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David L. Paterson

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REVIEW

Antibacterial agents active against Gram Negative Bacilli in phase I, II, or III clinical trials

David L. Paterson[a,b]

[a]ADVANCE-ID, Saw Swee Hock School of Public Health, National University of Singapore, Singapore; [b]Infectious Diseases Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

ABSTRACT

Introduction: Antimicrobial resistance is a major threat to modern healthcare, and it is often regarded that the antibiotic pipeline is 'dry.'

Areas covered: Antimicrobial agents active against Gram negative bacilli in Phase I, II, or III clinical trials were reviewed.

Expert Opinion: Nearly 50 antimicrobial agents (28 small molecules and 21 non-traditional antimicrobial agents) active against Gram-negative bacilli are currently in clinical trials. These have the potential to provide substantial improvements to the antimicrobial armamentarium, although it is known that 'leakage' from the pipeline occurs due to findings of toxicity during clinical trials. Significantly, a lack of funding for large phase III clinical trials is likely to prevent trials occurring for the indications most relevant to loss of life attributed to antimicrobial resistance such as ventilator-associated pneumonia. Non-traditional antimicrobial agents face issues in clinical development such as a lack of readily available and reliable susceptibility tests, and the potential need for superiority trials rather than non-inferiority trials. Most importantly, concrete plans must be made during clinical development for access of new antimicrobial agents to areas of the world where resistance to Gram negative bacilli is most frequent.

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1. Introduction

Antibiotic resistance in Gram negative bacilli is a major public health problem. Of the seven leading bacterial causes of death in 2019, five were Gram negative bacilli. Three of these are Enterobacterales (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp.), while two are non-fermentative Gram negative bacilli (*Pseudomonas aeruginosa*, *Acinetobacter baumannii*) [1,2]. For many years, carbapenems were the treatment of choice for serious infections for each of these pathogens [3]. However, carbapenem resistance has now become a significant issue worldwide (but most substantially in Asia, Latin America, the Middle East, and Eastern/Southern Europe) [4]. In the last 10 years, eight new therapies with activity against at least some carbapenem-resistant organisms have been approved by the United States Food and Drug Administration (FDA) [5]. These have bolstered the armamentarium against KPC-producing Enterobacterales (ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, and cefiderocol), carbapenem-resistant *Pseudomonas aeruginosa* (ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam, and cefiderocol), and carbapenem-resistant *Acinetobacter baumannii* (sulbactam-durlobactam, cefiderocol, and eravacycline). With the exception of cefiderocol [6], these newly approved antibiotics do not cover metallo-beta-lactamase (MBL) producing organisms (such as NDM producers), although FDA approval has been sought for two new options against these organisms (cefepime-taniborbactam and aztreonam-avibactam).

Despite this progress, Gram negative bacilli have emerged with resistance to each of these new options. Given the dominance of beta-lactam antibiotics or combinations of beta-lactams with beta-lactamase inhibitors, it is not surprising that newer mechanisms of resistance involve target site alteration or resistance to inhibition by newer beta-lactamase inhibitors. One of the most important emerging mechanisms of resistance is alteration of penicillin-binding proteins (PBPs), which are the target site for beta-lactam antibiotics. Amino acid insertions in PBP-3 in *E. coli* reduce the affinity of aztreonam, cephalosporins, and carbapenems, thereby contributing to resistance to aztreonam-avibactam, cefiderocol, and cefepime-taniborbactam [7–9]. Changes in the PBPs of *A. baumannii* can compromise sulbactam, while durlobactam, avibactam, vaborbactam, and relebactam hydrolyze MBLs poorly [10]. Mutations in genes encoding NDM beta-lactamases, which lead to resistance to cefepime-taniborbactam, have already been described [11].

There is clearly a need for new antibacterial agents active against Gram negative bacilli. With the help of 'push' incentives provided by organizations such as BARDA and CARB-X, a variety of new antibacterial agents are now in clinical development (Table 1). While many of these new antibacterial agents are 'traditional' small molecules, others are 'non-traditional' comprising phages, lysins, peptides, anti-virulence compounds, or antibody-based therapies [12]. The purpose of this review is to scope the field of new antibacterial agents in Phase I, II, or III clinical development and to provide opinion as to the most promising

CONTACT David L. Paterson david.antibiotics@gmail.com ADVANCE-ID, Saw Swee Hock School of Public Health, National University of Singapore, 10th Floor, Tahir Foundation Building, Science Drive 2, Singapore

Article highlights

- Carbapenem-resistant Gram negative organisms such as *Acinetobacter baumannii*, *Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* are responsible for substantial mortality.
- 28 small molecules active against Gram negative bacilli are currently in clinical trials. Nearly half of these are new beta-lactamase inhibitors combined with existing beta-lactam antibiotics.
- 21 non-traditional antimicrobial agents active against Gram negative bacilli are currently in clinical trials. These include phages, peptides, anti-virulence strategies, and antibody-based therapies.
- These non-traditional antimicrobial agents face difficulty in clinical development due to a lack of standardized susceptibility tests and the need for demonstration of superiority if they are an adjunct to standard of care antibiotics.
- Leakage from the clinical development pipeline is always to be expected due to toxicity and lack of investment returns.

entities. Potential barriers to success of clinical development and regulatory approval will also be discussed. Antimicrobial agents aimed at *Neisseria gonorrhoeae*, *Helicobacter pylori,* and *Haemophilus influenzae* will not be discussed in this review.

2. Small molecule antibacterial agents with activity against gram negative bacilli

2.1. Intravenously administered beta-lactamase inhibitors combined with beta-lactam antibiotics

2.1.1. Nacubactam-cefepime and nacubactam-aztreonam (Meiji Seika Pharma)

Nacubactam (OP0595) was discovered separately by Meiji Seika Pharma and Fedora Pharmaceuticals [13]. It is a diazabicyclooctane molecule which has antimicrobial activity in three ways: (a) it inhibits class A and C beta-lactamases almost as strongly as avibactam, (b) it has antibiotic activity via its strong binding to the PBP-2 of Enterobacterales, and (c) it is an 'enhancer' of the activity of beta-lactam antibiotics (piperacillin, cefepime, and aztreonam) that primarily target PBP-3 [13]. The presence of nacubactam at a fixed concentration lowered the MIC of these antibiotics by 4- to 32-fold but did not lower the MIC of meropenem [13]. Most likely this is because of the concurrent attack on different PBPs by nacubactam and the companion beta-lactam antibiotic [14]. Nacubactam does not inhibit MBLs [13]. However, aztreonam-

Table 1. Small molecule antibacterial agents with activity against Gram negative bacilli currently in, or recently completed, phase I, II, or III clinical trials.

Antibiotic	Company	Phase of Clinical Trial*	Key Characteristic or Differentiating feature
ANT3310, plus meropenem	Antabio	I	Class A, C and D beta-lactamase inhibitor, including the OXA-23 carbapenemases produced by Acinetobacter
APC148	AdjuTec Pharma	I	MBL inhibitor
APL-2301	Asieris	I	Dual mode Anti-Acinetobacter agent (outer membrane permeability and NDM inhibition)
Apramycin	Juvabis	I	Aminoglycoside that is not susceptible to most existing resistance mechanisms
Avibactam tomilopil plus ceftibuten	Pfizer	I	Orally administered class A, C and D beta-lactamase inhibitor
BRII-693	Brii (previously QPex)	I	Next generation polymyxin
BWC0977	BugWorks	I	Broad spectrum; potential for both IV and PO administration
KSP1007, plus meropenem	Sumitovant	I	Class A, B, C and D beta-lactamase inhibitor
Ledorbactam, plus orally administered beta-lactam	QPex	I	Orally administered beta-lactamase inhibitor
MRX-8	MicuRx	I	Next generation polymyxin
RECCE 327	Recce	I	Novel synthetic polymer
RG6319	Genentech	I	LepB inhibitor (*E. coli*)
SPR206	Spero	I	Next generation polymyxin
Xeruborbactam, plus meropenem (or cefiderocol)	Qpex Biopharma, Shionogi	I	Class A, B, C and D beta-lactamase inhibitor
Xeruborbactam prodrug, plus ceftibuten	Qpex Biopharma,Brii Biosciences, Shionogi	I	Orally administered class A, B, C and D beta-lactamase inhibitor
Zidebactam, plus ertapenem	Wockhardt	I	Beta-lactamase inhibitor and potentiator of other antibiotics; once daily
Zosurabalpin	Roche	I	Macrocyclic peptide active against Acinetobacter
Benapenem	Sihuan	II	Carbapenem with once daily administration
BV100	BioVersys	II	Rifamycin with Anti-Acinetobacter action
FL058, plus meropenem	QiLu Pharmaceutical	II	Class A and C beta-lactamase inhibitor
Gallium citrate (AR-501)	Aridis	II	Inhaled therapy for *P. aeruginosa* infected cystic fibrosis patients
Funobactam, plus imipenem	Evopoint Biosciences	III	Class A, C and D beta-lactamase inhibitor, including the OXA-23 carbapenemases produced by Acinetobacter
Nacubactam, Plus cefepime	Meiji Seika Pharma	III	Beta-lactamase inhibitor and potentiator of other antibiotics
Nacubactam, Plus Aztreonam	Meiji Seika Pharma	III	Beta-lactamase inhibitor and potentiator of other antibiotics
Tazobactam, Plus Cefepime	Wockhardt	III	Combination of widely used beta-lactamase inhibitor with cefepime in order to enhance activity against ESBL producers
Tebipenem	Spero, GSK	III	Orally administered carbapenem
Zidebactam, plus cefepime	Wockhardt	III	Beta-lactamase inhibitor and potentiator of other antibiotics

nacubactam is active against MBL producing Enterobacterales in a similar fashion to aztreonam-avibactam [14]. However, even cefepime-nacubactam was active against 90% of the MBL-producing Enterobacterales in one evaluation. This likely represents both the antibiotic activity and the enhancer effect of nacubactam [14]. Similar findings were seen with OXA-48 producing strains. Nacubactam does not potentiate aztreonam or cefepime against OXA or MBL producing *A. baumannii* [14]. Nacubactam inhibits the activity of pseudomonal AmpC and potentiates aztreonam and cefepime against *P. aeruginosa* strains with derepressed AmpC. It does not potentiate against MBL-producing *P. aeruginosa* or fully beta-lactam susceptible control strains [14].

Nacubactam was evaluated in a single ascending dose Phase I study (NCT02134834), recruiting 30 healthy volunteers who received nacubactam and 10 who received placebo [15]. Subsequently, it was evaluated in a multiple ascending dose study (NCT02972255), alone and then in combination with meropenem. Intravenously administered nacubactam was generally well tolerated, with no dose-related laboratory abnormalities or adverse effects. Nacubactam pharmacokinetics was linear, and it was excreted largely unchanged into the urine. Coadministration of nacubactam with meropenem did not significantly alter the pharmacokinetics of either drug [15]. A Phase I study evaluating the intrapulmonary penetration of nacubactam in 21 healthy volunteers was completed in 2017 (NCT03182504). The participants in this study received a single intravenous infusion of nacubactam in combination with meropenem and then underwent a bronchoalveolar lavage. The results of this study were not published.

The Phase I program of nacubactam was conducted by Roche. Subsequently, two phase III studies have been commenced in 2023 under the auspices of Meiji Seika Pharma. A 600-patient, randomized, double-blind phase III trial of nacubactam-cefepime or nacubactam-aztreonam in comparison to imipenem-cilastatin has commenced in the treatment of complicated urinary tract infection (cUTI) or acute uncomplicated pyelonephritis (NCT05887908). The second phase III trial is a 150-patient, randomized, single-blind trial of nacubactam-cefepime or nacubactam-aztreonam in comparison to best available therapy for cUTI, acute uncomplicated pyelonephritis, hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), and complicated intra-abdominal infection (cIAI) due to CRE (NCT05905055).

2.1.2. Zidebactam-cefepime and zidebactam-ertapenem (wockhardt)

Zidebactam (WCK5107), like nacubactam, is a diazabicyclooctane molecule which provides antimicrobial activity via (a) beta-lactamase inhibition, (b) antibiotic activity via potent binding to PBP-2, and (c) enhancement of the activity of other antibiotics [16]. Zidebactam rapidly acylates class A and C beta-lactamases, including KPC [16]. Despite not inhibiting MBLs, zidebactam in combination with cefepime resulted in synergy in time-kill studies and *in vivo* efficacy against VIM or NDM producing *K. pneumoniae* strains [17]. Zidebactam appears to have strong binding to PBP-2 not just of Enterobacterales but also *P. aeruginosa* and *A. baumannii*. It is likely that multiple PBP binding (the 'enhancer effect') leads to synergy between zidebactam and cefepime against *P. aeruginosa* strains with multiple mechanisms of resistance, including MBLs [18–20]. Development of resistance of *P. aeruginosa* to zidebactam-cefepime can occur, but requires multiple simultaneous mutations and leads to loss of fitness and virulence [21]. While zidebactam does not inhibit OXA-23 produced by *A. baumannii*, it does have strong binding to the PBP-2 of *A. baumannii* [22]. Combinations of zidebactam with cefepime or sulbactam result in enhanced killing of *A. baumannii* [22].

Phase I studies of intravenous zidebactam (NCT02674347, NCT02707107, NCT03554304, and NCT03630094) have shown that the pharmacokinetics of zidebactam and cefepime are linear and that both antimicrobial agents have similar pharmacokinetic parameters. Both zidebactam and cefepime are primarily excreted unchanged in the urine. In a lung penetration study, healthy volunteers received 2 grams cefepime and 1 gram zidebactam as a 1-hour infusion, every 8 hours, for seven doses. Bronchoalveolar lavage was performed at varying times after the seventh dose. Epithelial lining fluid to plasma penetration ratios were 0.39 for cefepime and 0.38 for zidebactam. Alveolar macrophage to plasma ratios were 0.27 for cefepime and 0.10 for zidebactam [23]. The effect of renal impairment on pharmacokinetics and safety of zidebactam and cefepime has also been studied (NCT02942810). In renal impairment, zidebactam-cefepime was safe and well tolerated, with dose adjustments being necessary according to the degree of renal impairment [24]. A 528-patient, randomized, double-blind phase III trial of zidebactam-cefepime in comparison to meropenem has commenced in the treatment of cUTI or acute uncomplicated pyelonephritis (NCT04979806).

Zidebactam-cefepime has been provided for compassionate use for an 18-year-old man with bacteremia and necrotizing fasciitis due to NDM producing *P. aeruginosa* (resistant to carbapenems, ceftazidime-avibactam, ceftolozane-tazobactam, and colistin) [25]. The patient was successfully treated. Zidebactam-cefepime has also been for compassionate use of a 50-year-old woman from whom NDM-producing *P. aeruginosa* (resistant to carbapenems, ceftazidime-avibactam, ceftolozane-tazobactam, and imipenem-relebactam) was grown from both endotracheal aspirate and abdominal tissue. The use of zidebactam-cefepime was associated with a successful outcome [26].

Ertapenem is administered once daily, providing an opportunity for administration outside the hospital. In contrast to zidebactam, which binds to PBP-2 of Enterobacterales, ertapenem binds to PBP-3. While ertapenem is typically active against ESBL producer, zidebactam extends its activity against Enterobacterales with various combinations of porin loss and ESBL or AmpC activity. Furthermore, zidebactam-ertapenem is active against many carbapenemase producers [27]. Higher MICs were only seen with MBL producers or isolates which produced a combination of MBLs and OXA-48 [27]. In a neutropenic mouse model, human simulated doses of zidebactam-ertapenem were effective against KPC or OXA-48 producing *K. pneumoniae* [28].

In terms of clinical development, zidebactam-ertapenem has been evaluated in a Phase I study of 52 healthy volunteers in order to assess the safety, tolerability, and pharmacokinetics of this combination (NCT05645757). This study was completed in November 2023, and results are not yet available.

2.1.3. Xeruborbactam (QPex, Shionogi)

Xeruborbactam (QPX7728) is a cyclic boronate beta-lactamase inhibitor with activity against both serine beta-lactamases and MBLs [29]. Xeruborbactam also has direct antibacterial activity against some Gram negative bacilli [29,30]. Xeruborbactam has affinity to multiple PBPs (1a, 1b, 2, 3) of *E. coli* and *Klebsiella* [30]. Xeruborbactam enhances potency of meropenem, cefepime, ceftolozane, ceftriaxone, aztreonam, piperacillin, and ertapenem, against clinical isolates of *Enterobacterales* that produce various class A, class C, and class D β-lactamases and carbapenem-resistant *Enterobacterales*, including MBL-producing isolates [29].

Xeruborbactam was evaluated in a single ascending dose and multiple ascending dose Phase I study (NCT04380207). The study was completed in August 2022, but the results have not yet been published. An interaction study between xeruborbactam and an undisclosed intravenously administered beta-lactam antibiotic ('QPX2014') has also been performed (NCT05072444). With the acquisition of QPex by Shionogi, it is noteworthy that a xeruborbactam–cefiderocol combination (S-649228) is scheduled to commence Phase I trials in early 2024 [31].

2.1.4. ANT3310 plus meropenem (Antabio)

ANT3310 is a diazabicyclooctane with activity against class A, C, and D beta-lactamases including KPC and OXA-48 (frequently found to be responsible for carbapenem resistance in Enterobacterales) and the OXA-23, −24, −51, and −58 beta-lactamases (frequently associated with carbapenem resistance in *A. baumannii*) [32]. This broad-spectrum serine beta-lactamase inhibition is similar to durlobactam [33]. However, while durlobactam is combined with sulbactam for specific activity against carbapenem-resistant *A. baumannii* [34], ANT3310 is combined with meropenem to enable it to have activity against CRE (except strains producing MBLs), carbapenem-resistant *A. baumannii* and carbapenem-resistant *P. aeruginosa* [32,35,].

A Phase I trial of intravenously administered ANT3310 alone and in combination with meropenem, involving 72 healthy subjects, is expected to be completed in 2024 (NCT05905913).

2.1.5. Funobactam plus imipenem (evopoint)

Funobactam (XNW4107) is a diazabicyclooctane with activity against class A, C, and D beta-lactamases including KPC and OXA-48, and the OXA-23, -24 beta-lactamases frequently associated with carbapenem resistance in *A. baumannii* [36,37]. It therefore restores the activity of carbapenems against these serine carbapenemases producing organisms. In one evaluation of 15 strains, imipenem MICs in combination with funobactam decreased for all isolates with a range of reduction of >4-fold to >256-fold. A novel pharmacokinetic/pharmacodynamic index best describes the *in vivo* activity of funobactam plus imipenem [36].

Four phase I trials have been completed (NCT04482569, NCT04787562, NCT04802863, and NCT04801043). A 450 patient Phase III trial comparing funobactam/imipenem-cilastatin with relebactam/imipenem-cilastatin in adults with HABP or VABP commenced in July 2022 and is expected to be completed in 2025 (NCT05204563). This involves subjects in the United States, Israel, Spain, and France. The primary outcome measure is 14-day, all-cause mortality. A 780 patient Phase III trial comparing funobactam/imipenem-cilastatin with meropenem in adults with cUTI including acute pyelonephritis is expected to be completed in 2025 (NCT05204368).

2.1.6. KSP-1007 plus meropenem (sumitomo)

KSP-1007 is a bicyclic boronate beta-lactamase inhibitor, active against class A, B, C, and D beta-lactamases. A Phase I trial (NCT05226923) evaluating intravenous KSP-1007 alone, and in combination with meropenem, was completed with no SAEs observed [38].

2.1.7. FL058 plus meropenem [qilu pharmaceuticals]

There is no published information in the English language literature on the nature of FL058. Three Phase I trials were completed in 2020 and 2021 evaluating the safety, tolerability, and pharmacokinetics of intravenous FL058 alone (NCT05055687, NCT05058118) and in combination with meropenem (NCT05058105). A 150 patient Phase II double-blind RCT comparing FL-058 plus meropenem versus piperacillin-tazobactam for cUTI or acute pyelonephritis was completed in 2022 (NCT05060419). No results of these trials or further information are available about the progress of FL058.

2.1.8. Tazobactam plus cefepime (wockhardt)

This combination would be expected to have considerable activity against ESBL- and AmpC-producing bacteria [39].

A 1000 patient Phase III non-inferiority trial to evaluate the efficacy, safety, and tolerability of intravenously administered tazobactam-cefepime versus meropenem in adults with cUTI or acute pyelonephritis is expected to commence recruitment in early 2024 with completion in early 2026 (NCT03630081).

2.1.9. APC148 (AdjuTec pharma)

APC148 (formerly ZN148) is a selective zinc chelator which is an MBL inhibitor. *In vitro* and in animal models, APC148 was able to restore the activity of meropenem against NDM-producing strains [40].

Funding for Phase I trials has been gained, with these expected to commence early in 2024 [41].

2.2. Polymyxins

Colistin and polymyxin B generally have high rates of *in vitro* activity against carbapenem-resistant Gram-negative bacilli. However, their utility is compromised by toxicity, especially nephrotoxicity [42]. Three new polymyxins are progressing in clinical trials:

2.2.1. BRII-693 (Brii biosciences)

BRII-693 (formerly QPX9003 [QPex] and F365 [Monash University]) is a novel synthetic lipopeptide [43]. It was optimized for activity against carbapenem-resistant isolates of *P. aeruginosa*, *A. baumannii,* and *K. pneumoniae* and minimization of nephrotoxicity, acute toxicity, and lung surfactant binding [43]. In a large panel of more than 400 carbapenem-resistant isolates, the MIC_{50} of F365 was 0.5 mg/L and MIC_{90} was 1 mg/L. In mouse studies, there was no significant nephrotoxicity or acute toxicity associated with F365.

Significant killing of polymyxin resistant *P. aeruginosa* and *A. baumannii* was seen in a neutropenic mouse model of pneumonia. F365 had no significant binding to lung surfactant, whereas polymyxin B lost 87.5% of its lung activity due to binding to surfactant. Finally, in a primate model, renal tubular changes were only observed at the highest examined dose (whereas polymyxin B caused renal changes at dosing less than the maximum recommended human dose) [43].

A Phase I ascending single and multiple-dose study was completed in 104 healthy adults in July 2022 (NCT04808414). No nephrotoxicity was observed and no subjects discontinued the trial. Further development for HABP and VABP is expected.

2.2.2. SPR206 (Spero)

SPR206 is a novel polymyxin derivative developed to have improved antibacterial potency and reduced renal cytotoxicity compared to polymyxin B [44]. SPR206 acts by permeabilizing the outer membrane of Gram negative bacilli, as demonstrated in multiple genera [45]. An *in vitro* assessment against carbapenem- and tigecycline-resistant strains of Enterobacterales and *A. baumannii* and carbapenem-resistant *P. aeruginosa* showed lower MICs with SPR-206 than with colistin or polymyxin B. However, the *in vitro* activity against colistin-resistant strains was comparable to that of colistin [46]. SPR206 had excellent *in vivo* efficacy against carbapenem-resistant *A. baumannii* in mouse thigh and mouse pneumonia models [44].

The first Phase I trial to be performed was completed in 2019 and assessed the safety, tolerability, and pharmacokinetics of single and multiple intravenous doses of SPR206 in 94 healthy adults (NCT03792308). SPR206 was generally safe and generally well tolerated, with no evidence of nephrotoxicity in participants given 14 days of 100 mg q8h dosing (a regimen anticipated to exceed the requirements for clinical efficacy) [47]. A second Phase I study assessed intrapulmonary concentrations of SPR206 in healthy adults who received three 100 mg doses 8 hours apart, and who then underwent bronchoscopy (NCT04868292). Epithelial lining fluid to unbound plasma penetration ratios was 0.264, and alveolar macrophage to unbound plasma ratios were 0.328. Mean SPR206 concentrations in ELF achieved lung exposures above the MIC for target Gram-negative pathogens for the entire 8-h dosing interval [48]. Finally, a Phase I study was performed to assess safety, tolerability, and pharmacokinetics in adults with varying degrees of renal dysfunction (NCT04865393). Dose adjustment will likely be necessary in patients with renal dysfunction [49].

The National Institute of Allergy and Infectious Diseases has funded a Phase II 'proof of concept' trial, but the design and timeline of this is not yet available.

2.2.3. MRX-8 (MicuRx)

Compared to BRII-693 and SPR206 there is considerably less information in the public domain on MRX-8. It is a next-generation polymyxin that has near identical *in vitro* activity against carbapenem-resistant Enterobacterales, *A. baumannii* and *P. aeruginosa* to colistin and polymyxin B [50]. It is not active against polymyxin-resistant strains [50,51]. In mouse thigh infection and pneumonia models, MRX-8 was more active than polymyxin B when dosed to achieve similar free-drug exposures [52].

A Phase I study designed to assess the safety and tolerability of single and multiple intravenous doses of MRX-8 in healthy adults was completed in December 2021 (NCT04649541). A Phase I trial commenced in China in November 2022 [53]. The results of these studies and the subsequent clinical development plan have not been released.

2.3. Other broad-spectrum intravenously administered antibacterial agents

2.3.1. BWC0977 (bugworks research)

BWC0977 is a novel dual-target topoisomerase inhibitor [54]. It is equipotent against DNA gyrase and topoisomerase IV. It has activity against carbapenem-resistant Enterobacterales, *A. baumannii* and *P. aeruginosa*. Against ciprofloxacin-resistant Enterobacterales, its MIC_{50} and MIC90 were 0.25 mg/L and 4 mg/L, respectively [55].

A Phase I study of intravenous BWC0977 was completed in May 2023 after enrolling 44 of planned 64 healthy adults (NCT05088421). A new Phase I study also studying the safety and tolerability intravenous BWC0977 in healthy volunteers commenced in August 2023 with estimated completion in July 2024 (NCT05942820). The subsequent clinical development plan has not been disclosed. An orally administered formulation is also being developed [56].

2.3.2. R327 (Recce)

R327 is a novel synthetic polymer, which disrupts ATP synthesis. It appears to have a broad spectrum of activity against Gram negative bacilli, although there are no published *in vitro* data. Single ascending dose Phase I trials of intravenously administered R327 in healthy adults have been registered (ACTRN12623000448640; ACTRN12621001313820). The drug was safe and well tolerated at a dose of 3000 mg administered intravenously over 30 minutes [57], with more rapid infusions being trialed.

2.3.3. Apramycin (Juvabis)

Apramycin (EBL-1003) is an aminoglycoside which is used in agriculture. However, unlike antibiotics used in animals such as florfenicol or oxytetracycline it does increase conjugation frequency of plasmids harboring genes encoding CTX-M type ESBLs or the carbapenemase, OXA-48 [58]. Apramycin is not affected by most aminoglycoside modifying enzymes or 16S rRNA methyltransferases [59]. *In vitro*, apramycin is highly active against carbapenem-resistant *A. baumannii*, *P. aeruginosa,* and Enterobacterales [60,61].

A first in human, single-ascending dose Phase I trial in healthy volunteers was completed in 2020. It was safe and well-tolerated, with a pharmacokinetic profile similar to gentamicin [61]. A subsequent, NIAID sponsored phase I trial of a single dose of 30 mg/kg administered intravenously with subsequent bronchoalveolar lavage commenced recruitment in June 2023 (NCT05590728).

2.4. Broad-spectrum, inhalable antibacterial agents

2.4.1. AR-501 (Aridis)

AR-501 is gallium citrate, which has been shown to have inhibitory activity and anti-biofilm activity, especially against *P. aeruginosa* [62]. Although previously evaluated as an intravenous therapy [63], it is now being developed as a once-per-week self-administered formulation via a commercially available nebulizer.

A Phase I single ascending dose and multiple ascending dose cohort study in healthy adults have been followed by a phase IIa multiple ascending dose study in patients with cystic fibrosis infected with *P. aeruginosa* (NCT03669614). AR-501 was found to be well-tolerated and achieve sputum concentrations many-fold higher than the MIC [64].

2.5. Broad-spectrum, topically applied antibacterial agents

2.5.1. R327 (Recce)

R327 (mentioned above) has also been trialed as a topically applied therapy in infected burn wounds (ACTRN12621000412831) and in a phase I/II phase trial of mild foot infections in diabetics (ACTRN12623000056695). Four of five patients with mild diabetic foot infections had a resolution of their infection with topical R327 only [57].

2.5.2. Pravibismane (Microbion)

Pravibismane (MBN-101) is a novel bismuth thiol which has *in vitro* activity against both Gram positive and Gram negative bacteria, including both Enterobacterales and non-fermenters [65]. It disrupts bacterial ATP production [66]. A Phase II trial commenced in June 2022, in which topically applied pravibismane was used as an adjunctive to systemic antibiotic treatment for diabetic patients with foot wound infections (NCT05174806). At the time of writing, the trial has not been completed.

2.6. Antibacterial agents targeted against Acinetobacter baumannii

Three antibacterial agents are being developed specifically against *Acinetobacter baumannii*, one of which is a peptide and will be described in the section on 'non-traditional' agents.

2.6.1. BV100 (Bioversys)

BV100 is an intravenous formulation of rifabutin [67]. Rifabutin, like all rifamycins, acts by inhibition of bacterial transcription by binding to the beta-subunit (RpoB) of DNA-dependent RNA polymerase. Rifabutin was approved by the FDA in 1992 as an orally administered drug for the prevention of disseminated *Mycobacterium avium* complex disease in patients with HIV infection and low CD4 counts. However, while rifamycins lack the ability to penetrate the outer membrane of Gram negative bacilli, rifabutin can 'hijack' an outer membrane protein and facilitate transport across the outer membrane of *A. baumannii*. Specifically, rifabutin undergoes active uptake through the tonB-dependent siderophore receptor FhuE [68]. Rifabutin has excellent activity against carbapenem-resistant *A. baumannii* with an MIC_{50} of 0.008 mg/L and MIC_{90} of 1 mg/L in one evaluation of 293 strains from Europe, the United States, and Asia collected during 2017–2019 [69]. It is noteworthy that rifabutin has minimal activity when tested in standard cation-adjusted Mueller–Hinton broth, which is nutrient rich. However, potent antibacterial activity against *A. baumannii* can be demonstrated in Roswell Park Memorial Institute 1640 (RPMI) medium supplemented with fetal calf serum (FCS), which is a nutrient limited medium [70]. In these nutrient-limited conditions, the siderophore receptor, FhuE, is over-expressed. Notably, rifabutin and cefiderocol use different iron uptake systems so cross-resistance should not occur.

Oral administration leads to subtherapeutic concentrations of rifabutin and may select for mutations reducing rifabutin uptake in *A. baumannii* [68]. Rifabutin prodrugs have been designed and synthesized so they have increased aqueous solubility in order to allow intravenous use [67]. This allows for sufficiently high concentrations that therapeutic concentrations with a low selection rate for mutations can be achieved. Furthermore, the combination of rifabutin with other antibiotics, such as colistin, is synergistic and also reduces the emergence of resistance [71].

A number of Phase I clinical trials of BV100 have been performed in healthy adults (NCT05087069, NCT04636983, NCT05684718, and NCT05537090). The pharmacokinetics and safety of BV100 have also been assessed in subjects with varying degrees of renal or hepatic impairment (NCT05086107, NCT05537142). A phase I study to assess the penetration of rifabutin in the lung after multiple intravenous doses of BV100 in healthy adults is currently enrolling (NCT05684705). A Phase II trial of intravenous BV100 in combination with polymyxin B, in comparison to best available therapy, in patients with VABP due to carbapenem-resistant *A. baumannii* has commenced with pharmacokinetics, safety, and efficacy being primary assessments (NCT05685615). This trial is expected to be completed in 2024.

2.6.2. Zosurabalpin (Roche)

Zosurabalpin (RO7223280) is the first representative of a novel class of tethered macrocyclic peptide antibiotics. It acts by blocking the transport of bacterial lipopolysaccharide from the inner membrane to its destination on the outer membrane, through inhibition of the $LptB_2FGC$ complex. It is specifically active against *Acinetobacter* spp., including carbapenem-resistant *A. baumannii*. It is inactive against other Gram negative bacteria, Gram positive bacteria, and yeasts (MIC > 64 mg/L). The spontaneous mutation frequency is within a range comparable to cefiderocol, colistin, or rifabutin. *In vivo* activity of zosurabalpin has been demonstrated in neutropenic mouse models of pneumonia and thigh infection, as well as an immunocompetent mouse intraperitoneal induced sepsis model [72].

One Phase I trial has been completed (NCT04605718) and one is ongoing (NCT05614895). The completed trial enrolled 124 healthy adults in a single ascending intravenous dose and then multiple ascending dose study. The most frequently

observed treatment-related adverse events were infusion-related reactions occurring in 9 of 64 participants administered a dose of zosurabalpin. Seven reactions were mild, and two were moderate in severity [73]. A subsequent Phase I trial has been completed in which critically ill participants with bacterial infections were given a single intravenous dose of 400 mg or 600 mg zosurabalpin (NCT05614895). The results of this trial of 48 individuals have not yet been released.

2.6.3. APL-2301 (asieris)

APL-2301 (formerly known as ASN-1733 and MET-102) is a novel nitroxoline derivative being developed against *A. baumannii*. It appears to have dual mechanisms of action – compromising the outer membrane integrity and inhibiting NDM [74].

A Phase I trial is scheduled to commence in 2024 in Australia [75].

2.7. Antibacterial agents targeted against Enterobacterales

2.7.1. Benapenem (sihuan pharm)

Benapenem has comparable *in vitro* activity to ertapenem against Enterobacterales [76]. This includes significant activity against ESBL producing *E. coli* and *K. pneumoniae*, but no significant activity against CRE.

Phase I and II trials have been completed. Phase I trials included single ascending dose (NCT03588156, NCT03578588) and multiple ascending dose studies (NCT03570970, NCT04200261) in healthy adults. These supported once daily intravenous dosing [77]. A Phase I trial was also performed in patients with renal impairment (NCT04476407) suggesting that no dose adjustment was needed in patients with mild or moderate renal impairment [78]. A Phase II trial comparing intravenous benapenem and intravenous ertapenem in patients with cUTI and acute pyelonephritis was completed in May 2020 (NCT04505683). There are no details of Phase III trial design in published English language literature, and it is unclear if it is still in development.

2.7.2. RG6319 (GDC-5780) (Genentech, Roche)

RG6319 is a novel antibiotic of the 'arylomycin' class. It is a LepB inhibitor being developed for complicated UTI [5]. LepB is a signal (also termed 'leader') peptidase isolated from *E. coli* [79]. There is no published information on whether the spectrum of activity of RG6319 extends beyond *E. coli*. Single ascending dose and multiple ascending dose Phase I trials have been registered (ISRCTN16073754 and ISRCTN15259645).

2.8. Orally administered antibacterial agents aimed at gram negative bacilli

2.8.1. Tebipenem (spero therapeutics in partnership with GSK)

Tebipenem is an orally administered carbapenem with activity against ESBL and AmpC producing Enterobacterales [80]. Tebipenem completed clinical development and a pivotal phase III trial of tebipenem versus ertapenem was completed for patients with complicated UTI and acute pyelonephritis [81]. However, the drug was not approved by the FDA. A large, randomized, double-blind, double-dummy, phase III trial of orally administered tebipenem pivoxil hydrobromide in comparison to intravenously administered imipenem-cilastatin has commenced in the treatment of cUTI or acute uncomplicated pyelonephritis (NCT06059846). The estimated time of completion of this 2,648 patient trial is March 2026. It is noteworthy that the tebipenem pivoxil hydrobromide dosing in this trial is 600 mg every 6 hours (in contrast to the 600 mg every 8 hours dosing in the prior Phase III trial [81].

2.8.2. Xeruborbactam oral prodrug – Ceftibuten (Qpex Biopharma, Shionogi)

An orally administered prodrug (QPX7831) that delivers xeruborbactam is being developed for use in combination with a beta-lactam antibiotic for activity against Gram negative bacilli. The orally administered combination of xeruborbactam and ceftibuten is now known as S-743229 [31].

A Phase I trial (NCT06079775) will commence in early 2024 in which 72 healthy volunteers will be assessed for the safety, tolerability, and pharmacokinetics of single and multiple doses of the drugs alone and in combination. One key objective will be to assess whether there is any pharmacokinetic interaction between the xeruborbactam oral prodrug and orally administered ceftibuten. The trial is scheduled for completion in late 2024.

2.8.3. Ledaborbactam Etzadroxil-Ceftibuten (Venatorx Pharmaceuticals)

Ledaborbactam etzadroxil (VNRX-7145/VNRX-5236 etzadroxil) is the orally administered prodrug of a boronic acid-containing β-lactamase inhibitor, ledaborbactam (VNRX-5236) [82]. Ledaborbactam inhibits class A, C, and D beta-lactamases produced by Enterobacterales [82,83]. Consequently, the combination of ledarobactam and ceftibuten is active against Enterobacterales producing ESBLs, AmpC, KPC, and OXA-48 [83–86]. The combination of oral administration and activity against most strains of Enterobacterales allows further development for UTI [85].

Three Phase I studies investigating ledaborbactam etzadroxil were completed in 2020–2022 (NCT04877379, NCT04243863, and NCT05527834) and one is ongoing (NCT05488678). These trials have encompassed safety, tolerability and pharmacokinetics, drug–drug interactions with ceftibuten and effect of food on pharmacokinetics in normal healthy volunteers and pharmacokinetics in patients with varying degrees of renal impairment. The design of subsequent Phase II and III clinical trials is not yet available in the public domain.

2.8.4. Avibactam tomilopil plus ceftibuten (Pfizer)

PF-07612577 is the combination of an oral prodrug of avibactam (avibactam tomilopil; ARX-1796) and ceftibuten. Avibactam inhibits class A beta-lactamases (ESBLs and KPCs), class C beta-lactamases (AmpC), and some class D beta-lactamases (OXA-48). Against a collection of more than 3000 isolates of Enterobacterales from patients with UTI worldwide, avibactam plus cetibuten was active against 97.6% isolates with the phenotype of an ESBL producer and 73.7% CRE isolates [87].

A Phase I trial (NCT05554237) was completed in June 2023 in which single ascending doses and then multiple ascending doses were assessed, culminating in one week's administration of every 8 hours dosing of avibactam tomilopil combined with ceftibuten. The results of this trial have not yet been published.

3. "Non-traditional" agents with activity against gram negative bacilli

Some new antimicrobial agents are not small molecules and are regarded as 'non-traditional' antimicrobial agents. This grouping includes bacteriophages, lysins, peptides, anti-virulence compounds, and antibody-based therapies (Table 2).

3.1. Bacteriophages

Bacteriophages have gained an enormous amount of media attention in recent years. Yet, none has received regulatory approval from major agencies such as the FDA or EMA. A number of companies are actively developing bacteriophages aimed at Gram negative pathogens:

3.1.1. TP-102 (Technophage)

TP-102 is a topically applied bacteriophage cocktail containing five phages active against *P. aeruginosa*, *A. baumannii,* and *Staphylococcus aureus*. A Phase I trial was completed in September 2022 to assess the safety and tolerability in 20 patients with diabetic foot ulcers (NCT04803708). Results have not yet been published, but a phase II double-blind, randomized, placebo-controlled trial in 80 patients with an infected diabetic foot ulcer and at least one of the three target organisms started in November 2023 (NCT05948592).

3.1.2. AP-PA02 (Armata pharmaceuticals)

AP-PA02 is a bacteriophage cocktail targeted at *P. aeruginosa*. Originally devised as a 3-phage cocktail, it has now been expanded to a 5-phage cocktail [88]. AP-PA02 has been trialed in a Phase Ib/2a study in stable patients with cystic fibrosis, who have grown *P. aeruginosa* susceptible to AP-PA02 in sputum cultures. A single and multiple ascending dose study (with phage delivered via inhalation) has been performed (NCT04596319). Inhaled AP-PA02 has also been trialed in a phase II, double-blind, placebo-controlled trial to assess safety, phage kinetics, and efficacy in patients with non-cystic fibrosis bronchiectasis who have chronic pulmonary *P. aeruginosa* infection (NCT05616221). This trial commenced in January 2023 and is expected to complete enrollment of 60 patients in 2024.

3.1.3. BX004-A (BiomX)

BX004-A is a nebulized cocktail of phages targeted at *P. aeruginosa*. A Phase Ib/2a double-blind, placebo-controlled study has been performed to assess the safety and tolerability of BX004-A in patients with cystic fibrosis with chronic *P. aeruginosa* pulmonary infection (NCT05010577) [89]. This study had two parts, the second of which randomized 23 patients with cystic fibrosis to nebulized B×004 twice daily for 10 days and 11 patients to placebo. B×004 was safe and well-tolerated. Fourteen percent (3/21) patients receiving B×004 converted to sputum culture negative for *P. aeruginosa* compared to none of the placebo treated patients. In a predefined small subgroup of patients with reduced baseline lung function, improvement in respiratory function (as measured by FEV1) and respiratory symptoms was observed in the B×004 group [90].

Table 2. 'Non-traditional' antibacterial agents with activity against Gram negative bacilli currently in, or recently completed, phase I or phase II clinical trials.

Non-traditional antibacterial agent	Company	Phase of Clinical Trial	Key Characteristic or Differentiating Feature
APT-CF phage (WRAIR-PAM-CF1)	Adaptive Phage Therapeutics	I	Phage cocktail targeted to *P. aeruginosa*
AP-PA02	Armata Pharmaceuticals	I	Phage cocktail targeted to *P. aeruginosa*
CF370	(Contrafect)	I	Lysin with broad Gram negative activity
CMTX101	Clarametyx	I	Monoclonal antibody targeted to protein essential for biofilms
GSK3882347	GSK	I	Anti-virulence – Targets an adhesive protein (FimH) found on the surface of *E. coli* to prevent binding to the bladder wall.
Murepavadin, for inhalation	Spexis	I	Peptidomimetic specific to *P. aeruginosa*; for use by inhalation
OMN6	Omnix Medical	I	Peptide targeting Acinetobacter
PLG0206	Peptilogics	I	Peptide with anti-biofilm activity
RESP-X (COT-143; INFEX702)	Infex Therapeutics	I	Monoclonal antibody targeting *P. aeruginosa*
SER-155	Seres	I	Consortium of commensal bacteria to augment microbiome
SNIPR001	Sniprbiome	I	CRISPRCas engineered phage cocktail targeting *E. coli*
TP-102	Technophage	I	Phage cocktail applied topically for diabetic foot infection
BX004	BiomX	Ib/II	Phage cocktail targeted to *P. aeruginosa*
AR-101	Aridis	II	Monoclonal antibody against *P. aeruginosa*
CAL02	Eagle Pharmaceuticals	II	'Lure' for bacterial virulence factors of both Gram positive and Gram negative bacteria
F598	Alopexx	II	Monoclonal antibody against poly N-acetyl glucosamine which is expressed by Enterobacterales and *A. baumannii*
Ftortiazinon	Gamaleya	II	Anti-virulence – Inhibits the type III secretion system
Rhu-plasma gelsolin	BioAegis	II	Recombinant human protein to replete levels caused by severe infections
Cysteamine	Novabiotics	III (CF002); II (CF001)	Antimicrobial and immunomodulatory activity
LBP-EC01	Locus Biosciences	III	Phage cocktail targeted to *E. coli*

3.1.4. WRAIR-PAM-CF1 (Adaptive Phage Therapeutics)

WRAIR-PAM-CF1 is a cocktail of four phages in a 1:1:1:1 combination, all of which are lytic against *P. aeruginosa* [91]. It is currently being studied in a Phase Ib/II trial (NCT05453578). The protocol has been published in full [91] and outlines its aim to assess safety and microbiological activity in clinically stable adults with cystic fibrosis chronically colonized with *P. aeruginosa*. The sample size is 72, and the trial is projected to be completed in June 2024.

3.1.5. LBP-EC01 (Locus biosciences)

LBP-EC01 is a recombinant CRISPR-Cas3-enhanced bacteriophage cocktail aimed at *E. coli* strains responsible for UTI. A Phase I trial to assess LBP-EC01 was performed in 2020 to assess its safety, tolerability, pharmacokinetics, and pharmacodynamics (NCT04191148). A 580 patient phase II/III trial commenced enrollment in September 2022 and is expected to be completed in December 2025 (NCT05488340). Patients enrolled in this trial have a history of recurrent UTI and who present with an acute uncomplicated UTI. Patients with indwelling urinary catheters and urinary tract anatomical abnormalities are excluded. After a 30-patient dose regimen selection study, in which both intraurethral and intravenous dosing are evaluated, the preferred LBP-EC01 regimen will be compared to orally administered trimethoprim-sulfamethoxazole (NCT05488340).

3.1.6. SNIPR001 (Sniprbiome)

SNIPR001 is a cocktail of four bio-engineered phages that selectively target and eliminate *E. coli* that are resistant to fluoroquinolones. The phages were engineered with CRISPR-CAS [92]. SNIPR001 could be used alone or in combination with fluoroquinolone as a decolonization strategy in patients at high-risk of antibiotic-resistant *E. coli* infections such as those undergoing chemotherapy.

A proof-of-concept Phase I clinical trial has been completed (NCT05277350). In this trial in 36 healthy adults, orally administered SNIPR001 was well tolerated and its use was associated with decreased *E. coli* levels in feces [93].

3.2. Microbiome therapeutics

3.2.1. SER-155 (Seres)

SER-155 is a consortium of commensal bacteria designed to be administered orally in order to augment the microbiome, and therefore prevent bloodstream infections and acute graft-versus-host disease in stem cell transplant recipients.

A Phase Ib trial has commenced in which adults undergoing hematopoietic stem cell transplantation are pretreated with oral vancomycin and then ascending doses of SER-155 (or placebo). The primary outcome measures are safety and tolerability of SER-155 as well as engraftment of SER-155 (that is, prevalence of SER-155 in subject's stool) (NCT04995653). It is estimated that the study will be completed in October 2024.

3.3. Lysins

3.3.1. CF-370

CF-370 is an engineered lysin targeting Gram negative bacilli. Lysins are enzymes produced by bacteriophages during their lytic cycle and cleave bonds in the bacterial cell wall, resulting in the death of the bacteria within seconds after contact [94]. CF-370 has *in vitro* activity against *P. aeruginosa*, *A. baumannii,* and Enterobacterales. It is synergistic with most antibiotic classes, including beta-lactams, aminoglycosides, quinolones, or polymyxins [95], and is capable of suppressing resistance to these antibiotics in serial passage studies. CF-370 was scheduled to enter its first in human Phase I trials in late 2023, but Contrafect declared bankruptcy in December 2023.

3.4. Peptides

3.4.1. PLG0206 (Peptilogics)

PLG0206 is a 24-amino-acid peptide containing only arginine, valine, and tryptophan residues. It was engineered to maximize its bacterial membrane binding while minimizing toxicity [96,97]. It has rapid bactericidal activity against *A. baumannii* and *P. aeruginosa*, as well as *S. aureus* and *E. faecium* [98]. The MIC_{50} and MIC_{90} for both *K. pneumoniae* and *E. coli* were 8 mg/L and 16 mg/L, respectively. PLG0206 has potent anti-biofilm activity [98].

Given these attributes, it has proceeded to a 14 patient Phase I trial in which PLG0206 was delivered as an irrigation during surgery (NCT05137314). Patients enrolled in this trial had prosthetic joint infection (PJI) of a knee arthroplasty managed using debridement and implant retention (DAIR). No treatment-related serious adverse events were reported [99]. An earlier Phase I trial has been performed of PLG0206 given intravenously [100].

3.4.2. OMN6 (Omnix medical)

OMN6 is a novel, engineered, 40-amino acid cyclic peptide based on Cecropin A [101]. Cecropins are small cationic peptides of 29–42 amino acids that are insect host defense peptides. The target of OMN6 is assumed to be the bacterial membrane. *In vitro*, OMN6 is active against *A. baumannii*, with MIC_{50} 4 mg/L and MIC_{90} 8 mg/L [101,102]. No cross-resistance was observed with colistin. There was no impact of lung surfactant on OMN6. Serial passage did not lead to resistance development. OMN6 was highly active in mouse bacteremia and mouse pneumonia models [102].

The Phase I program for OMN6 involved 80 healthy adults, including elderly patients. The study was designed as a single, ascending dose. No serious adverse events were observed [103]. A phase IIa, double-blind, placebo-controlled trial of OMN6 in HABP or VABP due to *A. baumannii* is scheduled to start in early 2024 (NCT06087536). Three dosing regimens of OMN6 will be assessed in order to assess safety and pharmacokinetics. OMN6 will be given for a single day and will be in addition to conventional antibiotics for *A. baumannii*.

3.5. Peptidomimetics

3.5.1. Inhaled murepavadin (Spexis)

Murepavadin is a novel 'macrocycle,' specifically active against *P. aeruginosa* [104]. It has a novel, non-lytic mechanism of action and is referred to as an outer membrane protein targeting antibiotic. Nine clinical trials, recruiting 290 participants in total, evaluated intravenous formulations. The final phase III trials evaluating intravenous murepavadin for VABP due to *P. aeruginosa* were halted because acute kidney injury was observed in many participants.

As a result, murepavadin is now being developed as an inhaled drug for *P. aeruginosa* in patients with cystic fibrosis. *In vitro*, murepavadin is highly active against *P. aeruginosa* strains from these patients [105,106]. A Phase I trial of inhaled murepavadin has been performed. This showed low systemic absorption but concentrations in the epithelial lining fluid which exceeded the MIC90 of *P. aeruginosa* isolates obtained from patients with cystic fibrosis [107].

3.6. Anti-virulence compounds

3.6.1. GSK3882347 (GSK)

GSK3882347 targets an adhesive protein (FimH) found on the surface of *E. coli*. The binding of GSK3882347 to FimH prevents *E. coli* from binding to the bladder wall.

A Phase I single ascending and multiple ascending dose trial enrolling 61 healthy adults was completed in May 2021 (NCT04488770). Subsequent clinical trials (NCT05138822 and NCT05760261) have been suspended to allow analysis of data from supplementary non-clinical studies, and the strategic direction for future trials is not yet known.

3.6.2. NM002 and NM001 (Novabiotics)

NM002 is an intravenously administered aminothiol which is a small molecule with both immunomodulatory and antimicrobial activities. The active entity is cysteamine, which has multiple mechanisms by which it may potentiate antibiotic activity, including against *P. aeruginosa* [108]. NM001 is orally administered (or delivered by inhalation) and has the same activity.

NM002 is now in Phase III trials via the REMAP-CAP platform trial of community-acquired pneumonia. The first patient in the cysteamine domain of this trial was recruited in December 2021 [109]. No results have been released.

NM001 is being developed for pulmonary infectious exacerbations in patients with cystic fibrosis or non-CF bronchiectasis. Phase II trials in cystic fibrosis patients have been completed (NCT03000348).

3.6.3. Ftortiazinon (gamaleya national center of epidemiology and microbiology)

Ftortiazinon has fluorothiazinon as its active moiety. This is an inhibitor of the type III secretion system of many bacteria, including *P. aeruginosa* and *A. baumannii* [110]. It suppresses the pathogenicity of the bacteria but does not suppress the growth of the bacteria.

A phase II trial of orally administered ftortiazinon plus intravenously administered cefepime versus placebo plus cefepime for complicated UTI due to *P. aeruginosa* commenced in 2018 (NCT03638830), although its results are not available in any English language literature.

3.6.4. CAL02 (eagle pharmaceuticals)

CAL02 is a novel 'anti-toxin' [111] which consists of liposomes engineered to capture virulence factors produced by both Gram positive and Gram negative bacteria. It is designed to be administered in addition to standard of care antibiotics (eagleus.com, accessed 1 January 2024).

Intravenously administered CAL02 is currently in a placebo-controlled Phase II trial, in addition to standard of care in patients with severe community-acquired bacterial pneumonia (NCT05776004). The first patients in this 276 patient trial were enrolled in July 2023 [112].

3.7. Recombinant proteins

3.7.1. Rhu-pGSN (bioAegis)

Plasma gelsolin (pGSN) enhances immune clearance of microbial and host-derived toxins. In severe infections (and in some other life-threatening conditions such as major trauma and burns), circulating pGSN levels decline precipitously. A recombinant human (Rhu) form has been developed, and in animal models of multidrug resistant *P. aeruginosa* pneumonia, survival and lung injury were improved when Rhu-pGSN was administered along with antibiotics [113].

A phase 1b/2a study on the safety and pharmacokinetics of Rhu-pGSN in hospitalized patients with CAP has been completed (NCT03466073). A 520 patient, phase II trial is scheduled to start in 2024 in patients with moderate-to-severe acute respiratory distress syndrome (ARDS) who have had pneumonia or other severe infections (NCT05947955).

3.8. Immunotherapy

3.8.1. CMTX-101 (Clarametyx)

CMTX-101 is an anti-DNABII humanized monoclonal antibody [114]. DNABII proteins are bacterial DNA-binding proteins that have an essential extracellular role in biofilm formation, stabilization, and maturation. The removal of DNABII proteins from the biofilm results in the rapid collapse of the biofilm [114]. The primary amino acid sequence of DNABII proteins in the DNA-binding region is generally conserved across bacterial pathogens. Therefore, CMTX-101 is 'pathogen-agnostic' and can assist in the management of infections caused by both Gram-negative and Gram-positive bacteria. The rapid collapse of biofilms using anti-DNABII antibodies has been demonstrated for Gram negative bacilli in *A. baumannii*, *P. aeruginosa,* and Enterobacterales [114].

A two-part, phase I study started in November 2022 and is expected to be completed in 2024 (NCT05629741). In the first part of the study, it was demonstrated that single doses of intravenous infusion of CMTX-101 were safe in healthy adults and that no anti-drug antibodies were developed [115]. As a result, CMTX-101 moved into the second part of its phase I study. In this double-blind, randomized, placebo-controlled study intravenous CMTX-101 will be given in addition to standard-of-care antibiotics in patients hospitalized with community-acquired bacterial pneumonia. Although this study is primarily evaluating safety, exploratory efficacy biomarkers will also be measured.

3.8.2. RESP-X (INFEX therapeutics)

RESP-X (also known as INFEX702) is a novel, humanized, monoclonal antibody targeting the type 3 secretion system of *P. aeruginosa* [116], therefore enhancing neutrophil mediated killing of *P. aeruginosa* and reducing tissue damage mediated by exotoxins.

A Phase I ascending single-dose study in healthy adults has been completed (ISRCTN17978477). No serious adverse events or infusion reactions were reported. RESP-X had a 30-day half-life [117]. A Phase IIa dose-ranging study has been initiated in patients with non-cystic-fibrosis bronchiectasis colonized with *P. aeruginosa*, with the purpose of reducing exacerbations of infection (ISRCTN17978477).

3.8.3. AR-101 (Shenzen Arimab Biopharmaceuticals)

AR-101 is a monoclonal antibody targeted against *P. aeruginosa* lipopolysaccharide serotype 011. It is intended to be adjunctive to standard of care antibiotics for patients with severe pneumonia due to *P. aeruginosa* [64].

A Phase IIa trial was reported in 2014 [118], but clinical development has been rejuvenated in China and other countries outside of the United States, Europe, Canada, Australia, and Japan [64].

3.8.4. F598 (Alopexx)

F598 is a fully human IgG1 monoclonal antibody targeting poly N-acetyl glucosamine (PNAG) which is a molecule expressed on the surface of a wide range of bacteria and fungi. This includes Gram negative bacteria such as *E. coli*, *K. pneumoniae* and *A. baumannii*, but not *P. aeruginosa* [119]. F598 is planned to be administered as a single intravenous infusion with protection against PNAG-expressing pathogens that may persist for 2–3 months [120].

It is being studied in Phase I and II trials for therapeutic and prophylactic use in newly admitted ICU patients [120].

4. Conclusion

Overall, 28 small molecules and 20 non-traditional antimicrobial agents active against Gram-negative bacilli are currently in clinical trials. Their target indications could be described as broad-spectrum intravenously administered agents (defined as having activity against Enterobacterales, P. aeruginosa, and A. baumannii), A. baumannii-specific intravenously administered agents, Enterobacterales specific intravenously administered agents, orally administered agents, prevention of exacerbation of P. aeruginosa infections in patients with cystic fibrosis or bronchiectasis, topical therapy for wound infection, biofilm activity, and therapy adjunctive to antibiotics for serious life-threatening infections.

5. Expert opinion

In a review of 'leakage' from the antimicrobial pipeline in the 2010s, Prasad and colleagues found that most small molecule Gram-negative active candidates which were withdrawn showed safety concerns in Phase I trials. One was withdrawn because of the development of antibiotic resistance and none was withdrawn explicitly for efficacy concerns [121]. It should therefore be expected that some of those agents currently in clinical trials may face toxicity issues or be abandoned due to commercial concerns. Apart from support from the AMR Action Fund, BARDA, GARDP, and the Cystic Fibrosis Foundation, there are few other investors providing financial backing for clinical trials of antimicrobial agents. This is a major risk potentially preventing clinical advances from finding their place in the clinical armamentarium.

In my opinion, the greatest unmet needs in the field of antibiotic therapy are safe and effective treatments for (1) carbapenem-resistant Acinetobacter, (2) carbapenem-resistant Enterobacterales due to MBL producers, and (3) orally administered therapies for Gram negative organisms resistant to ciprofloxacin and trimethoprim-sulfamethoxazole. These challenges are potentially met by antimicrobial agents currently in clinical trials.

5.1. Carbapenem-resistant A. baumannii

Therapy for carbapenem-resistant *A. baumannii* was enhanced by the May 2023 approval of sulbactam-durlobactam. In the pivotal phase III trial, sulbactam-durlobactam was non-inferior to colistin in terms of all-cause mortality but was significantly less nephrotoxic [122]. However, even prior to the approval of sulbactam-durlobactam it was known that resistance could be mediated by a number of mechanisms such as co-production of an MBL or mutation of PBPs leading to decreased affinity to sulbactam [123]. While these mechanisms are currently rare, there is clearly a need to provide alternatives to sulbactam-durlobactam. The entities in clinical trials specifically targeted to *A. baumannii* (BV-100, zosurabalpin, APL-2301, and OMN6), would definitely complement the anti-Acinetobacter armamentarium if found to be effective and well-tolerated. Zosurabalpin is a completely novel entity which provides a degree of comfort in that beta-lactamases or PBP changes will not influence its activity. BV-100 also provides this advantage of not being a beta-lactam antibiotic. It is currently being trialed with polymyxin B and will likely always be used in partnership with another antimicrobial agent. Cefiderocol is typically highly active *in vitro* against carbapenem-resistant *A. baumannii*, although it is not yet clear how useful it is in clinical practice. It would be interesting to consider the combination of sulbactam-durlobactam or cefiderocol with the new entities active against *A. baumannii*.

A number of the broad-spectrum antimicrobial agents mentioned above also have *in vitro* activity against carbapenem-resistant *A. baumannii*. Firstly, funobactam and ANT3310 are quite similar to durlobactam in their spectrum of beta-lactamase inhibition. They are being partnered with imipenem and meropenem, respectively, and presumably would restore the activity of carbapenems against OXA-producing strains. It is not clear whether the combination of sulbactam-durlobactam-meropenem would have an advantage over funobactam-imipenem or ANT3310-meropenem by having the additional anti-Acinetobacter activity of sulbactam. Zidebactam-cefepime has *in vitro* and animal model activity against carbapenem-resistant *Acinetobacter* as do BWC0977,

the new polymyxins and apramycin. In my opinion, it is crucial that all of these agents are evaluated in phase III clinical trials of HABP and VABP, including patients with carbapenem-resistant *A. baumannii*.

Finally, bacteriophage therapy has been used as salvage therapy for carbapenem-resistant *A. baumannii*. Interestingly, TP-102 which is being used for topical therapy for diabetic foot infection includes a phage active against *A. baumannii*. No other phage therapies active against *A. baumannii* are in clinical trials at this time. From a clinical perspective, it is important to signal that adjunctive phage therapy for *A. baumannii* could be very useful, either delivered by the inhalational route or by intravenous therapy. The recent success of nebulized amikacin as a successful preventative therapy in patients at high risk of VABP [124] opens a pathway of nebulized phage therapy as a means of preventing *A. baumannii* pneumonia in those at risk of VABP due to this pathogen.

5.2. MBL-producing enterobacterales

At the present time, the combination of ceftazidime-avibactam with aztreonam is regarded as the first choice for CRE infections when an MBL is implicated [125]. This combination is cumbersome and has never been evaluated in a clinical trial. Aztreonam-avibactam has completed its clinical trial program, although disappointingly a study specifically against MBL-producing organisms was abandoned due to low enrollment. Cefiderocol is a currently available option against MBL-producing organisms. Unfortunately, NDM-producing *E. coli* increasingly have an insertion in PBP-3 leading to decreased susceptibility to aztreonam-avibactam or cefiderocol [126]. It is interesting to speculate whether the combination of xeruborbactam with cefiderocol would enhance cefiderocol's activity against NDM producing strains. The clinical effectiveness of taniborbactam-cefepime has not yet been ascertained against MBL producing organisms, even though there is typically *in vitro* activity. However, changes in the NDM beta-lactamase as well as the previously mentioned PBP-3 insertion could compromise its activity against MBL-producers [8]. It is disappointing that the phase III trial of taniborbactam-cefepime for HABP/VABP (NCT06168734) has meropenem as a comparator. This prohibits the assessment of this compound against the carbapenem-resistant organisms for which it is being developed. Cefiderocol would be a much better choice as a comparator given it is approved for HABP/VABP.

It is clearly not easy to design a beta-lactamase inhibitor that inhibits class B as well as class A, C, and D enzymes. Specific inhibitors of class B enzymes (for example, APC148 or MET-X) are in development and could be clinically useful in combination with a carbapenem. This would only be useful if the MBL producing organism did not co-produce OXA-48 or another OXA-type carbapenemase, so an additional strategy to protect meropenem would have to be developed. It is interesting to contemplate whether it would be commercially viable, or acceptable from a regulatory standpoint, for beta-lactamase inhibitors to be available as standalone entities with 'free choice' of companion antibiotic(s) so that therapy could be tailored to the specific beta-lactamases produced by any given bacteria.

Despite nacubactam or zidebactam not having specific activity against class B enzymes, the ability to *in vitro* and animal model activity of nacubactam-cefepime or zidebactam-cefepime against MBL producers is noteworthy. The combination of nacubactam-aztreonam, currently in clinical development, is particularly interesting with respect to MBL producers. Zidebactam-ertapenem would be convenient, and potentially useful in outpatient parenteral therapy, given that it could be used once daily. The new polymyxins, apramycin, BWC0977, and CF370 also have *in vitro* activity against MBL producers, and it would be worthwhile if their phase II or III clinical trials could be performed in regions where NDM producers are highly prevalent. Not-for-profit clinical trial networks such as ADVANCE-ID, which have large numbers of sites in Asia, are likely to be useful partners in clinical development of new agents active against MBL producers or *A. baumannii*.

5.3. Orally administered therapy for UTI

ESBL producers are frequently resistant to orally administered antibiotics such as fluoroquinolones, trimethoprim-sulfamethoxazole, and cephalosporins. While they may retain susceptibility to orally administered fosfomycin, its clinical utility has been put in some doubt [127]. Nitrofurantoin, which is only useful for uncomplicated UTI, requires multiple daily doses and can be associated with significant adverse effects. Neither gepotidacin nor sulopenem, both of which have completed their clinical trials programs, has not yet been approved by the FDA for uncomplicated UTI. Therefore, there is definitely a need in the modern armamentarium for new orally administered options both for uncomplicated and complicated UTIs, acute pyelonephritis and for patients with bacteremia who could be transitioned from intravenous therapy. Combinations of the pro-drugs of xeruborbactam, avibactam, and ledaborbactam with ceftibuten may provide an answer to this unmet need with the additional benefit of activity against some of the carbapenem-resistant organisms. Tebipenem was not approved by the FDA as a treatment for complicated UTI when studied as a three-times per day therapy [81]. A new phase III trial using a four times per day dosing regimen will soon commence, although the acceptability of this regimen in clinical practice could be questioned given that adherence may be suboptimal. It could be speculated that the combination of a beta-lactamase inhibitor with tebipenem may lower MICs such that pharmacodynamic target attainment could be achieved with three times per day dosing.

BWC0977 is potentially administrable orally although this has not yet been trialed clinically. It would represent a convenient option if available in both IV and PO forms as patients could be seamlessly transitioned to the PO form when ready for hospital discharge.

It is noteworthy that phage therapy targeted at *E. coli* is being clinically evaluated in a phase III trial for uncomplicated UTI. This is clearly a wonderful step forward in the clinical application of phage therapy. However, the choice of either intra-urethral or intravenous administration for uncomplicated UTI is not consistent with current clinical practice.

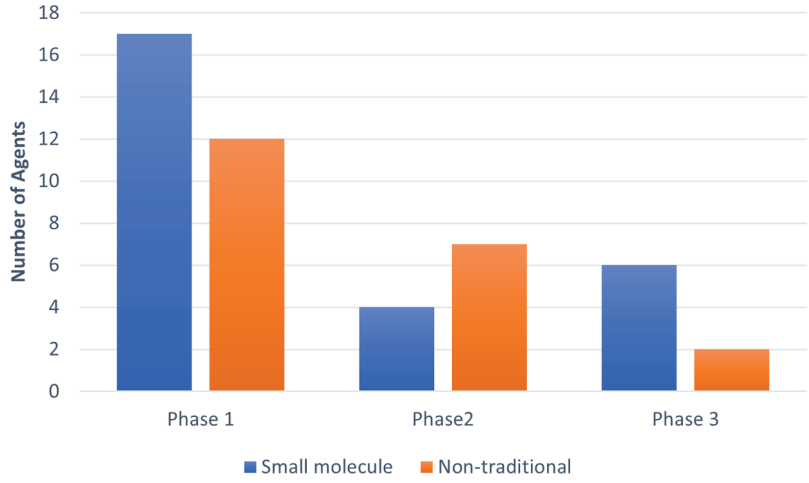

Figure 1. Small molecules and non-traditional antimicrobial agents currently in clinical trials against infections caused by gram negative bacilli.
*Cefepime-taniborbactam is not included since a New Drug Application has been submitted to the Food and Drug Administration.

5.4. The opportunities and challenges of non-traditional antimicrobial agents

While phage therapy has received a large amount of media attention, there remain a number of obstacles to non-traditional therapies succeeding in clinical trials and gaining acceptance by prescribers. One issue, which is not unique to non-traditional therapies, is difficulty with susceptibility testing [128,129]. No susceptibility testing may be available at all for anti-virulence compounds or antibody-based therapies. This has implications for the investigators participating in clinical trials, for regulators and for clinicians subsequently aiming to judiciously use the product. Another key consideration is the design of pivotal clinical trials. If it is likely that a non-traditional antimicrobial agent will need to be combined with standard of care antibiotics, then by default, some demonstration of superiority in efficacy of the combination over standard of care alone will likely need to be demonstrated. Colistin should no longer be considered a 'go-to' comparator agent given that cefiderocol and other beta-lactam antibiotics with activity against carbapenem-resistant organisms are now available. Phase II trials will need to be designed in such a way that a 'signal' of superiority can be demonstrated, as well as the more standard parameters of safety and tolerability. Novel trial designs, careful consideration of inclusion and exclusion criteria and innovative endpoints may need to be explored in both Phase II and III trials. Unfortunately, proving superiority is a much 'taller order' than demonstrating non-inferiority and will be a major challenge for the development of non-traditional antimicrobial agents.

5.5. Final remarks

Despite these challenges, the mere fact that nearly 50 antimicrobial agents active against Gram negative bacilli are in clinical development (Figure 1) is testament to those who have advocated for ongoing investment in antibiotics despite poor investment returns. Organizations such as The Wellcome Trust, CARB-X, BARDA, Novo REPAIR Impact Fund, the WHO, IDSA, the BEAM Alliance, and the AMR Action Fund are some which have had crucial involvement. Of course, within these organizations, a relatively small number of key individuals have led activities aimed at promoting clinical development of antibiotics. Finally, these efforts will amount to very little if access to new antimicrobial agents is available only in a select number of high-income countries. The vast majority of patients needing safe and effective antimicrobial agents active against Gram negative bacilli live in middle- and low-income countries in Asia, Eastern and Mediterranean Europe, Africa, and Latin America. Pathways to access new antimicrobial agents must be part of the clinical development of these life-saving therapies.

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D Paterson's institution has received research grants or been provided equipment for research from Shionogi, Merck, Pfizer, Gilead, BioVersys, Accelerate, T2 Diagnostics, and BioMerieux. He has been paid by Shionogi and Entasis for giving presentations at FDA Advisory Committee Meetings (related to approval considerations for cefiderocol and sulbactam-durlobactam, respectively). He has provided consultancy or received honoraria from Pfizer, Merck, GSK, Roche, QPex, Spero, Entasis, Venatorx, Arrepath, Aurobac, Mutabilis, BioMerieux and Cepheid and has received travel assistance from Wockhardt.

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