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Review

New agents for the treatment of infections with Gram-negative bacteria: restoring the miracle or false dawn?

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ABSTRACT

Background: Antibiotic resistance in Gram-negative resistance has developed without a commensurate response in the successful development of antibiotic agents, though recent progress has been made.
Aims: This review aims to provide a summary of the existing evidence on efficacy, spectrum of activity and the development of resistance of new agents that have been licensed or have completed advanced clinical trials and that possess activity against resistant Gram-negative organisms.
Sources: A review of the published literature via MEDLINE database was performed. Relevant clinical trials were identified with the aid of the clinicaltrials.gov registry. Further data were ascertained from review of abstracts from recent international meetings and pharmaceutical companies.
Content: Data on the mechanism of action, microbiological spectrum, clinical efficacy and development of resistance are reported for new agents that have activity against Gram-negative organisms. This includes the β-lactam/β-lactamase inhibitor combinations ceftazidime/avibactam, ceftolozane/tazobactam, imipenem/cilastatin/relebactam, meropenem/vaborbactam and aztreonam/avibactam; cefiderocol, a siderophore cephalosporin; plazomicin and eravacycline.
Implications: The development of new agents with activity against multidrug-resistant Gram-negative pathogens has provided important therapeutic options for clinicians. Polymyxins appear to have been supplanted by new agents as first-line therapy for *Klebsiella pneumoniae* carbapenemase producers. Cefiderocol and ceftazidime/avibactam/aztreonam are promising options for metallo-β-lactamase producers, and cefiderocol and ceftolozane/tazobactam for multiply resistant *Pseudomonas aeruginosa*, but definitive data showing clinical efficacy is as yet lacking. Reports of the development of resistance early after the release and use of new agents is of concern. Orally administered options and agents active effective against *Acinetobacter baumannii* are under-represented in clinical development. **H. Wright, Clin Microbiol Infect 2017;23:704**

The advent of antibiotics in the middle of the twentieth century revolutionized medical care. The increasing threat of antibiotic resistance poses a significant danger to the miraculous advances that effective antibiotic therapy has wrought. Serious infections caused by Gram-negative bacteria are becoming an increasingly difficult clinical challenge. The emergence of organisms producing extended-spectrum β-lactamases (ESBLs) has become a major public health concern globally [1]. Resistance to broad-spectrum antibiotics such as third-generation cephalosporins (e.g. ceftazidime and ceftriaxone) in *Escherichia coli* and *Klebsiella pneumoniae* is widespread [2]. A concomitant increase in the use of carbapenems has increased the selection pressure for carbapenem resistance [3]. Increasing rates of carbapenem-resistant *Enterobacteriaceae* (CRE) are seen in the nosocomial setting and beyond with invasive infections from these organisms resulting in a high mortality [4]. Multidrug-resistant (MDR) isolates from common nosocomial pathogens *Pseudomonas aeruginosa* and *Acinetobacter* spp. frequently harbour multiple resistance mechanisms and there are few available therapeutic options to combat them. The threat of the development of pan-resistance, with isolates non-susceptible to all therapeutic options available,

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has been realized [5,6], with the potential to cause significant outbreaks [7].

With the development of new agents languishing, a re-emergence of older, abandoned antibiotics was seen in response. Polymyxins, discarded because of toxicity concerns, are now seen as a 'last line of defence' against many Gram-negative bacteria and have been reclassified by the WHO as critically important for human medicine [8]. Polymyxin use in the setting of CRE infection, often as a component of combination therapy, is common in clinical practice and now the subject of clinical trials [9,10]. Dosing and pharmacokinetic optimization to limit toxicity and maximize efficacy has been a focus of research [11]. Fosfomycin trometamol, most commonly used in uncomplicated urinary tract infections, and intravenous fosfomycin for more serious infections, have become the subject of further investigation, though the development of resistance to this agent is problematic [12,13].

The public health need has led to a response from governments. In the USA the GAIN act (Generating Antibiotic Incentives Now) provides economic incentives and a streamlined review process for new antibacterial agents. The Innovative Medicines Initiative (IMI) ND4BB (New Drugs for Bad Bugs) by the European Union provided funding to combat antimicrobial resistance, including the formation of public–private partnerships to develop the anti-infective drug pipeline. Significant progress has been achieved with two agents (ceftolozane/tazobactam and ceftazidime/avibactam) receiving US Food and Drug Administration and European Medicines Agency approval, in 2015, and over 30 molecules in clinical development [14]. Most of these agents belong to existing classes of antibiotics, with new β-lactamase inhibitors combined with established β-lactams, and newly synthesized tetracycline and aminoglycosides.

This review will examine some of the new agents that have been recently approved or that are in clinical development that are active against resistant Gram-negative organisms, including their mechanism of action and the risk of developing resistance. Results from clinical trials have been summarized in Tables 1 and 2.

Existing β-lactam antibiotics paired with new β-lactamase inhibitors

Significant progress was made in the development of new β-lactamase inhibitors active against Ambler class A and C β-lactamases including activity against *Klebsiella pneumoniae* carbapenemase (KPC) -producing organisms. Some of these new β-lactamase inhibitors include avibactam, relebactam, vaborbactam and AAI101. Class B β-lactamases have proven to be a much more significant hurdle, although early reports suggest that a novel β-lactamase inhibitor with high affinity to PBP-2, zidebactam, in combination with cefepime, may be active against some strains of bacteria producing class B enzymes [15]. As mentioned below, aztreonam in combination with avibactam, may also have considerable activity against bacteria producing class B enzymes.

Ceftazidime/avibactam

At the time of writing, ceftazidime/avibactam is the only combination with a new β-lactamase inhibitor that is US Food and Drug Administration and European Medicines Agency approved. It is a combination agent containing the semi-synthetic third-generation cephalosporin ceftazidime with the non-β-lactam, diazabicyclooctane β-lactamase inhibitor avibactam. Avibactam is a potent inhibitor of many β-lactamases, protecting ceftazidime from hydrolysis by Gram-negative organisms producing Ambler class A and C β-lactamases and some Ambler class D enzymes [16]. Unlike other

Table 1
Recent trials in complicated urinary tract infections and outcomes

Study	Design	Drug	Comparator	Duration of therapy	End point	Time end point assessed	Outcome drug versus Comparator
EPIC cUTI	Phase III Non-Inferiority	Plazomicin 15 mg/kg q24h	Meropenem 1 g q8h	4–7 days IV, option to change to PO levofloxacin to complete 7–10 days total treatment	Composite end point clinical cure and microbiological eradication mMITT TOC (FDA) Microbiological eradication TOC (EMA)	15–19 days after first dose	81.7% vs 70.1% 87.4% vs 72.1%
APEKs cUTI	Phase III Non-Inferiority	Cefiderocol 2g q8h	Imipenem-cilastatin 1 g/1 g q8h	7–14 days IV Mean duration 9 days	Composite end point clinical response and microbiological eradication mMITT TOC (FDA)	7 days after end of treatment	72.6% vs 54.6%
TANGO – 1	Phase III Non-Inferiority	Meropenem-vaborbactam 2 g/2 g q8h	Piperacillin-tazobactam 4.5 g q8h	5–10 days IV, option to change to PO levofloxacin after 5 days to complete 10 days total treatment	Clinical cure or improvement and microbiological eradication (FDA) Microbiological eradication mMITT TOC (EMA)	End of IV therapy (5 –14 days post first dose) 5–9 days post end of treatment	98.4% vs 94% 66.7% vs 57.7%
RECAPTURE	Phase III Non-Inferiority	Ceftazidime-avibactam 2.5 g q8h	Doripenem 500 mg q8h	10–14 days, option to change to PO antibiotics after 5 days	Composite end point clinical cure and microbiological eradication mMITT TOC (FDA) Microbiological eradication TOC (EMA)	21–25 days after randomization	71.2% vs 64.5% 77.4% vs 71%
ASPECT-cUTI	Phase III Non-Inferiority	Ceftolozane-tazobactam 1.5 g q8h	Levofloxacin 750 mg q24h	7 days	Composite end-point clinical cure and microbiological eradication mMITT TOC	5–9 days after end of treatment	76.9% vs 68.4%

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration;IV, intravenous; mMITT, microbiologically modified intention to treat; q24h, 24-hourly; TOC, test of cure.
From references [35], [50], [71], [84], [93].