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Review

Treatment Options for Infections Caused by Multidrug-Resistant Gram-Negative Bacteria

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Abstract

Multidrug-resistant (MDR) *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are of great concern and often related to the production of extended-spectrum beta-lactamases (ESBL) and carbapemenase - producing bacteria, which represent an increasing global threat. The therapy of nosocomial infections due to these MDR Gram-negative bacteria is challenging also because some of the new active drugs are not available in Bulgaria. In this paper we review the potencial of some drugs (ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, plazomicin, cefiderocol, eravactclin) and their action *in vitro* on Gram-negative bacteria that pose a major problem in hospital infection pathology. The recommendations to the use of these new drugs can be evaluated from a clinical point of view as an alternative for the treatment of severe life-threatening infections, but also as an opportunity to give an opinion in this field, while awaiting more definitive data after we have gained good practical experience.

Keywords: MDR bacteria, new antimicrobial drugs

Резюме

Множествено-резистентните щамове *Enterobacteriaceae*, *Pseudomonas aeruginosa* и *Acinetobcter baumannii*, продуциращи широко-спектърни бета-лактамази (ESBL) и карбапеменази, представляват нарастваща глобална заплаха като терапевтичен проблем. Лечението на нозокомиалните инфекции, причинени от тези множествено-резистнетни Грам-отрицателни бактерии е предизвикателство и поради факта, че някои от новите антимикробни средства не са налични в България. В това съобщение представяме литературни данни относно възможностите за *in vitro* оценка на някои нови антибактериални препарати (ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, plazomicin, cefiderocol, eravacyclin) върху проблемни за болничната патология Грам-отрицателни бактерии. Препоръките за употреба на тези препарати могат да бъдат оценени от клинична гледна точка като алтернатива за третиране на тежки живото-застрашаващи инфекции, а също и като възможност да се изрази мнение по въпроса, докато бъдат получени повече дефинитивни данни след тяхната употреба в практиката.

Introduction

The recent emergence, in European hospitals and globally, of bacteria that are totally, or almost totally, resistant to currently available antibiotics is ever more threatening since treatment options for infected patients are extremely limited (Souli *et al*., 2008; Lepape and Monnet, 2009; Nordmann *et al.*, 2009; Freire-Moran, 2011). Infections due to MDR Gram-negative bacteria are associated with increased morbidity and mortality and prolonged hospitalization, which is a significant economic burden on the healthcare system (Cerceo *et al.,* 2016). Patel *at al.* (2008) reported about lethality rates of 40–50% in patients with bloodstream infection caused by carbapenem-resistant *Klebsiella pneumonia*, which is very close to the WHO estimate of 50-60% mortality rate of Ebola virus disease (WHO, 2018). Moreover, the economist and current Commercial Secretary to the Treasury in the UK Jim O'Neill postulated, that if the rise in resistance continued at the current rate, ten million people would die each year by 2050 and the Gross Domestic Product would fall by 2-3.5%, costing the world up to $100 trillion (Solon, 2016). According to our data, the percentage of Gram-negative bacteria isolated at the Military Medical Academy /MMA/ in 2015 is about 49%, and five species – *Escherichia coli*, *Acinetobcter baumannii*, *K. pneumoniae*, *P. aeruginosa* and *P. mirabilis* are among the first ten most commonly isolated microorganisms for that year (Bulletin MMA, 2016). Over time, most of these bacteria have become resistant to all beta-lactams, including carbapenems, often referred to as last-resort antibiotics. After a long time of a serious deficit in new antimicrobial development, several novel antibiotics have been presented that address the treatment of infections caused by such "nightmare" bacteria.

The aim of this paper is to review the possible implementation of several new antimicrobial drugs like ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, plazomicin as an alternative for the treatment of - life-threatening infections caused by MDR Gram-negative bacteria. All these new antimicrobials are improved derivatives of well-known antibiotic groups and used in the treatment against Gram-negative bacteria with class-specific resistance mechanisms.

Ceftolozane-Tazobactam and Ceftazidime-Avibactam

Ceftolozane-tazobactam combines a novel cephalosporin (ceftolozane) - structurally similar to ceftazidime, with a classic beta-lactamase inhibitor – tazobactam. This combination shows high affinity to PBPs, as for *P. aeruginosa* they are PBP1b, PBP1c and PBP3 and for *E. coli* - it is PBP3, with good activity for Gram-negative (*E. coli* and *K. pneumoniae*) producing ESBL, Amp C producers, but not against KPC (Sucher *et al*., 2015). The drug was approved by the FDA and European Medicines Agency (EMA) for treatment of adults with complicated intraabdominal infections (cIAI) in combination with metronidazole and complicated urinary tract infections (cUTI), including pyelonephritis. (Sucher *et al*., 2015; Rodriguez-Bano *et al*., 2018).

Ceftazidime-avibactam combines ceftazidime /third-generation cephalosporin/ with a new/non beta-lactam/beta-lactamase inhibitor. Avibactam inhibits serine enzymes (class A enzymes), including ESBLs and *K. pneumoniae* carbapemenases (KPCs) as well as AmpC and carbapemenases class D – OXA-beta-lactamases – OXA 48, but is not active against carbapemenase class B (metallo-beta-lactamases (Rodriguez-Bano *et al.*, 2018). This combination shows non-inferiority to meropenem and imipenem and was approved by the FDA and the EMA for the treatment of cIAI in combination with metronidazole, and cUTI. The EMA also includes an indication for HAP as carbapenem-sparing treatment and other infections due to Gram-negative bacteria with limited treatment options (Bassetti *et al*., 2018; Rodriguez-Bano *et al*., 2018). Ceftazidime-avibactam plus metronidazole can present a clinical response against ceftazidime-nonsusceptible *Enterobacteriaceae* – 80% of them were ESBL producers and also showed an efficacy similar to that of the best available therapy/ carbapenems/ in a pathogen-directed trial of patients with cUTI and cIAI caused by ceftazidime-resistant *Enterobacteriaceae* (Carmeli *et al*., 2016; Rodriguez-Bano *et al*., 2018). Also, according to Rodriguez-Bano *et al.* (2018), because of potential value against extensively drug resistant (XDR) *P. aeruginosa* in the case of ceftolozane-tazobactam and KPC or OXA - 48 producing *Enterobacteriaceae* in the case of ceftazime-avibactam, it seems prudent to reserve these drugs for these particular organisms. Unfortunately, Shields *et al*. (2018) reported recently about resistance development to ceftazidime-avibactam in 77 patients with CRE infection treated with CAZ-AVI. Microbiological failure of 33% was recorded and development of pneumonia was identified as a risk factor.

Imipenem-Relebactam and Meropenem-Vaborbactam

Relebactam is a non-beta-lactam, bicyclic diazabicyclooctane, beta-lactamase inhibitor that is structurally related to avibactam. Vaborbactam is also a non-beta-lactam, cyclic, boronic acid-based, beta-lactamase inhibitor. Both inhibitors display activity against class A, including ESBLs, KPCs and class C beta-lactamases (AmpC) (Zhanel *et al*., 2018). However, these inhibitors do not enhance the activity of the antibiotics imipenem and meropenem against MBL/NDM or VIM/ or OXA-48 producers, respectively. (Rodriguez-Bano *et al*., 2018). The addition of relebactam improves imipenem activity against most representatives of *Enterobacteriaceae* by lowering the minimum inhibitory concentration (MIC) 2 to 128 fold, depending on the presence or absence of beta-lactamase enzymes. With respect to *P. aeruginosa*, relebactam also enhances imipenem activity since MIC is reduced eightfold. It is important to note that based on the data available, the imipenem-relebactam combination does not show activity against *A. baumannii*, *Stenotrophomonas maltophilia* and most anaerobes. According to Thaden *et al*. (2016) little or no reduction was seen in OXA-48 producing *K. pneumoniae*, and no significant activity against class D enzymes. Phase II clinical trials show that the combination imipenem-relebactam is as effective as imipenem alone for the treatment of complicated intraabdominal infections and complicated urinary tract infections, including acute pyelonephritis. The results from phase III clinical trials also demonstrated that this combination is effective for the treatment of imipenem-resistant infections as well as hospital-associated bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) (Zhanel *et al*., 2018).

The addition of vaborbactam to meropenem, like the combination imipenem-relebactam, leads to a significant reduction (2 to > 1024-fold MIC) and improves the activity of meropenem against most representatives of *Enterobacteriaceae*, depending on the presence or absence of beta-lactamase enzymes. Limited data are available that the addition of vaborbactam does not improve the activity of meropenem with respect to *A. baumannii*, *P. aeruginosa* and *S. maltophilia* strains (Zhanel *et al*., 2018). Vaborbactam was recently approved by the FDA for the treatment of cUTI- if the enterobacteria are sensitive. This decision was accepted on the basis of data, obtained from a phase III trial in which meropenem-vaborbactam showed non-inferiority to piperacillin-tazobactam (Bidair *et al*., 2017). Similarly to imipenem-relebactam, the combination meropenem-vaborbactam demonstrated high efficiency in the treatment of carbapenem-resistant *Enterobacteriaceae*, as well as for HABP and VABP (Zhanel *et al*., 2018). Little effect on *A. baumannii* containing OXA-type carbapenemases or *P. aeruginosa* was observed (Wright *et al*., 2017).

In vitro and *in vivo* pharmacodynamic studies showed bactericidal activity for both combinations against various problematic Gram-negative beta-lactamase producing bacteria /(ESBL, KPC and Amp C beta-lactamases) that are not inhibited by their respective carbapenems alone. The usage of these new combinations will likely become the standard of care in patients with CRE infections (Zhanel *et al*., 2018).

Plazomicin

Plazomicin, a new aminoglycoside related to sisomycin antibiotic that inhibits protein synthesis by binding to the ribosomal 30S subunit of bacteria, with an option for carbapenem-resistant *Enterobacteriaceae* (CRE) treatment. Plazomicin has been synthesized to be active against most bacteria containing aminoglycoside-modifying enzymes (Aggen *et al*., 2010; Haidar *et al*., 2016; Wright *et al*., 2017; Theuretzbacher *et al*., 2018). Plazomicin has demonstrated greater activity against *Enterobacteriaceae*, including carbapenem-resistant isolates and those with ESBL production, and have shown better activity in this respect in comparison with amikacin, gentamicin and tobramycin, but the resistance to this antibiotic has been noted in MDR strains expressing 16S rRNA methyltransferases, which modify the ribosomal binding site (Livermore *et al*., 2011). Plazomicin is less active against non-fermentative Gram-negative bacteria compared with *Enterobacteriaceae*. The activity of plazomicin against MDR *P. aeruginosa* strains was similar to MICs for other aminoglycosides (Walkty *et al*., 2014). Regarding OXA-producing *A. baumannii*, significantly improved activity was observed in isolates treated with plazomicin compared with other aminoglycosides - MICs 16-to-32 - fold lower (Garsia-Salguero *et al*., 2015). Additionally, results of phase III randomized trial, comparing the use of plazomicin /15 mg/kg/day/ and meropenem /1g/8h/ for treatment of cUTI, including acute pyelonephritis, have been reported (Cloutier *et al.,* 2017).

Cefiderocol

Cefiderocol is a novel siderophore cephalosporin antibiotic with a catechol part at the 3-position side chain. The catechol side chain allows the active transport of the ferric iron ion into bacteria via ferric iron transport systems with subsequent destruction of cell wall synthesis (Mollmann *et al*., 2009; Dobias *et al*., 2017; Wright *et al*., 2017). Cefiderocol has potential in vitro against *Enterobacteriaceae*, including KPC, NDM, IMP, VIM-producing strains, but showed less activity against some strains of *E. coli*, expressing NDM-1 (Kohira *et al*., 2016). The MIC values ranged between <0.125 and 4mg/L against KPC-producing strains. At a dose of 2 g every 8h it reaches > 50% time above the MIC for MICs of up to 8mg/L (Katsube *et al*., 2017). Cefiderocol demonstrated also in vitro good activity with respect to *A. baumannii* producing carbapenemase OXA-type beta-lactamases, *P. aeruginosa* producing metallo-beta-lactamases with MIC90 of 8mg/L and *S. maltophilia* isolates as well. This activity is probably due not only to efficient uptake via the active siderophore systems, but also to the high stability of cefiderocol against carbapenemase hydrolysis (Wright *et al*., 2017). Preliminary results of phase III trial with cefiderocol use reported non-inferiority to imipenem against cUTI (Portsmouth, 2017).

Eravacycline

Eravacycline is a novel fluorocycline antibiotic which is bound to the bacterial ribosome and inhibits the bacterial protein synthesis, with in vitro activity against MDR Gram-positive and Gram-negative pathogens, including carbapemenase-producing *Enterobacteriaceae* (Livermore *et al*., 2016; Zhanel *et al*., 2016; Rodriguez-Bano *et al*., 2018). Similarly to tigecycline, it avoids many resistance mechanisms seen for other tetracyclines, with no loss of antibacterial activity in the presence of tetracycline ribosomal protection proteins and most tetracycline-specific efflux pumps (Bassetti *et al*., 2014). However, elevated MICs have been noted for eravacycline against strains in the presence of tet (A) efflux pump (Grosman *et al*., 2012). Two modifications at the C-7 and C-9 positions of tetracycline expand the spectrum of eravacycline, maintaining its activity against MDR bacteria (Zhanel *et al*., 2016). Eravacycline shows good activity against *Enterobacteriaceae* including strains that exhibited carbapenem-resistance associated with KPC, OXA and NDM production (Bassetti *et al*., 2014; Zhanel *et al*., 2016). It is an usual correlation between tigecycline and eravacycline susceptibilities, but in a study (Livermore *et al*., 2016) eravacycline demonstrated two- to four-fold more activity than tigecycline against carbapenem-resistant *Enterobacteriaceae* and *A. baumannii* isolates. The drug is not significantly active against *Burholderia* spp. or *P. aeruginosa* strains (Bassetti *et al*., 2014). Also, eravacycline has shown non-inferiority to ertapenem in the treatment of cIAI in a phase III trial (Solomkin *et al*., 2017).

Conclusion

The therapy of infections caused by MDR *Enterobacteriaceae*, *P. aeruginosa* and *A. baumannii* is a serious problem and the current situation, because of limitation of antimicrobials, is unsatisfactory for clinicians. Therefore, the progress in the development of new antimicrobials in the past years for the treatment of these severe infections is very important and gives hope to the specialists. Drug development as a tool for the treatment of such infections in the face of growing resistance, promises new favourable opportunities for the antibiotic armamentarium. However, from the above information it is difficult to evaluate the clinical evidence of the efficacy and safety of these new drugs, and to draw definitive conclusions in this respect would be unjustified due to insufficient information. Most of these new agents are the result of modifications or reinforcement of already known molecules. There is a lack of drugs, belonging to new classes of antibiotics, inhibiting novel cellular targets that are not burdened by pre-existing or cross resistance. The situation requires extensive discussion and action. It is important, because pathogenic bacteria will continue to evolve a response to this new selection pressure and early reports of resistance, for example to ceftazidime/avibactam after the start of clinical use, requires careful monitoring for the development and spread of resistance to any new drugs. It is well known that the decisions about empirical therapy should be made in accordance with local information about the etiological structure of infection and the pathogen resistance, together with individual risk factors and infection severity. On the other hand, there is a suggestion that the therapy of infections, caused by MDR bacteria must be individualized according to the susceptibility type, the severity of infection and the condition of the patient. It is important to develop realistic strategies involving experienced and motivated knowledge, and there is a necessity for integration of rapid diagnostics into the standard workflow in microbiology laboratories for point-of-care testing as well as sufficient information on the prudent use of antimi-

crobials, including new ones.

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