and "new antibiotics". **EXPERT OPINION:** Newer drugs approved for the combat of MDR pathogens for hospital pneumonia include cephalosporins active against MRSA and β-lactamases and as: ceftolozane combined with avibactam and ceftazidime with tazobactam. Other antibiotics active against ESBL are the combinations of carbapenems Cilastatin/imipenem/relebactam and meropenem/Vaborbactam, plazomicin a semisynthetic derivative of sisomycin, and a new cephalosporine cefiderocol.
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1. INTRODUCTION

Nosocomial pneumonia (NP) is a common nosocomial bacterial infection and is most prevalent in intensive care units (ICUs)[1] in individuals undergoing mechanical ventilation (MV) defined as ventilator associated pneumonia (VAP) but can also develop in nonventilated patients, named as hospital acquired pneumonia (HAP)[2]. It accounts for 11% of Hospital acquired infections (HAIs) outside of ICUs and 26% of HAIs in the ICUs.[3,4] VAP represents a major clinical and economical problem in critically ill patients due to its associated morbidity, prolonged MV-days, and ICU length of stay (LOS), which translates to elevated health care costs. NP carries a crude mortality rate of 30% to 70% with an estimated attributable mortality rate to pneumonia between with an attributable mortality of 3-17%[5].

2. MICROBIAL ETIOLOGY

The principal sources of pathogens in HAP cases are the health care environment and the patient's own microbial flora. The microbial etiology of HAP in the ICU varies according to patient population, hospital ICU settings, the country, and the type of presentation (early- or late-onset).

A review of published studies of the causes of pneumonia in hospitalized patients and the results of the SENTRY Antimicrobial Surveillance Program in the United States[6] concluded that six pathogens cause approximately 80% of HAP cases: *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella spp.*, *Escherichia coli*, *Acinetobacter spp*., and *Enterobacter spp*.

Gram-negative bacteria (GNB) are implicated in 50 to 80% of the cases of HAP in an ICU[7]. Gram-positive pathogens account for 20 to 30% of HAP cases. The most common Gram-positive pathogens isolated from patients with HAP include *S. aureus* [methicillin-sensitive (MSSA) and methicillin-resistant (MRSA)], *Streptococcus* species, and *Streptococcus pneumoniae.*

The first global report on surveillance of antimicrobial resistance with data from 114 countries was published by World Health Organization (WHO) in 2014, this report confirm that antibiotic resistance is no longer a potential but a current major threat to global public health. The three pathogens with major concern about resistance were: *E. coli* (resistance to third-generation cephalosporins and fluoroquinolones), *K. pneumoniae (*resistance to third-generation cephalosporins and carbapenems), and *S. aureus* (resistance to methicillin) that are together with multi-drug resistant *P. aeruginosa* the principal pathogens involved in HAP infections.

Defining the frequency of MDR pathogens in each lactamase organisms, have contributed to the escalating rates of ICU is essential, since patients being treated in an ICU with more than 25% MDR pathogens have an increased risk of MDR VAP, regardless of other risk factors[2].

3. GUIDELINES THERAPY

When the clinical suspicion of HAP is high, it is essential to promptly start appropriate antimicrobial therapy as both delayed and inadequate treatment have been correlated with increased rate of morbidity and mortality[1,15]. Previous studies reported a mortality rate associated with VAP of 30%-50% and even more when shock is present[2,17,18]. In fact, in a large series involving patients with HAP, Alvarez Lerma et al[17] revealed that patients who received adequate antibiotic treatment had lower mortality than did those who received inadequate therapy (16% vs 25%).

ATS/IDSA new guidelines for management of NP, published in 2016 in CID[2], first they define HAP as pneumonia in the non-ventilated patients and then they recommend selection of initial empirical treatment for HAP and VAP according to risk factors for MDR bacteria (underlying diseases and previous antibiotic prescription) and local susceptibilities.

According to the guidelines, the major risk factor for MDR HAP and for MDR *Pseudomonas* pneumonia and MRSA pneumonia also, was prior use of intravenous antibiotics[9].

1) Empirical therapy for VAP

In patients with suspected VAP, the recommendation including coverage for *S. aureus, P. aeruginosa,* and other GNB in all empiric regimens. The combination antibiotic therapy in VAP from *P. aeruginosa* suggested only in cases when: a) a risk factor for antimicrobial resistance exists, b) patients in units where >10% of gram-negative isolates are resistant to an agent being considered for monotherapy, and c) patients in an ICU where local antimicrobial susceptibility rates are not available[2].

Optimal combinations include meropenem or doripenem plus either levofloxacin or aztreonam or amikacin[20].

Regarding MRSA coverage; guidelines recommend either linezolid or vancomycin[1,2].

2) Empirical therapy for HAP

For patients being treated empirically for HAP, we have to cover *S. aureus.* But, when the patient has risk factors for MRSA HAP (Table 1) vancomycin or linezolid is the recommended option[2].

Combination antibiotic therapy is recommended when we have suspicion for *Pseudomonas* or other gram-negative infection or a high risk for mortality[2] (need for ventilator support due to HAP and septic shock).

At the moment, multidrug resistance in GNB is the

TABLE 1. Risk factors for MRSA HAP[18]

1. Prior intravenous antibiotic use within 90 days
2. Hospitalization in a unit where >20% of *S. aureus* isolates are methicillin resistant
3. The prevalence of MRSA in the hospital is not known
4. Patient at high risk for mortality

greater threat, with multidrug resistance rates more than 40% among GNB[21], because the rates of resistance of *Enterobacteriaceae,* particularly carbapenem-resistant *enterobacteriacea*e (CRE) is increasing rapidly worldwide[22-24]. In the ICUs of US[22] reported VAP isolates with third-generation cephalosporin resistance among *Escherichia coli* 67.5% and similarly 68.9% for *K. pneumoniae*; carbapenem resistance 42.7% among *P. aeruginosa* isolates and 66.3% among *A. baumannii*. Antimicrobial resistance increases on ICU through antibiotic use, patient to-patient transmission and medical procedures.

Facing the epidemic of MDR-GNB, antipseudomonal carbapenems (imipenem/cilastatin and meropenem) have become the most empirically prescribed β-lactams in European ICU for HAP/VAP[25].

Once the results of respiratory cultures become available, therapy can de-escalate, based on the identity of pathogens and their susceptibility to specific antibiotics, in order to avoid prolonged use of a broader spectrum of antibiotic therapy, preventing the development of more resistance. IDSA/ATS panel suggests using procalcitonin (PCT) levels plus clinical criteria to guide the discontinuation of antibiotic therapy[26].

4. CURRENTLY AVAILABLE OPTIONS

A few new therapeutic agents have been approved for clinical use the last decade for HAP and VAP; these include the antibiotics telavancin and ceftobiprole.

1) Telavancin

Telavancin (TLV), it is a lipoglycopeptide analogue of vancomycin, with a dual mechanism of action and potent in vitro activity against Gram(+) pathogens, including MRSA and isolates with reduced vancomycin susceptibility (VISA, hVISA)[35]. PK/PD analyses support the concentration-dependent activity and once-daily dosing regimen of TLV. TLV achieves a higher volume of distribution into tissues and penetrates the pulmonary epithelial lining fluid (ELF) and alveolar macrophages.

A worldwide evaluation of in vitro antimicrobial activity against 15 480 Gram(+) pathogens revealed that MICs of TLV are comparable or better than those for comparator antimicrobials[36]. Specially, TLV has at least two-fold superior potency against staphylococci, including MRSA strains, compared with the other antibiotics. Data from the two prospective RCTs phase III, of 1503 patients with HAP (ATTAIN)[37], were published by Rubinstein et al. indicating that TLV is noninferior to vancomycin (cure rates TLV was 58.9% compared with 59.5% with VAN) on the basis of clinical response in the treatment of HAP due to Gram(+) pathogens, mainly MRSA. In addition, at clinically attainable doses TLV inhibits Gram-(+) isolates of antibiotic-resistant strains from biofilm models[35].

Renal function should be monitored in all patients receiving TLV, and dosage adjustments are required in patients whose CrCl is <50 mL/min. Owing to TLV's renal toxicity, both European and US labels for the antimicrobial contain boxed precautions for its use. In the European label TLV is contraindicated in patients with pre-existing acute renal failure and those with severe renal impairment.

In Europe, EMA accepted TLV for the treatment for adults with NP and VAP known or suspected to be caused by MRSA, in patients without renal insufficiency. In 21/6/2013, FDA accepted it with the same indication as well[37,38].

2) Ceftobiprole

Ceftobiprole a novel, broad-spectrum, parenteral cephalosporin[38], with enhanced activity against Gram (-) pathogens, including *Escherichia coli*, *Klebsiella pneumoniae*, *A. baumannii*, *P. aeruginosa* and other *Enterobacteriaceae*, but inactive against bacteria expressing extended spectrum β-lactamases (ESBL). Similar to ceftaroline, ceftobiprole exhibits greater binding affinity than the other cephalosporins for PBP_2a in MRSA.

In a large European antimicrobial resistance surveillance study[39], published in 2014, ceftobiprole showed activity against *P. aeruginosa* (64.6% susceptible by the EUCAST non- species-specific susceptibility breakpoint of 4μg/ml) that was lower than but similar to those of cefepime (78.6% susceptible) and ceftazidime (75.4% susceptible). Ceftobiprole was shown to be noninferior to ceftazidime plus linezolid for the treatment of HAP in a phase III RCT, including 781 patients (210 VAP), but the clinical cure rate in the population with VAP favored the linezolid/ceftazidime arm over the ceftobiprole arm, 56.7% versus 38.5%, respectively ($p < 0.05$)[40].

The standard dose of ceftobiprole is 500 mg every 8 h; dose adjustment of ceftobiprole is recommended in patients with moderate or severe renal impairment.

Ceftobiprole developed by Basilea ph.(Basel, Switzerland) is currently approved in 13 European countries and is the first cephalosporin monotherapy approved in the EU (October 2013) for the treatment of both CAP and HAP (excluding VAP).

In a review[41] about ceftobiprole, 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).

5. NEW APPROVED ANTIBIOTIC CHOICES

Among the newer drugs in pipeline, five drugs have been approved by the FDA since May 2014, namely, ceftolozane/tazobactam, ceftazidime/avibactam, tedizolid phosphate, plazomicin (Table 2).

Clinical trials showed non-inferiority to comparators of both cephalosporin combinations when used in the treatment of complicated urinary tract infections (UTI) and complicated intra-abdominal infections(cIAI) (when used with metronidazole).

1. Ceftazidime-avibactam (C/A)

Ceftazidime-avibactam is combination of an established broad-spectrum cephalosporin(ceftazidime) and a novel β-lactamase inhibitor (avibactam) with activity against class A, class C, and some class D β-lactamases[42,43]. Against *Pseudomonas aeruginosa*, the addition of avibactam also improves the activity of ceftazidime (~ fourfold MIC reduction). The role for C/A includes the treatment of suspected or documented infections caused by resistant GNB producing ESBL, KPCs and/or AmpC beta-lactamases[44].

A Phase III, RCT Comparative Study to Determine the Efficacy, Safety And Tolerability of C/A Versus Meropenem in the Treatment of NP/VAP showed 77.4% cure rate in the C/A group compared to 78.1% in the meropenem group, proving its noninferiority[45].

Clinical studies documented that CAZ-AVI, 2000 mg/500 mg every 8 hours, is the optimal dose regimen to achieve the PK/PD target attainment in patients with HAP.

It has been approved by FDA in February 2015 for the treatment of cIAI in combination with metronidazole and cUTI. Afterwards, on April 2016 EMA approved the antibiotic Zavicefta, intended for the treatment of UTI, IAI, HAP and infections due to aerobic GNB where treatment options are limited[46].

2. Ceftolozane–tazobactam (C/T)

Ceftolozane/tazobactam (brand name Zerbaxa), a novel cephalosporin in combination with an established β-lactamase inhibitor, is approved by FDA in December

TABLE 2. New Antibiotics for HAP/VAP

Drug (Company)	Company	Antibiotic class	Activity spectrum/ MDR targeted	Phase and Potential indications
Plazomicin (Zemdri)	Achaogen	Aminogylcoside	Gram(-) including CRE	Phase III for IAI and HAP/VAP caused by CRE
Tedizolid phosphate (Sivextro)	Cubist Pharmaceuticals/ Merck Sharp & Dohme	Oxazolidinone	Gram(+), including MRSA and linezolid-resistant MRSA	Approved for ABSSI, in phase III for HAP/VAP
Ceftolozane+ tazobactam (Zerbaxa)	Cubist Pharmaceuticals/ Merck Sharp & Dohme	Cephalosporin + BLI	Gram(-), including carbapenem, piperacillin + tazobactam and ceftazidime-resistant *Pseudomonas aeruginosa*, ESBL-producing strains	Approved for cUTI and cIAI/ in phase III for VAP and phase I for paediatric use
Ceftazidime+ avibactam (Avycaz)	AstraZeneca/ Actavis	Cephalosporin + new BLI	Gram–, including MDR *P. aeruginosa*, ESBL-producing strains and KPC	FDA Approved 2015 for cIAI, f cUTI, in phase III for cIAI and HAP/VAP
Meropenem+Vaborbactam (Carbavance or Vabomere)	Medicines Company	Carbapenem +BLI	MDR Gram(-), including CRE	Phase III cUTI, cIAI, HAP
Cilastatin/relebactam/ imipenem (Recarbrio)	Merck Sharp & Dohme	Carbapenem +BLI	MDR Gram(-), including CRE	FDA approved for cIAI cUTI, Phase III Bacterial infections; Pneumonia

BLI: b-lactamase inhibitors; cUTI: complicated urinary tract; cIAI: complicated intra-abdominal infections

2014, for the treatment of cIAIs and cUTIs caused by ESBL-producing *Enterobacteriaceae* species, drug-resistant *P. aeruginosa,* and some *Streptococcus* species[47].

Ceftolozane is a new cephalosporin based on the ceftazidime with the exception of a modified side-chain at the 3-position of the cephem nucleus, which confers potent antipseudomonal activity. The combination with tazobactam, in a ratio 2:1, increases its benefit against *enterobacteriaceae* with ESBL production, such as *E. coli* and *K. pneumoniae*. It did not demonstrate activity against serine group of carbapenamases, ie, KPC and metallo-β-lactamases[48]. C/T also demonstrated superior *in vitro* activity against ceftazidime-resistant *Escherichia coli* and *K. pneumoniae* when compared with ceftriaxone, cefepime, and piperacillin/tazobactam[49].

Its antipseudomonal activity is attributed to its ability to evade the multitude of resistance mechanisms employed by *P. aeruginosa*, including efflux pumps, reduced uptake through porins and modification of PBPs[50].

In the single-dose studies, ceftolozane had a mean plasma half-life (t1/2) of 2.6 hours (range, 2.43–2.64) and a volume of distribution at steady state (Vss) of 5.1 L/h (ceftolozane alone) and 12.3 L/h (C/T). The clearance of ceftolozane, alone and with tazobactam, was shown to occur exclusively via renal elimination.

C/T is approved in a dosage of 1 g/0.5 g administered every 8 hours by intravenous infusion over 1 hour for the treatment of cIAI in combination with metronidazole for 4-14 days and cUTI for 7 days.

A RCT, phase III (ASPECT-NP) of C/T compared with meropenem for 726 patients with VAP completed its recruitment recently and results are pending[51].

C/T is not currently approved for pneumonia but seems promising in this indication due to its specific action in severe infections caused by MDR and extensively drug resistant *P. aeruginosa*[52,53], the high cure rates displayed in patients with pulmonary exacerbation of cystic fibrosis, and for the good profile of tolerability.

3. Tedizolid Phosphate

Tedizolid (formal name Sivextro) was the third antibiotic approved by the FDA for ABSTI in 2014 and has also been recommended for approval by EMA's CHMP. Tedizolid is an oxazolidinone derivate and is available in oral and intravenous forms. It demonstrates antimicrobial activity across abroad range of Gram (+) pathogens and greater potency than linezolid against wild-type and MDR pathogens, including linezolid-resistant *Staphylococcus aureus* strains[54]. Tedizolid is active against MRSA that possess the *cfr* gene[55] and VRE. The higher intrinsic activity shown with lower MIC values when tested in protein-free media may be partly offset in vivo by a high protein binding of about 90%[56]. Tedizolid was 2- to 8-fold more potent than vancomycin against *staphylococci*, 4-fold more potent than linezolid against *enterococci* and *streptococci*, and up to 4-fold more potent than linezolid against anaerobic species, in a large survey of 1063 isolates[57]. Livermore and colleagues[58] observed that tedizolid was 4-fold more potent than linezolid, with MIC values tightly clustered around 0.5 μg/mL vs 2.0 μg/mL for linezolid. The current FDA approved clinical breakpoint for tedizolid susceptibility is ≤0.5 mg/L.

With its half-life of approximately 12 h, tedizolid is dosed once daily. It demonstrates linear pharmacokinetics, has a high oral bioavailability of approximately 90%, and is primarily excreted by the liver as an inactive, non-circulating sulphate conjugate. Tedizolid does not require dosage adjustment in patients with any degree of renal dysfunction or hepatic dysfunction[59]. Data from the two completed Phase III clinical trials demonstrated that the studied tedizolid regimen (200 mg once daily for 6 days) had significantly less impact on hematologic parameters as well as significantly less gastrointestinal treatment-emergent adverse effects than its comparator linezolid.

A RCT, phase III, with primary objective is to determine the noninferiority (NI) in all-cause mortality (ACM) within 28 days after randomization of tedizolid (200 mg daily for 7 days) compared with i.v. linezolid (600 mg twice daily for 10 days) in ventilated participants with VAP has completed its recruitment[60].

Although much of the role of tedizolid in HAP/VAP remains to be defined by expanding clinical experience, tedizolid is likely a welcomed addition to the mere handful of agents available for the treatment of multidrug-resistant Gram-positive infections.

4. Plazomicin

It is an aminoglycoside derivative of sisomicin; the first of the new generation aminoglycoside, known as neoglycoside[61]; inhibits bacterial protein synthesis and exhibits dose-dependent bactericidal activity. It has enhanced activity against many MDR GNB as *K. pneumoniae, E. coli* and *Enterobacter* species with MIC_{50} and MIC_{90} of 1 and 2 μg/ml respectively[62]. Plazomicin was also found to have lower MIC for *Acinetobacter baumanii* when compared with the licensed aminoglycosides[63].

Interestingly, it has shown potent activity against Gram-positive bacteria such as MRSA, including aminoglycoside-resistant isolates[64]. The compound is now being studied in a global phase III trial enrolling patients with bloodstream infections or NP due to carbapenem-resistant *Enterobacteriaceae*.

Significantly improved activity has been observed in OXA-producing *A. baumannii* compared with other aminoglycosides. In a study of Salguero et al[63] have found that plazomicin has the potential to be useful for the treatment of carbapenem-resistant *A. baumannii* isolates combined with different antibiotics, primarily carbapenems.

It exhibits synergy with daptomycin and ceftobiprole against MRSA and also against *Pseudomonas* when combined with cefepime, doripenem, and piperacillin-tazobactam[65]. In similar assays with 25 isolates of *P. aeruginosa*, plazomicin was synergistic with piperacillin/tazobactam, cefepime, doripenem, and imipenem in 92%, 80%, 80%, and 68% of the isolates[66].

Intravenous dosing of plazomicin of 15 mg/kg yielded a maximum concentration of 113 μg/ml, the half-life was 3 hours and the steady-state volume of distribution was 0.24 l/kg. The lung penetration is poor with the ratio ELF/plasma AUC being 13%, similar to amikacin (14%). Trials on healthy volunteers have shown no evidence of ototoxicity or nephrotoxicity[67].

The phase III CARE study (ClinicalTrials.gov Identifier NCT01970371) evaluated the efficacy and safety of plazomicin versus colistin as part of a definitive combination regimen for the treatment of serious infections (bloodstream infections or NP or cUTI) due to CRE and has been recently completed[68]. Plazomicin showed reduced all cause mortality of 11,8% at day 28 compared with 40% of colistin. A lower rate of mortality or serious disease-related complications was observed for plazomicin compared with colistin (23.5 versus 50.0%, respectively; 90% CI: 0.7, 51.2%). Furthermore, plazomicin was also associated with a lower incidence of nephrotoxicity than colistin.

However, small sample sizes (68 patients) limit the interpretation of the findings in the CARE trial.

While initial data with plazomicin appear promising, broad use of this mediation may be limited by clinicians' underlying hesitancy to use aminoglycosides given the adverse effects of nephrotoxicity or ototoxicity associated with older agents in this class. Additionaly, it has variable activity against *P. aeruginosa* and no activity against *A. baumannii, S. maltophilia,* streptococci, enterococci, and anaerobic organisms[69].

Plazomicin (ZEMDRI) is approved by the FDA for adults with complicated urinary tract infections (cUTI), including pyelonephritis, caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Enterobacter cloacae*, in patients who have limited or no alternative treatment options[70].

5. Meropenem/Vaborbactam (M/V)

Meropenem/Vaborbactam (M/V)(brand name Vabomere), is a combination of meropenem with a beta-lactamase inhibitor, vaborbactam that is being developed for the treatment of gram-negative infections, such as cUTIs, HAP including those due to carbapenem-resistant *Enterobacteriaceae* (CRE)[71]. The combination has no in vitro activity against Class B metallo-β-lactamases and OXA-48-β-lactamases[72]. The combination achieved greater kill of KPC-producing Enterobacteriaceae compared with meropenem alone. Both agents are able to reach the ELF in appreciable amounts in healthy adult volunteers, with an unbound ELF/plasma ratio of 0.65 for meropenem and 0.79 for vaborbactam[73].

It can be administered as a fixed combination by i.v. infusion.

The FDA has approved its use for cUTI (August 2017) on the basis of the double-blind, double-dummy RCT TANGO-I (NCT02166476), in which the primary efficacy endpoint (clinical cure or improvement and microbiological clearance at the end of intravenous therapy) was observed in 188 patients receiving M/V (98.4%) vs. 171 patients receiving piperacillin/tazobactam (94.0%), meeting superiority criteria[74].

Another TANGO study, a Phase III RCT[75], including 150 patients with serious infections (including cUTIs, cIAIs, bacteremia, or HAP/VAP) due to Antibiotic carbapenem -resistant enterobacteriacae comparing MER/VAP to best available therapy, terminated on March 2019 and has announced its results.

In summary, MER/VAB has demonstrated success against a wide range of KPC -positive Enterobacteriae, as a viable option against MDR GNBs.

6. Upcoming new antimicrobials

1. Imipenem /Cilastatin + Relebactam (IMI/REL)

Another combination of imipenem/cilastatin with relebactam (brand name Recarbrio) a class A and C beta-lactamase inhibitor, is designed to restore imipenem activity against certain imipenem-resistant GNB, including *Pseudomonas aeruginosa* and *KPCs*[76].

In a collection of a total of 2,778 isolates of *E. coli* were

gathered during the 3-month surveillance study the combination of imipenem with relebactam demonstrated activity against KPC-producing *Enterobacteriaceae* and multidrug-resistant *P. aeruginosa*. However, IMI/REL is not active against imipenem-resistant Enterobacteriaceae expressing IMPs, VIMs or NDM MBLs , *A. baumanii*, or IMP-or-VIM- producing *P. aeruginosa*. The addition of relebactam did not improve the activity of imipenem against *A. baumannii*, however[77].

Two comparative studies for IMI/REL has completed:

a) The RCT study (NCT02493764) aims to compare treatment with IMI/REL to piperacillin/tazobactam (PIP/TAZ) in patients with HAP/VAP[78] and
b) The RESTORE-IMI 1 study (NCT02452047) comparing IMI/REL to colistinmethate sodium in combination with imipenem/cilastatin for the treatment of imipenem-resistant bacterial infections, including those caused by *P. aeruginosa* and KPC-producing organisms, in patients with HAP/VAP, c UTI and cIAI[79,80]. It demonstrated a higher clinical response (71.4% vs, 40%) and lower all-cause mortality (9.5% vs. 30%) when compared with cilastatin/colistimethase sodium.

On July 2019, FDA has approved Recarbrio (imipenem, cilastatin and relebactam), to treat adults with cUTI and - cIAI[81].

2. Cefiderocol

Cefiderocol is a siderophore cephalosporin based on the mechanism of bacterial cell entry binding to ferric iron.

It has recently been developed to combat a variety of bacterial pathogens, including β-lactam- and carbapenem-resistant organisms, as carbapenem-resistant Enterobacteriaceae (CRE) and meropenem (MER)-resistant *P aeruginosa, Stenotrophomonas maltophilia*, and *A baumannii*. Furthermore, cefiderocol showed activity against classes A, B, and D carbapenemase-producing isolates, comprising metallo-β-lactamase (MBL)– producing Enterobacteriaceae[82].

In one surveillance study including 282 meropenem-nonsusceptible isolates collected from Greek hospitals, cefiderocol produced the lowest MIC values among 10 comparators against *P. aeruginosa*, *A. baumannii*, *K. pneumoniae,* and *Providencia stuartii*[83]. In a larger surveillance study including isolates collected from both North America and Europe, cefiderocol MICs were ≤4 μg/mL for 6,078 (99.9%) Enterobacteriaceae isolates, including 164 (97%) meropenem-nonsusceptible strains (88). Results were similar for *P. aeruginosa*, with 353 (100%) meropenem-nonsusceptible strains exhibiting MICs ≤4 μg/mL[84]. Additionally, activity against *A. baumannii* (n=839) was reported ($MIC_{90/50}$ 1/0.12 μg/mL).

The suggested dosage is 2 g every 8 hours with a 3 hour infusion. In case of renal impairment, the dosage has to be adjusted. Concerning safety, the adverse events are mild and well tolerated in healthy volunteers[85].

A multicenter Phase III trial, including 150 patients, comparing cefiderocol i.v. to best available therapy against serious infections caused by carbapenem-resistant pathogens (CREDIBLE) completed on April 2019 (NCT02714595).

Another RCT phase III has recently completed, involving 300 patients, will investigate cefiderocol versus meropenem, both groups in combination with linezolid, for the treatment of NP (HCAP, HAP, VAP) caused by GNB (APEKS-NP, NCT03032380).

Considering its profile, cefiderocol is a promising cephalosporin with an important potential for the treatment of pneumonia due to carbapenem-resistant GNB, including CRE, MDR *P. aeruginosa,* and *A. baumannii.*

3. Murepavadin

Murepavadin, is a peptidomimetic that acts on LptD protein involved in transport of the lipopolysaccharide component of the outer cytoplasmic membrane of *P. aeruginosa*[86]. It belongs to a novel class of antibiotics called the Outer Membrane Protein Targeting Antibiotics (OMTAs).

Key features of murepavadin include strong activity against *P. aeruginosa* among over 1500 worldwide isolates (MIC_{90} ≤0.25 μg/mL) and proven efficacy in animal infection models with evidence of ample penetration into lung epithelial lining fluid (ELF)[87].

The results of two Phase II trials in patients with VAP and non-cystic fibrosis bronchiectasis, though abbreviated findings are summarized on the company website. Of note, clinical cure rate at test-of-cure (7±2 days after end-of-treatment) was 91% in 12 patients with confirmed VAP caused by *P. aeruginosa*, including 9 patients with confirmed MDR pathogens. Murepavadin was administered for 10-14 days in this study at a dose of 2.5 mg/kg as a 2-hour IV infusion three times[88].

Nephrotoxicity, however, remains a concern associated with the use of murepavadin and requires further investigation.

In contrast to commonly used broad-spectrum antibiotics, murepavadin is a precision medicine and as such it supports the growing practice known as "antibiotic stewardship", which seeks to reduce the excessive use of broad-spectrum products to avoid the buildup of resistance and to preserve the microbiome of the patients.

6. INHALED ANTIBIOTICS

During the last decade, inhaled antibiotics, especially colistin, has been widely used worldwide as a therapeutic option, supplementary to conventional intravenous antibiotics, for the treatment of MDR Gram-negative HAP and VAP. The use of inhaled antibiotics achieves high drug concentrations at the site of infection and may help reduce prolonged systemic antibiotic use by eradicating MDR Gram-negatives more rapidly and effectively than systemic therapy alone.

The IDSA/ATS recommends[2] inhaled antibiotics for VAP due to GNB that are susceptible to only aminoglycosides or polymyxins (colistin or polymyxin B) and includes both inhaled and systemic antibiotics. The antibiotics can be used for inhalation are colistin, levofloxacin, liposomal amikacin, Fosfomycin/tobramycin and aztreonam lysine. The Society of Infectious Diseases Pharmacists recommends that the typical dose for tobramycin is 300 mg every 12 h and colistin 150 mg every 12 h, and for colistin a dose of 150 mg every 12 h.

Effective treatment of VAP caused by MDR organisms such as *P. aeruginosa* and *Acinetobacter baumannii* has been reported with high dose nebulized colistin, even achieving airway eradication[89]. In a meta-analysis found that nebulized antibiotics might be associated with higher rates of clinical cure, but there were no differences regarding the other secondary outcomes, including microbiological cure, mortality or renal toxicity[90]. Their use is currently restricted by technical issues, as a lack of specifically formulated solutions for inhalation and a limited number of devices designed for the nebulization of antibiotics[91,92]. Ongoing, prospective, RCTs with aerosolized antibiotics appear to be promising, such as a combination amikacin– fosfomycin solution delivered via a PARI eFlow inline system[93], and the Amikacin Inhale, an integrated drug–device combination for the delivery of specially formulated Amikacin Inhalation Solution through a Pulmonary Drug Delivery System.

7. CONCLUSION

Considering the dramatic increase in rates of MDR VAP, clinicians must be aware of current MDR pathogens and appropriate management. Optimal treatment of MRSA pneumonia involves vancomycin, linezolid and the new agents telavancin and ceftobiprole. In the targeted GNB area, there are 3 new drugs ceftazidime-avibactam, ceftolozane-tazobactam, plazomicin and two carbapenem's combinations (meropenem/Vaborbactam and Cilastatin/imipenem/relebactam). Interestingly, Murepavadin is a pathogen specific antibiotic, has been granted Qualified Infectious Disease Product (QIDP) and fast track designation from the FDA for the treatment of VABP due to *Pseudomonas aeruginosa*. Inhalation has been used as an adjuvant to systemic therapy in VAP caused by MDR GNBs in combination with systemic antibiotics.

Although more responsible antibiotic prescribing may help optimizing the management of NP research needs to continue to try and identify new antibiotics and adjunctive therapies.

Finally, with few new antibiotics in the pipeline, the emphasis is still on prevention and control of the spread of MDR GNBs. Effective infection control practices, surveillance measures, antimicrobial stewardship programs have been implemented to attempt to reduce the occurrence of nosocomial GNB infections.

ΠΕΡΙΛΗΨΗ

Νέα αντιβιοτικά για τη νοσοκομειακή πνευμονία

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Η νοσοκομειακή πνευμονία (ΝΠ) είναι μία κοινή νοσοκομειακή λοίμωξη και συνδέεται με αυξημένη θνησιμότητα και αυξημένο κόστος νοσηλείας. Στη θνητότητα συμβάλλουν τα ανθεκτικά μικρόβια [κυρίως Gram(-)] που είναι συχνοί αιτιολογικοί παράγοντες ιδίως της πνευμονίας του αναπνευστήρα (ΠΑ). Μελέτες αναφέρουν ποσοστό θνησιμότητας που σχετίζεται με το ΠΑ 30%-50% και ακόμη υψηλότερο σε σηπτικό σοκ. Όταν η κλινική υποψία της ΝΠ είναι υψηλή, είναι απαραίτητη η έναρξη έγκαιρης και κατάλληλης αντιμικροβιακής θεραπείας γιατί η καθυστέρηση και η ανεπαρκής θεραπεία έχουν συσχετιστεί με αυξημένη νοσηρότητα και θνησιμότητα. Για να αντιμετωπίσουμε την απειλή της μικροβιακής αντοχής, ειδικά στη

θεραπεία της ΝΠ, νέα αντιβιοτικά έχουν εγκριθεί και άλλα είναι σε τελικής φάσης μελέτες. Η τελαβανσίνη, λιπογλυκοπεπτίδιο, με δράση κατά των Gram(+) και ειδικά του MRSA, η κεφτοβιμπρόλη μια κεφαλοσπορίνη με αυξημένη δραστικότητα κατά των Gram(-) της ΝΠ, όχι όμως της ΠΑ, έχουν εγκριθεί τα τελευταία χρόνια για τη θεραπεία της ΝΠ. Ακολούθως, δύο συνδυασμοί κεφαλοσπορινών με συνδυασμό αναστολέων β-λακταμασών εγκρίθηκαν από τον FDA προσφάτως. Είναι η κεφταζιδίμη/αβιβακτάμη και η κεφταζολένη/ταζοβακτάμη και οι δύο ιδιαιτέρως δραστικές εναντίον της Pseudomonas aeruginosa. Μία καινούρια αμινογλυκοσίδη, η πλαζομισίνη με αυξημένη δραστικότητα εναντίον ανθεκτικών Gram(-) και MRSA και ο συνδυασμός μεροπενένης/βαπορμπακτάμης που χορηγείται για τη θεραπεία αρνητικών κατά Gram λοιμώξεων, όπως είναι η cUTIs, ΝΠ συμπεριλαμβανομένων αυτών που οφείλονται σε Enterobacteriaceae ανθεκτικά σε καρβαπενέμη (CRE). Επίσης, αντιβιοτικά προς έγκριση αποτελούν η σιδηροφόρος κεφαλοσπορίνη κεφιδερόλη και η μουρεπαβαδίνη ένα πεπτίδιο-αντιβιοτικό ειδικό για τη Pseudomonas. Στη φαρέτρα μας κατά των ανθεκτικών Gram(-) στη ΝΠ συμμετέχουν και τα εισπνεόμενα αντιβιοτικά, ιδίως η εισπνεόμενη κολιστίνη και τομπραμυκίνη. Όλοι οι νέοι αντιμικροβιακοί παράγοντες πρέπει να χορηγηθούν σωστά, με βάση τις αρχές της φαρμακοκινητικής και φαρμακοδυναμικής, για τη βέλτιστη θεραπεία του ασθενή με πνευμονία στη ΜΕΘ.

Πνεύμων 2019, 32(3):89-100.

Λέξεις - Κλειδιά: *Νοσοκομειακή πνευμονία, Νέα αντιβιοτικά, Αντιμικροβιακή αντοχή, Telavancin, Avibactam, Cefiderocol*

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