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REVIEW ARTICLE

Development of novel antibacterial drugs to combat multiple resistant organisms

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Abstract
Background Infections due to multidrug-resistant (MDR) bacteria are increasing both in hospitals and in the community and are characterized by high mortality rates. New molecules are in development to face the need of active compounds toward resistant gram-positive and gram-negative pathogens. In particular, the Infectious Diseases Society of America (IDSA) has supported the initiative to develop ten new antibacterials within 2020. Principal targets are the so-called ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae*).
Purpose To review the characteristics and the status of development of new antimicrobials including new cephalosporins, carbapenems, beta-lactamase inhibitors, aminoglycosides, quinolones, oxazolidones, glycopeptides, and tetracyclines.
Conclusions While numerous new compounds target resistant gram-positive pathogens and have been approved for clinical use, very few new molecules are active against MDR gram-negative pathogens, especially carbapenemase producers. New glycopeptides and oxazolidinones are highly efficient against methicillin-resistant *S. aureus* (MRSA), and new cephalosporins and carbapenems also display activity toward MDR gram-positive bacteria. Although new cephalosporins and carbapenems have acquired activity against MRSA, they offer few advantages against difficult-to-treat gram-negatives. Among agents that are potentially active against MDR gram-negatives are ceftozolane/tazobactam, new carbapenems, the combination of avibactam with ceftazidime, and plazomicin. Since a relevant number of promising antibiotics is currently in development, regulatory approvals over the next 5 years are crucial to face the growing threat of multidrug resistance.

Keywords New antibiotics · Multidrug resistance · FDA

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Introduction

The dramatic increase in resistance of both gram-negative and gram-positive pathogens poses a great concern since these infections are characterized by high mortality rates, prolonged hospitalization, and associated costs [1, 2]. Bacteria bearing resistance to one or more antimicrobials from at least three different antimicrobial classes, defined as multidrug resistance (MDR) bacteria, have become increasingly common, especially in the hospital setting [3].

The acronym "ESKAPE pathogens" refers to the most frequently reported MDR bacteria, including *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae*, and it underlines their ability to escape the antimicrobial treatment [1].

Specifically, gram-negative bacteria have shown increasing resistance to penicillins, cephalosporins, and quinolones [4]. In particular, the emergence of MDR strains of *P. aeruginosa* and extended-spectrum beta-lactamases (ESBLs)-producing *Enterobacteriaceae* has significantly narrowed the choices for a targeted antimicrobial therapy [4]. As a consequence, broad-spectrum antimicrobials (e.g., piperacillin/tazobactam, carbapenems, fluoroquinolones) have registered a progressive increase in their use, leading to the emergence of isolates that are resistant to all current available molecules, called extreme

drug-resistant strains (XDR) [5, 6]. In the past decades, the increase in gram-negative MDR bacteria has not been counterbalanced by the availability of new molecules; thus, the emergence of infections for which there are limited treatment options currently represents a critical unmet medical need [7].

Due to the limited therapeutic options, clinicians aiming to target MDR gram-negative bacteria had to rediscover the use of old drugs, such as polymixins and fosfomycin, or to increase the recommended dose of broad-spectrum antimicrobials, such as carbapenems or tigecycline, in order to achieve therapeutic benefit. Nevertheless, these strategies may be correlated to an increase in drug-related toxicity.

Novel pharmaceutical molecules such as linezolid, daptomycin, and tigecycline have been discovered and introduced into clinical practice in the last few years to target resistant gram-positive bacteria. Neverthelass, pathogens such as methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE) are still extremely challenging to eradicate. Furthermore, *S. aureus* (including MRSA) is the leading cause of hospital-acquired infections (HAI) in the USA, with the global spread of some strains approaching epidemic proportions [8]. Although vancomycin has been considered the drug of choice for MRSA and is still extensively used for this indication, recent studies suggest that vancomycin is less effective against MRSA in the presence of minimum inhibitory concentration (MIC) values that are at the high end of the susceptibility range [9–11].

In this dramatic scenario, the need of new molecules to address the presence of both gram-negative and gram-positive pathogens is mandatory. In the past 10 years, the lack of new antibiotics has been the main concern of professional agencies such as the Infectious Diseases Society of America (IDSA) that have stressed the necessity of new pharmaceutical investments in the area of antimicrobial development [12]. In 2010, the IDSA launched the so-called 10×′20 initiative in order to develop ten new antibiotics by 2020 and address the limited number of novel therapeutics in development to treat drug-resistant pathogens [13].

In this review, we have reported the characteristics of the most recently developed antimicrobials for the treatment of resistant gram-positive and gram-negative bacteria that have completed at least phase 2 trials.

Beta-lactams

Cephalosporins

Cephalosporins are among the most prescribed antimicrobials due to their broad spectrum of activity and a favorable safety profile. Like other beta-lactams, their mechanism of action consists in binding to penicillin-binding proteins (PBPs) leading to irreversible inhibition of the bacterial cell wall synthesis.

New, fifth generation cephalosporins include ceftaroline and ceftobiprole that are characterized by an extended spectrum of activity toward resistant gram-negative pathogens and a unique activity against MRSA

Ceftaroline fosamil is a novel semisynthetic anti-MRSA cephalosporin with broad-spectrum activity, which is currently completing phase 4 clinical trials. Ceftaroline presents enhanced activity toward MDR gram-positive pathogens including MRSA, heteroresistant vancomycin-intermediate *S. aureus* (hVISA), and vancomycin-resistant *S. aureus* (VRSA). Its activity against MRSA is due to a higher effect on PBP2a inhibition compared to other beta-lactams [14]. Although ceftaroline maintains good activity against gram-negative pathogens, increased MIC and potential selection of resistance have been shown toward AmpC-producing strains [15, 16]. Furthermore, the activity of ceftaroline was lower compared to aztreonam toward *P. aeruginosa* and *Proteus mirabilis* [17]. Ceftaroline has been approved by the US Food and Drug Administration (FDA) in 2010 and by the European Medical Agency (EMA) in 2012 for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) and community-acquired pneumonia (CAP). Pooled success frequency in the treatment of CAP, including infections with MDR *S. pneumoniae*, was 84.3 % [18]. For the treatment of ABSSSI, including infections with MRSA, pooled success frequency was 91.6 % [17].

Ceftobiprole medocaril is a new cephalosporin with expanded activity against gram-positive bacteria. Similarly to ceftaroline, it has high affinity for PBP2a. Ceftobiprole is stable against class A temoneira (TEM-1) and class C AmpC beta-lactamase but, similarly to ceftazidime, is labile to hydrolysis by class B, class D, and class A ESBL and carbapenemases [19]. Ceftobiprole is active against *Enterococcus faecalis* but not against *E. faecium.* Toward *P. aeruginosa*, ceftobiprole activity is superior to that of cefepime [20]. *In vitro* activity of ceftobiprole against *S. pneumoniae* showed MIC90 of 0.5 μg/mL, the lowest among all other cephalosporins. Ceftobiprole has been approved for use in Canada and Switzerland and is under review in the USA and Europe. In phase 3 trials, ceftobiprole was non-inferior to linezolid in association with ceftazidime or ceftriaxone in hospital-acquired pneumonia (HAP) and CAP requiring hospitalization, respectively [21]. In patients with ventilator-associated pneumonia (VAP), ceftobiprole is not recommended since its non-inferiority was not demonstrated in this subset of patients. Good results were also shown in the treatment of complicated SSSIs [22]. Ceftobiprole was generally well tolerated.

Ceftozolane/tazobactam represents the association of a novel cephalosporin and the beta-lactamase inhibitor tazobactam. The chemical structure of ceftolozane is similar to that of

ceftazidime, with the exception of a modified side chain at the third position of the cephem nucleus, which confers potent antipseudomonal activity. Ceftolozane displays increased activity against gram-negative bacilli, including those that harbor classical beta-lactamases such as TEM-1 and SHV-1 [23]. Similar to other cephalosporins, such as ceftazidime and ceftriaxone, ESBL and carbapenemases may compromise its activity. The addition of tazobactam expands its spectrum and allows activity against ESBL-producing bacteria and *Bacteroides* spp. [24]. Thanks to its ability to escape various resistance mechanisms (e.g., PBP mutations, efflux pumps), ceftolozane offers unique activity versus *P. aeruginosa*, including carbapenem, piperacillin/tazobactam, ceftazidime-resistant, and MDR isolates [25]. Overall efficacy including superiority to levofloxacin in complicated urinary tract infections (cUTIs) and comparable efficacy to meropenem in complicated intra-abdominal infections (cIAI) have been recently demonstrated in phase 3 trials [26–29]. A favorable safety profile was demonstrated in phase 3 cUTI and cIAI trials in which ceftolozane/tazobactam was administered intravenously (IV) as 1.5 g every 8 h. A phase 3 trial to assess the safety and efficacy of ceftolozane/tazobactam at a dose of 3 g every 8 h compared to meropenem for the treatment of HAI is expected to be completed in 2018.

Carbapenems

Carbapenems are broad-spectrum beta-lactam antibiotics characterized by stability to hydrolysis by the majority of ESBLs. Currently, meropenem and imipenem/cilastatin are widely used and are recommended for treatment of HAP, cUTIs, cIAIs, and bloodstream infections (BSI). New molecules differ regarding their activity toward difficult-to-treat non-fermenting pathogens (such as *P. aeruginosa* and *A. baumannii*) and MRSA. Similarly to other widely used compounds, such as imipenem and meropenem, new carbapenems that are active toward *P. aeruginosa* and *A. baumannii* but not MRSA include doripenem and biapenem. Conversely, tomopenem and razupenem display activity against MRSA but not against non-fermenting bacilli. Panipenem and tebipenem, like ertapenem, do not have activity against non-fermenting pathogens and MRSA.

Tebipenem/pivoxil is a novel oral carbapenem for the treatment of upper respiratory tract infections (RTIs). Its activity includes MDR *S. pneumoniae* and other gram-positives, *K. pneumoniae* and *Escherichia coli* [30]. Phase 2 clinical studies are ongoing in Japan.

Panipenem/betamipron is a parenteral carbapenem approved in China, Korea, and Japan and for the treatment of UTIs, lower RTI, obstetrical/gynaecological, and surgical infections. The combination of panipenem with betamipron, similarly to imipenem/cilastatin, is necessary because betamipron inhibits the renal uptake of panipenem. Panipenem is highly active against *Enterobacteriaceae* such as *E. coli*, *K. pneumoniae*, *Proteus* spp. and *Citrobacter* spp., but is inactive against *Stenotrophomonas maltophilia*. Its activity toward *P. aeruginosa* is comparable to imipenem but significantly lower than meropenem. Good activity has also been demonstrated against *Bacteroides fragilis* [31]. The clinical efficacy of panipenem/betamipron was demonstrated in three randomized phase 3 clinical trials in comparison with imipenem/cilastatin for the treatment of adults with respiratory and UTIs [32]. Panipenem/betamipron is administered as 0.5/0.5 g twice daily. Mild adverse effects have been associated with panipenem; its co-administration with valproic acid can favor the occurrence of seizures and is contraindicated [32].

Doripenem has a molecular structure that confers beta-lactamase stability and resistance to inactivation by renal dehydropeptidases [33]. Doripenem is characterized by a broad spectrum of activity against gram-negative pathogens. Its activity is similar to that of meropenem against *E. coli*, *Citrobacter* spp., and *Burkholderia cepacia*; higher MIC compared with meropenem have been displayed toward ESBL-producing *K. pneumoniae*, *P. mirabilis*, *Serratia* spp., *B. fragilis*, *P. aeruginosa* and *A. baumannii.* Doripenem is active against MSSA, *S. pneumonia*, and CoNS but it is not active against MRSA and VRE. Doripenem is effective against ESBL or AmpC producers, but reduced activity has been documented against metallo beta-lactamases [34]. Combination of doripenem with colisitin showed in vitro synergistic action against colistin-resistant, carbapenemase producing *K. pneumoniae* (KPC). In vivo, doripenem has been used with benefit used in dual carbapenem therapy (e.g., in association with ertapenem) against pandrug-resistant KPC infections [35–37]. The benefit was thought to be related to a preferential affinity of carbapenemase for ertapenem that is consumed by the enzyme leaving higher concentrations of doripenem to exert its antibacterial effect. An alternative explanation is based on the initial reduction in inoculum density by ertapenem thereby permitting doripenem to express its successful activity [38]. The recommended dosage of doripenem is 500 mg IV every 8 h with dose adjustments in patients with moderate renal impairment [39]. Doripenem was approved by the FDA in 2007 for the treatment of pyelonephritis, cUTI, and cIAIs. Doripenem has also been approved by the EMA for the treatment of HAP and VAP. The most frequent adverse events reported are nausea (3.7 %) and diarrhea (2.5 %); the incidence of seizures with doripenem was lower compared to other carbapenems [39].

Biapenem is a new parenteral carbapenem that has been approved in Japan in 2002, and it is currently undergoing phase 2 clinical studies in the USA. Biapenem is characterized by an optimal penetration in the respiratory tissue along with a broad spectrum of activity including penicillin-resistant *S. pneumoniae*, *A. baumannii*, ESBL-producing *Enterobacteriaceae*, *E. cloacae*, *S. marcescens*, and

Citrobacter freundii. Moderate activity has been displayed against *P. aeruginosa;* biapenem is not active against MRSA and *Enterococci* [40]. Biapenem is administered at a dosage of 300 mg twice daily and requires dose adjustment in case of reduced glomerular filtration rate. A multicenter randomized controlled clinical study comparing biapenem with imipenem/cilastatin in RTIs and UTIs showed similar efficacy and tolerability profile [41]. The most commonly reported adverse effects with biapenem were nausea, skin eruption, vomiting, and diarrhea in 2 to 3.4 % of cases [42].

Tomopenem (CS-023) is characterized by a spectrum of activity that includes both MDR gram-positive and gram-negative strains. Tomopenem has a good activity against penicillin-resistant *S. pneumoniae*, ceftazidime-resistant *P. aeruginosa*, ESBL-producing *Enterobacteriaceae*, and MRSA [43, 44]. Other favorable features include a wide distribution in vivo due to a low rate of protein binding and a reduced potential for selection of resistances [45]. Tomopenem has been studied for the treatment of cSSSI and HAP.

Razupenem (PTZ601) has a broad-spectrum activity against gram-positive and gram-negative pathogens, including penicillin-resistant *S. pneumoniae* MRSA, vancomycin-resistant *E. faecium*, ampicillin-resistant *H. influenzae*, and ESBL-producing bacteria [46, 47]. Razupenem has reduced activity against AmpC enzymes and carbapenemases [46, 48]. Razupenem has shown excellent activity in the treatment of cSSSI.

Beta-lactamase inhibitors

Beta-lactamase inhibitors enhance the activity of beta-lactam agents by protecting them from enzymatic hydrolysis. The goal of the new combinations of beta-lactam/beta-lactamase inhibitors is to expand the activity against class C and class D beta-lactamases.

Avibactam (NXL104) is a beta-lactamase inhibitor characterized by high affinity with class A and class C beta-lactamases and the potential to inhibit ESBLs, KPCs, OXA, and AmpC [49].

Avibactam is currently being investigated in phase 3 studies in combination with ceftazidime and is in clinical development in association with ceftaroline and aztreonam (phase 1 trials). Specifically, its combination with aztreonam offers a potential option against NDM-1 producing bacteria [50].

Ceftazidime/avibactam combination has shown in vitro activity against strains OXA-48, ESBL or AmpC strains, and *Klebsiella* KPC, but not against metallo-beta-lactamase producers [51, 52]. Results of ceftazidime-avibactam phase 2 trials in cUTIs compared to imipenem reported 70.4 and 71.4 % success rates, respectively [53]. In cIAIs with meropenem as comparator, success rates among microbiologically documented infections were over 90 % in both arms. Among isolates presumed to be ESBL producers, the clinical efficacy of both arms was 96 % [54]. Phase 3 studies are ongoing to investigate the activity of avibactam/ceftazidime in cIAIs, cUTIs, HAP, and VAP.

MK-7655 is a novel beta-lactamase inhibitor under investigation in combination with imipenem/cilastatin showing in vitro activity against class A and class C carbapenemases [55]. Two phase 2 trials are ongoing for the treatment of cIAIs and cUTIs [9].

Glycopeptides

Glycopeptides include well known molecules such as vancomycin and teicoplanin. Glycopeptides display a limited spectrum of action and are effective mainly against gram-positive cocci. Their mechanism of action consists in the inhibition of a late stage in bacterial cell wall synthesis binding to acyl-D-alanyl-D-alanine in peptidoglycan [56]. New derivatives of this class, telavancin, oritavancin, and dalbavancin, have been developed to overcome the emergence of MRSA strains with reduced susceptibilities to vancomycin and to increase the penetration into tissues and into the cerebrospinal fluid. These new molecules are lipoglycopeptides (i.e., they present a lipophilic side chains linked to glycopeptides) and are characterized by longer half-life compared to vancomycin, this allowing for infrequent dosing, greater potency, and less potential for development of resistant organisms.

Telavancin is a vancomycin derivative characterized by the addition of a hydrophobic side chain and a hydrophilic group. Its mechanism of action consists in the blockage of both the transpeptidation and transglycosylation steps and in a direct effect on the bacterial membrane causing changes in cellular permeability. Telavancin has a time-dependent killing activity. Its half-life is around 8 h, and it has shown a high level of protein binding (93 %) in plasma [57]. Compared with vancomycin, telavancin is administered once daily and characterized by a potent in vitro antibacterial activity against a broad range of gram-positive bacteria, including MRSA, penicillin-resistant *S. pneumoniae*, and isolates with reduced glycopeptide susceptibility including glycopeptide-intermediate *S. aureus* (GISA) and Van-A type *Enterococci* [58–61]. Specifically, telavancin displays excellent activity toward *Staphylococci*. MICs for MRSA were two to eight times lower than those observed for vancomycin, teicoplanin, and linezolid [62]. Regardless of MRSA subset, telavancin had MIC90 and MIC100 results of 0.06 and 0.12 μg/mL, corresponding to a susceptibility of 100 % [63]. Telavancin received approval from the FDA for the treatment of cSSSI. Results from phase 2 and 3 clinical trials demonstrated similar efficacy and tolerability compared to standard anti-staphylococcal beta-lactams and vancomycin [64–67]. The overall results of the two phase

3 studies, including a total of 40 % documented MRSA cSSSI, were analyzed [68]. Cure rates were 91 % for telavancin and 90 % for vancomycin among patients with major abscesses, 87 % and 88 % for telavancin and vancomycin-treated patients, respectively, in infective cellulitis and 85 % in the telavancin group and 86 % in the vancomycin group in patients with wound infections. Cure rates for each type of cSSSI in patients infected with MRSA were similar between the treatment arms and among patients infected with Panton-Valentine leucocidin (PVL)-positive MRSA. Telavancin has also shown good penetration in the alveolar macrophages, and unlike daptomycin, its activity is not affected by pulmonary surfactant [62]. Telavancin demonstrated non-inferiority compared to vancomycin for the treatment of HAP, including HAP due to MRSA [69, 70]. Nevertheless, in patients with pre-existing renal impairment (CrCl<50 mL/min), telavancin presented an increased mortality compared to vancomycin. Based on the results of the clinical trials, telavancin was approved by EMA for the treatment of adult with HAP and VAP suspected or known to be caused by MRSA only when other alternatives are not suitable. Telavancin use has been related to the potential elevation of serum creatinine. Otherwise, it displays a favorable safety profile, with gastrointestinal discomfort being the most common side effect [71]. A phase 3 is ongoing to evaluate the efficacy of telavancin in *S. aureus* bacteremia [72].

Oritavancin is characterized by a rapid bactericidal activity against gram-positive bacteria, including resistant MRSA, methicillin-resistant CoNS, and VRE isolates [73]. No resistance to oritavancin has been observed among *S. aureus* strains including VISA, but VAN-A and VAN-B strains of *Enterococci* with reduced susceptibility to oritavancin have been obtained in vitro. Its concentration-dependent activity and long half-life (393±73.5 h) allow for single-dose treatment. Furthermore, oritavancin does not require dosage adjustment for renal or mild to moderate hepatic dysfunction. The results of a randomized, double-blind trial in over 1000 adults with ABSSSIs receiving either a single intravenous 1200-mg dose of oritavancin or 7–10 days of vancomycin have been recently published [74]. Clinical cure and proportion of patients with at least 20 % reduction in lesion area were 83 vs 81 % and 85.9 vs 85.3 % for oritavancin vs vancomycin, respectively. The efficacy by pathogen, including MRSA, and the frequency of adverse events were also similar between treatment groups [73]. In 2014, the FDA approved oritavancin for the treatment of ABSSSIs due to MSSA, MRSA, *Streptococcus* spp,. and *E. faecalis*.

Dalbavancin

Dalbavancin has shown in vitro activity against MSSA, MRSA, VISA, meticillin-resistant *S. epidermidis* (MRSE) and *Enterococci*, although poor activity was demonatrated toward VanA-type *Enterococci* and VRSA [75–77]. Due to its long half-life (range, 147 to 258 h), the standard dose of dalbavancin is 1000 mg once a week [78]. Two randomized phase 3 studies showed non-inferiority of dalbavancin compared to vancomycin and linezolid in ABSSTI [79, 80]. A pooled analysis of the trials showed an early clinical response in 80 % of patients in both dalbavancin and vancomycin–linezolid groups. For patients infected with MRSA, clinical success was 91 % for patients treated with dalbavancin and 94 % of those treated with vancomycin–linezolid. Adverse events were less frequent in the dalbavancin group compared to comparators and included nausea, diarrhea, and pruritus [79].

In 2014, the FDA approved dalbavancin for treatment of adults with skin infections, including those caused by MRSA.

Oxazolidinones

Oxazolidinone antibiotics are a relatively new class of synthetic antibiotics with activity against a broad spectrum of gram-positive pathogens including MRSA and VRE. The first member of this new class to be commercialized, linezolid, was approved in 2000, and it is nowadays widely used in clinical practice for the treatment of severe gram-positive infections. Linezolid is characterized by excellent oral bioavailability and tissue penetration in bone, lung, and cerebrospinal fluid. New oxazolidinones with potent activity toward MDR gram-positive pathogens have been recently developed.

Tedizolid phosphate (TR-701) has been studied for the treatment of infections caused by MDR gram-positive bacteria, including strains showing linezolid, vancomycin, or daptomycin resistance [81]. Similarly to linezolid, tedizolid can be administered both orally and intravenously and has shown optimal tissue penetration, but its in vitro efficacy against *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp. is superior than linezolid. Compared to linezolid, tedizolid can be admnistered once daily and displays a better safety profile. No hematological side effects were reported at the therapeutic dose of 200 mg [82]. Furthermore, tedizolid has low potential for interactions with serotonergic drugs since it does not inhibit the monoamine oxidase pathway [82]. Overall rates of related adverse effects were similar to linezolid, with nausea being the most commonly reported adverse effect associated with tedizolid use in 16 % of patients. Tedizolid has been compared with linezolid in a phase 3 study for the treatment of ABSSTI. In this indication, a short, 6-day course of tedizolid was as effective as a 10-day course of linezolid with 85 and 83 % of the patients achieving early clinical response, respectively [83]. In 2014, tedizolid received FDA approval for the use in ABSSSI. Studies

investigating the potential role of tedizolid in the treatment of pneumonia and bacteremia have been planned.

Radezolid (RX-1741) is characterized by an excellent activity toward linezolid susceptible and resistant gram-positive bacteria, as well as certain gram-negative bacteria commonly found in CAP. Radezolid showed higher efficacy than linezolid against *S. pneumoniae* and *S. pyogenes*. MIC_{90} values ranged from 1 to 4 μg/mL for *Staphylococci* and from 0.5 to 1 μg/mL for *Enterococci* [84]. Among gram-negatives, radezolid was active against *H. influenzae* and *Moraxella catarrhalis*, with MIC_{90} of 1 and 0.5 μg/mL, respectively [85]. Radezolid has succesfully completed two phase 2 clinical trials. One trial was for uncomplicated SSSI in comparison with linezolid and the other clinical trial was for CAP [86, 87]. Phase 3 studies to further assess its tolerability and efficacy are awaited [88].

Quinolones

Quinolones were introduced into clinical practice with nalidixic acid in 1962. Since then, new molecules have been synthetized and widely used after the addition of a fluorine atom. Fluoroquinolones have a unique mechanism of action targeting two enzymes in DNA replication (i.e., DNA gyrase and topoisomerase IV) and show a good tissue penetration [89]. An activity mainly against gram-negative pathogens was displayed by the fluoroquinolones that were initially used, such as norfloxacin, ciprofloxacin, and ofloxacin [90]. To meet the target of efficacy toward gram-positive pathogens, new compounds such as moxifloxacin and gatifloxacin were then developed and widely used in CAP and HAP. Quinolones have shown an overall good safety profile and are currently used in RTIs, UTIs, SSSI, and IAIs [90–92]. Starting from the mid-1990s, the resistance to fluoroquinolones began to increase in almost all gram-positive and gram-negative species. Recent surveillance studies demonstrated a continued increase in the resistance rates, preventing their use in certain clinical indications [93]. New molecules in this class have been developed to be active against MDR bacteria and to provide a low potential for developing bacterial resistance.

Delafloxacin has a chemical structure that differs from other fluoroquinolones since it lacks a strongly basic group at the C-7 position, resulting in weak acidity. This feature enhances its antibacterial potency in environments with reduced pH, such as the urinary tract during infections and the phagolysosomes where the MICs of delafloxacin are reduced [94]. Various in vitro studies have supported delafloxacin low potential for the selection of resistances due to a dual mechanism of inhibition of DNA targets (i.e., gyrase and topoisomerase IV), supporting its potential use in empirical therapy [95]. Delafloxacin has shown potent antibacterial activity against quinolone susceptible and resistant strains of MRSA and against gram-negative MDR isolates such as *K. pneumoniae* and *E. coli* [95–97]. Furthermore, delafloxacin demonstrated potent activity against resistant strains of *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and against *Legionella* thus representing a valid choice for the treatment of CAP and HAP. Furthermore, delafloxacin can be administered both IV and orally, this supporting its role in sequential therapy. Delafloxacin showed comparable efficacy to tigecycline in the treatment of cSSSI including *S. aureus* (85 % of cases with approximately 70 % of MRSA strains) [74]. Delafloxacin's MIC_{90} against all MRSA, including quinolone-resistant MRSA strains, was 0.06 μg/mL. Another phase 2 trial compared the efficacy of IV formulations of delafloxacin (300 mg twice daily), linezolid, and vancomycin in 256 adults with SSSI. Success rates for delafloxacin, linezolid, and vancomycin were 74.4, 73.3, and 68.4 %, respectively. A reduction of over 20 % of erythema was more common in delafloxacin-treated patients compared to vancomycin [98]. Delafloxacin is currently evaluated in two phase 3 studies for the treatment of ABSSSI caused by gram-positive (including MRSA) and gram-negative bacteria [99, 100].

Nemonoxacin (TG-873870) is a novel, non-fluorinated quinolone characterized by an excellent activity against pathogens responsible for CAP. Since three different mutations are required in resistance determining regions, nemonoxacin has a low predisposition for selecting resistance [101]. Nemonoxacin has a half-life of more than 10 h. Higher efficacy compared with levofloxacin has been demonstrated against gram-positive bacteria including ciprofloxacin-resistant MRSA, levofloxacin-resistant *S. pneumoniae* and VRE, and gram-negative pathogens [102]. Similarly to moxafloxacin, reduced activity has been shown toward *P. aeruginosa*. Phase 2 and phase 3 studies of oral nemonoxacin (500 or 750 mg once daily) and phase 2 studies of IV nemonoxacin have been completed in patients with CAP demonstrating its efficacy and safety compared to levofloxacin [103, 104]. A phase 3 study of IV nemonoxacin in the treatment of CAP is currently ongoing [105].

Zabofloxacin (DW-224a) is a novel fluoroquinolone that showed higher activity compared to ciprofloxacin, moxifloxacin, and gemifloxacin against gram-positive strains, including MRSA, *S. pyogenes*, and *E. faecalis*. Zabofloxacin has shown efficacy against pathogens involved in CAP and COPD exacerbation such as *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* [106]. Similarly to other new molecules of this class, zabofloxacin displays a low potential for the selection of resistances due to a double mechanism of binding to the DNA–enzyme complex. No adverse effects on the central nervous system, cardiovascular system and respiratory system have been shown, although a QT interval prolongation has been reported [107]. In a phase 2 clinical trial, zabofloxacin administered 400 mg orally

displayed the same clinical and microbiological results as moxifloxacin in patients with mild-to-moderate CAP [108]. The study comparing zabafloxacin with levofloxacin in the treatment of CAP was terminated for financial reasons [109].

Finafloxacin (BAY35) is characterized by lower MIC at acidic pH against *E. coli*, *K. pneumoniae*, MRSA, and *P. aeruginosa* compared to levofloxacin and ciprofloxacin. For this reason, finafloxacin can be used to treat infections located within the urinary tract, gastric mucosa, or skin where the pH is lower [110]. Finafloxacin has also shown activity toward ciprofloxacin-resistant strains of *A. baumannii* [111]. Compared to other fluoroquinolones, finafloxacin did not show electrocardiogram changes or neurotoxicity during safety studies. A phase 2 study has been completed showing comparable efficacy finafloxacin administered 300 mg bid versus ciprofloxacin 250 mg bid in uncomplicated UTIs [112]. A phase 2 clinical trial is ongoing comparing IV and oral finafloxacin (800 mg once daily) with ciprofloxacin (400 mg bid IV or 500 mg bid orally) in cUTI and acute pielonephritis [113].

Compound named JNJ-Q2 has a dual mechanism of action on DNA enzymes similarly to other new molecules of this group. Furthermore, its activity does not seem affected by efflux pumps. JNJ-Q2 displays good activity against MRSA (MIC50 values 0.12 μg/mL); toward *S. pneumoniae*, it was 16 times and 128 times more potent than moxifloxacin and levofloxacin, respectively. Good activity was also demonstrated against *H. influenzae*, *M. catarrhalis*, and *N. gonorrhoeae* [114]. A phase 2 clinical trial in SSTI compared with linezolid was successfully completed while a trial in CAP was suspended because the number of participants recruited was not sufficient [115, 116].

Other new quinolones include WCK771, that has high activity against MRSA and *S. pneumoniae*, and two topic compounds, ozenoxacin and besifloxacin [117]. Ozenoxacin has excellent activity toward gram-positive pathogens and has been studied to reduce the time of treatment of cSSSI [118]. Besifloxacin is a topical ophthalmic fluoroquinolone, approved by the FDA in 2009 to treat bacterial conjunctivitis. Besifloxacin is active against *S. aureus*, *S. pneumoniae*, *H. influenzae*, and VRE [119].

Table 1 Clinical indications of new antibiotics and FDA status

Antimicrobial class	Molecule	Clinical indication	Development status
Cephalosporin	Ceftaroline	SSSI, CAP	FDA approval (2010)
	Ceftobiprole	SSTI, HAP, hospitalized CAP	Phase 3*
Carbapenem	Tebipenem pivoxil	RTIs	Phase 3**
	Panipenem metamipron	RTIs, UTIs	Phase 3
	Doripenem	UTIs, IAIs, HAP, VAP	FDA approval (2007)
	Biapenem	RTIs, UTIs	Phase 2
	Tomopenem	SSSI and HAP	Phase 2
	Razupenem	SSSI	Phase 2
Beta-lactam+	Ceftozolane/tazobactam	UTIs, IAIs, HAP, VAP	Phase 3
Beta-lactamase inhibitor	Ceftazidime/avibactam	cIAIs, cUTIs, HAP and VAP	Phase 3
Glycopeptide	Telavancin	cSSTI, HAP, VAP	FDA approval (2013)
	Oritavancin	SSSI	FDA approval (2014)
	Dalbavancin	SSSI	FDA approval (2014)
Oxazolidinone	Tedizolid phosphate	SSSI	FDA approval (2014)
	Radezolid	CAP, SSSI	Phase 2
Quinolone	Delafloxacin	SSSI	Phase 3
	Nemonoxacin	CAP	Phase 3
	Zabofloxacin	CAP	Phase 2
	Finafloxacin	CAP	Phase 2
	JNJ-Q2	UTIs	Phase 2
	WCK771	SSSI	Phase 2
Aminoglycoside	Plazomicin	IAIs and UTIs	Phase 3
Tetracycline	Eravacycline	IAIs and UTIs	Phase 2
	Omadacycline	SSSTI	Phase 2

*Approved for clinical use in Canada and Switzerland

**Approved for clinical use in Korea, Japan, and China

Aminoglycosides

The aminoglycosides are antibiotics mainly prescribed alone or in combination with other molecules (e.g., beta-lactams or quinolones) for the treatment of infections caused by aerobic gram-negative bacilli. Although resistance to this class has been increasing in the past years, the emergence of strains resistant to molecules such as gentamycin and amikacin is less common compared to other antimicrobials.

Plazomicin (ACHN-490) is a new aminoglycoside characterized by a dose-depending activity against both gram-positive and gram-negative pathogens [120]. In vitro synergism was shown with daptomycin and ceftobiprole against MRSA and VISA and with doripenem, imipenem, piperacillin/tazobactam, and cefepime against *P. aeruginosa* [121]. A phase 2 study showed comparable efficacy to levofloxacin in patients with cUTI and acute pielonephritis [122]. A phase 3 clinical trial for the treatment of patients with BSI or HAI due to carbapenem-resistant *Enterobacteriaceae* comparing plazomicin to colistin in association with a second antibiotic (e.g., tigecycline or meropenem) is currently ongoing [123].

Tetracyclines

Tetracyclines are a group of broad-spectrum antibiotics whose use in clinical practice has been reduced due to the development of bacterial resistance. Doxycycline and minocycline are nowadays used in certain indications. Tigecycline is the defining member of a new class of tetracyclines known as glycylcyclines, which greatly extend the spectrum including tetracycline-resistant microorganisms.

Eravacycline is a novel, broad-spectrum fluorocycline developed for the treatment of infections caused by tetracycline-resistant bacteria. Eravacycline is not subject to mechanisms conferring specific resistance to other tetracycline derivatives such as efflux pumps and ribosomal protection proteins [124]. Eravacycline has shown potent, broad-spectrum gram-positive and gram-negative antibacterial effect exhibiting activity against MRSA, VRE, and *Enterobacteriaceae* expressing resistance genes from multiple classes of ESBL or carbapenemases [125, 126]. Compared with tigecycline, eravacycline demonstrated lower MIC toward difficult-to-treat gram-negative pathogens and, similarly to tigecycline, has no activity against *P. aeruginosa* [126]. Eravacycline has been studied for both IV and oral administration and is promising for the treatment of cIAI. In fact, its wide spectrum of

Table 2 Activity of new antibiotics against MRSA and ESBL and carbapenemases-producing gram-negative pathogens

Drug	Antibiotic class	Spectrum	MRSA	Carbapenemases
Biapenem	Carbapenem	Gram-negative and gram-positive	−	−
Ceftaroline	Cephalosporin	Gram-positive	+	−
Ceftazidime/avibactam	Beta-lactam+beta-lactamase inhibitor	MDR gram-negative (no metallo-beta-lactamases)	−	+/−
Ceftobiprole	Cephalosporin	Gram-positive	+	−
Ceftozolane/tazobactam	Beta-lactam+beta-lactamase inhibitor	Gram-negative	−	−
Dalbavancin	Glycopeptide	MDR gram-positive	+	−
Delafloxacin	Quinolone	Gram-negative and gram-positive	+	−
Doripenem	Carbapenem	Gram-negative	−	−
Eravacycline	Tetracycline	Gram-negative (no Pseudomonas)	+	+
JNJ-Q2	Quinolone	Gram-positive	+	−
MK-7655	Beta-lactamase inhibitor	Gram-negative	−	+
Nemonoxacin	Quinolone	Gram-positive and gram-negative	+	−
Omadacycline	Tetracycline	Gram-positive and gram-negative	+	+
Oritavancin	Glycopeptide	MDR gram-positive	+	−
Panipenem	Carbapenem	Gram-negative and gram-positive	−	
Plazomicin	Aminoglycoside	MDR gram-negative including metallo-beta-lactamase	+	+
Radezolid	Oxalidinone	MDR gram-positive	+	−
Razupenem	Carbapenem	Gram-negative and gram-positive	+	−
Tebipenem	Carbapenem	Gram-negative and gram-positive	−	−
Telavancin	Glycopeptide	MDR gram-positive	+	−
Telizolid	Oxalidinone	MDR gram-positive	+	−
Tomopenem	Carbapenem	Gram-positive and gram-negative	+	−

activity includes pathogens from the enteric tract that are frequently the cause of peritonitis and abdominal abscesses. One prospective, randomized, double-blind, phase 2 study evaluating the safety and efficacy of eravacycline dosed once or twice daily versus ertapenem in cIAI has been completed. The results demonstrated clinical cure rates above 90 %, including infections caused by ESBL-producing, levofloxacin, and ertapenem-resistant organisms [127]. This study also displayed good tolerability for eravacycline when compared with ertapenem. Phase 3 clinical trials are planned to further evaluate its efficacy for the treatment of cIAIs and cUTIs.

Omadacycline (PTK796) is a semisynthetic aminomethylcycline with in vitro activity against both gram-positive and gram-negative bacteria. It presents activity against MSSA, MRSA, VRE, *S. pneumonia*, *K. pneumoniae*, *Proteus* spp., *Providencia* spp., *Morganella morganii*, and *Bacteroides fragilis* [128]. In a phase 2 study in SSSI, the efficacy of omadacycline administered 100 mg once daily IV and subsequently 200 mg oral step-down was comparable to linezolid [129]. A phase 3 study in ABSSSI has been suspended in order to comply with the new FDA guidance on cSSTI trials.

Tables 1 and 2 summarize the indications, the development status of the new drugs, and their spectrum of microbiological activity.

Conclusions

The spread of MDR pathogens is causing an unprecedented public health crisis. The incidence of MDR bacteria continues to increase despite the efforts of implementing the antimicrobial stewardship and stringent measures of infection control in hospitals. Gram-negative bacteria such as carbapenemase-producing *Enterobacteriaceae*, XDR *A. baumannii*, and *P. aeruginosa* present very limited therapeutic options and remain a serious problem.

Among agents that are potentially active against gram-negatives are ceftozolane/tazobactam, new carbapenems, the combination of avibactam with beta-lactamsinhibitors and plazomicin. Nevertheless, although fifth generation cephalosporins and new carbapenems have acquired activity against MRSA, they offer few advantages against difficult-to-treat gram-negatives. Associations of beta-lactams with beta-lactamase inhibitors seem promising against MDR pathogens, but their real clinical utility will be known only after results of large clinical trials are available.

Less critical appears the situation toward MDR gram-positive pathogens. New glycopeptides and oxazolidinones are highly efficient against MRSA and VRE, and new cephalosporins and carbapenems also display activity toward MDR gram-positive bacteria.

Since 2010, when the IDSA established its initiative for developing ten new antibiotics by 2020, five new antibiotics have been approved (mainly targeting gram-positive bacteria) and eight new antibiotics targeting MDR gram-negative bacilli are in phase 2 or 3 trials. A relevant number of promising antibiotics is currently in development and has reached a preclinical stage or is involved in phase 1 trials. Thus, regulatory approvals are crucial over the next 5 years to achieve the possibility to use new antibiotics to face the growing threat of multidrug resistance.

Conflicts of interest None.

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