



The threat of multidrug-resistant/extensively drug-resistant Gram-negative respiratory infections: another pandemic

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Antimicrobial resistance continues to rise among Gram-negative bacteria, leading to greater morbidity, mortality, lengths of stay and costs. The level of resistance is approaching pandemic proportions, requiring an urgent call to address this problem. <https://bit.ly/3NTnDqK>

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Abstract

Antibiotic resistance is recognised as a global threat to human health by national healthcare agencies, governments and medical societies, as well as the World Health Organization. Increasing resistance to available antimicrobial agents is of concern for bacterial, fungal, viral and parasitic pathogens. One of the greatest concerns is the continuing escalation of antimicrobial resistance among Gram-negative bacteria resulting in the endemic presence of multidrug-resistant (MDR) and extremely drug-resistant (XDR) pathogens. This concern is heightened by the identification of such MDR/XDR Gram-negative bacteria in water and food sources, as colonisers of the intestine and other locations in both hospitalised patients and individuals in the community, and as agents of all types of infections. Pneumonia and other types of respiratory infections are among the most common infections caused by MDR/XDR Gram-negative bacteria and are associated with high rates of mortality. Future concerns are already heightened due to emergence of resistance to all existing antimicrobial agents developed in the past decade to treat MDR/XDR Gram-negative bacteria and a scarcity of novel agents in the developmental pipeline. This clinical scenario increases the likelihood of a future pandemic caused by MDR/XDR Gram-negative bacteria.

Introduction

Respiratory infections are among the most common indications for hospitalisation to include admission to an intensive care unit (ICU) [1]. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) respiratory virus pandemic is estimated to have accounted for >7 million deaths worldwide [2] and resulted in significant economic distress with the global economy contracting by 3.5% in 2020 [3]. Another “silent” pandemic that has been going on for more than three decades is the increasing prevalence of bacterial infections attributed to multidrug-resistant (MDR) and extremely drug-resistant (XDR) Gram-negative bacteria [4]. The United Nations Interagency Coordination Group on Antimicrobial Resistance Report considers bacterial antimicrobial resistance to be a major threat to human health, and a recent Wellcome Trust report suggests that nearly 300 million individuals will die over the next several decades as a direct result of antimicrobial resistance [5, 6]. Similarly, in the United States, antibiotic-resistant pathogens cause >2 million infections and 23 000 deaths per year, as reported by the United States Centers for Disease Control and Prevention [7]. Despite the introduction of novel antibiotics, the continued escalation of resistance among Gram-negative bacteria suggests that the problem of antibiotic resistance is likely to intensify in the future, leading to antimicrobial inadequacies and a potential full-blown pandemic [8].



The Extended Study on Prevalence of Infection in Intensive Care III (EPIC III) found that among the 15 165 qualifying patients, 8135 (54%) had at least one suspected or proven infection on the study day, with most being respiratory infections [1]. Moreover, antibiotic-resistant pathogens including vancomycin-resistant *Enterococcus*, *Klebsiella* species resistant to β -lactam antibiotics or carbapenem-resistant *Acinetobacter* species were associated with the highest risk of in-hospital death [1]. Given the importance of escalating antibiotic resistance among Gram-negative bacteria as a cause of mortality, morbidity and economic hardship, we brought together in this issue of the *European Respiratory Review* a multidisciplinary group of authors to discuss this possible next pandemic. The goal of this review is to provide a concise appraisal of the problem of escalating antibiotic resistance among Gram-negative bacteria as an important class of agents for respiratory infections. It is also important to understand that pandemics are not mutually exclusive, as evident by the SARS-CoV-2 pandemic which contributed to outbreaks of MDR/XDR Gram-negative infections including pneumonia [9, 10]. Therefore, as a medical community we must maintain a state of preparedness in order to deal with future pandemics, to which antibiotic resistant Gram-negative bacteria will likely contribute, if not cause outright.

Antibiotic resistant Gram-negative pulmonary infections: key organisms and their epidemiology

According to recent estimates, antibiotic-resistant infections were associated with nearly 5 million deaths globally in 2019 alone [11]. The most common site of infection among these was the lower respiratory tract, which accounted for 1.5 million of the deaths and >75 000 000 disability-adjusted life-years [11]. Although not delineated according to infectious syndrome by the authors, the Gram-negative pathogens associated with the most deaths included *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, each associated with >250 000 deaths in 2019, although incidence of the pathogens and death rates varied substantially by region [11].

Among individual pathogen–antimicrobial combinations, in 2019, >50 000 deaths each were directly attributable to third-generation cephalosporin-resistant *K. pneumoniae* and *E. coli*, carbapenem-resistant *A. baumannii* and *K. pneumoniae*, and fluoroquinolone-resistant *E. coli* (figure 1) [11]. The deaths associated with and attributable to antimicrobial resistance as estimated by the Antimicrobial Resistance Collaborators [11] were derived from a variety of data sources from across the world. However, these estimates were derived from 2019 data among patients who became ill before the onset of the SARS-CoV-2 pandemic. Studies showed that even before the SARS-CoV-2 pandemic, cases of pneumonia due to antimicrobial-resistant Gram-negative bacteria were on the rise in many regions throughout the world [12]. 3 years into the pandemic, we know that patients hospitalised with SARS-CoV-2 receive antimicrobials at very high rates ($\geq 75\%$ in some instances), a situation which will only exacerbate the global antimicrobial resistance crisis that was burgeoning pre-pandemic [13]. In a vicious positive-feedback cycle, patients with SARS-CoV-2 are known to have higher rates of ventilator-associated pneumonia (VAP) [14], a situation which will lead to increased levels of broad-spectrum antimicrobial use, and subsequent development of antimicrobial resistance. In addition, despite the high numbers of antimicrobial-resistant lower respiratory infections found in the aforementioned study [11], this may be an underestimate, as causative pathogens in pneumonia are identified in only ~30–60% of patients [15–18].

In the study by the Antimicrobial Resistance Collaborators, methicillin-resistant *Staphylococcus aureus* (MRSA) and drug-resistant *E. coli* were the two most common organisms causing mortality [11].

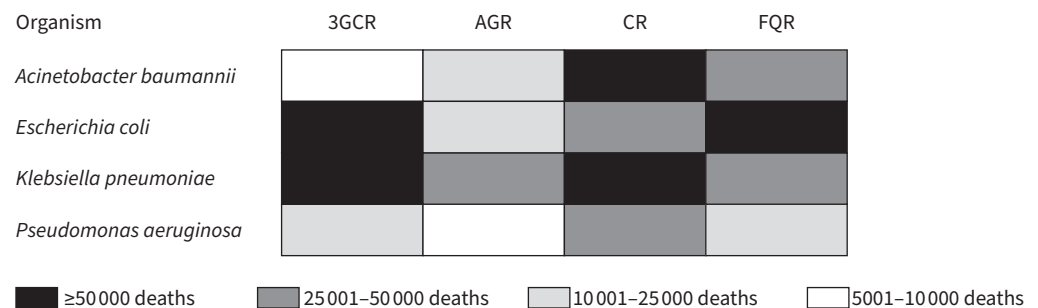


FIGURE 1 Global deaths in 2019 directly attributable to Gram-negative antimicrobial resistance by pathogen–antimicrobial. Data from [11]. 3GCR: third-generation cephalosporin resistance; AGR: aminoglycoside resistance; CR: carbapenem resistance; FQR: fluoroquinolone resistance.

For patients with pneumonia, there is good evidence that MRSA nares swabs have a high negative predictive value and can be used in antimicrobial stewardship efforts to stop unnecessary anti-MRSA antimicrobial use [19]. Unfortunately, there is no easy analogue/stand-in to assist in ruling out drug-resistant Gram-negative pneumonia. Some efforts have attempted to understand the relationship between intestinal colonisation with antimicrobial-resistant Gram-negatives, including those producing extended-spectrum β -lactamases and/or carbapenemases, and the development of future infection, but operationalising such practices has proven challenging and may lead to overtreatment with novel antimicrobials, which must be preserved to prevent development of new resistance [20–23]. Even before the SARS-CoV-2 pandemic, the match between prescribed antimicrobials and recovered pathogens was poor, with MRSA and *Pseudomonas* being treated far more often than they were detected [24].

At the individual level, patients with antimicrobial-resistant Gram-negative pneumonia are more likely to have been treated previously with antibiotics, be bed-bound, have longer lengths of hospitalisation, have a previous microbiology history of resistant organisms, and to have certain acute and chronic medical comorbidities, with variation by hospital case-mix and region [16, 24–29]. Understanding the risk factors for infection with antibiotic-resistant organisms is crucial for effective empiric treatment decision making. One helpful tool is the “PES” score aimed at identifying antibiotic-resistant *Pseudomonas*, Enterobacterales and MRSA in patients with pneumonia [30] (table 1).

With continued antimicrobial selection pressure, additional mechanisms of antimicrobial resistance are likely to evolve, as has happened with each new antimicrobial that has been developed and used clinically. Identifying risk factors for the development of antimicrobial resistance and the prospective use of algorithms to predict which hospitalised patients will go on to develop antimicrobial resistance may be helpful in certain instances and/or localities, but rapid detection of pathogens and their antimicrobial resistance profiles is likely to be more sensitive for resistance detection [31]. The implementation of rapid molecular diagnostics, especially for pneumonia and bloodstream infections, may be a key step forward in minimising antimicrobial overuse.

Overview of main resistance mechanisms

Resistance mechanisms contributing to the development of multidrug-resistant Gram-negative organisms include enzymatic inactivation, efflux pumps, porin mutations and target site modifications [32] (figure 2). Mutations leading to resistance may be intrinsic to the organism or acquired *via* plasmid-mediated transmission [33]. Each plasmid-mediated conjugation may contain multiple resistance determinants, thus conferring a multidrug-resistant phenotype [32]. Table 2 summarises the relevant resistance mechanisms discussed in this section, in addition to organisms commonly harbouring such mechanisms, the phenotypic result and potential therapeutic approaches.

β -Lactamases

β -Lactamases are categorised molecularly with the Ambler classification based on the enzymatic active site structure and amino acid sequences, dividing them into classes A (narrow and extended-spectrum β -lactamases), C (AmpC cephalosporinases) and D (oxacillinases), which all utilise serine for hydrolysis, and B (metallo- β -lactamases), which utilise zinc ions for hydrolysis [34]. Functionally, β -lactamases are categorised into Bush–Jacoby groups, based upon their hydrolysis and inhibition profiles [34–36].

TABLE 1 The “PES” score to assess the risk of pneumonia due to *Pseudomonas aeruginosa*, Enterobacteriaceae with extended-spectrum β -lactamases and methicillin-resistant *Staphylococcus aureus* pathogens

Age, years	
<40	0
40–65	1
>65	2
Male	1
Previous antibiotic use	2
Chronic respiratory disorder	2
Chronic renal disease	3
At emergency	
Consciousness impairment	2
Fever	–1
Risk scores for infection are low: ≤ 1 , moderate: 2–4, high: ≥ 5 .	

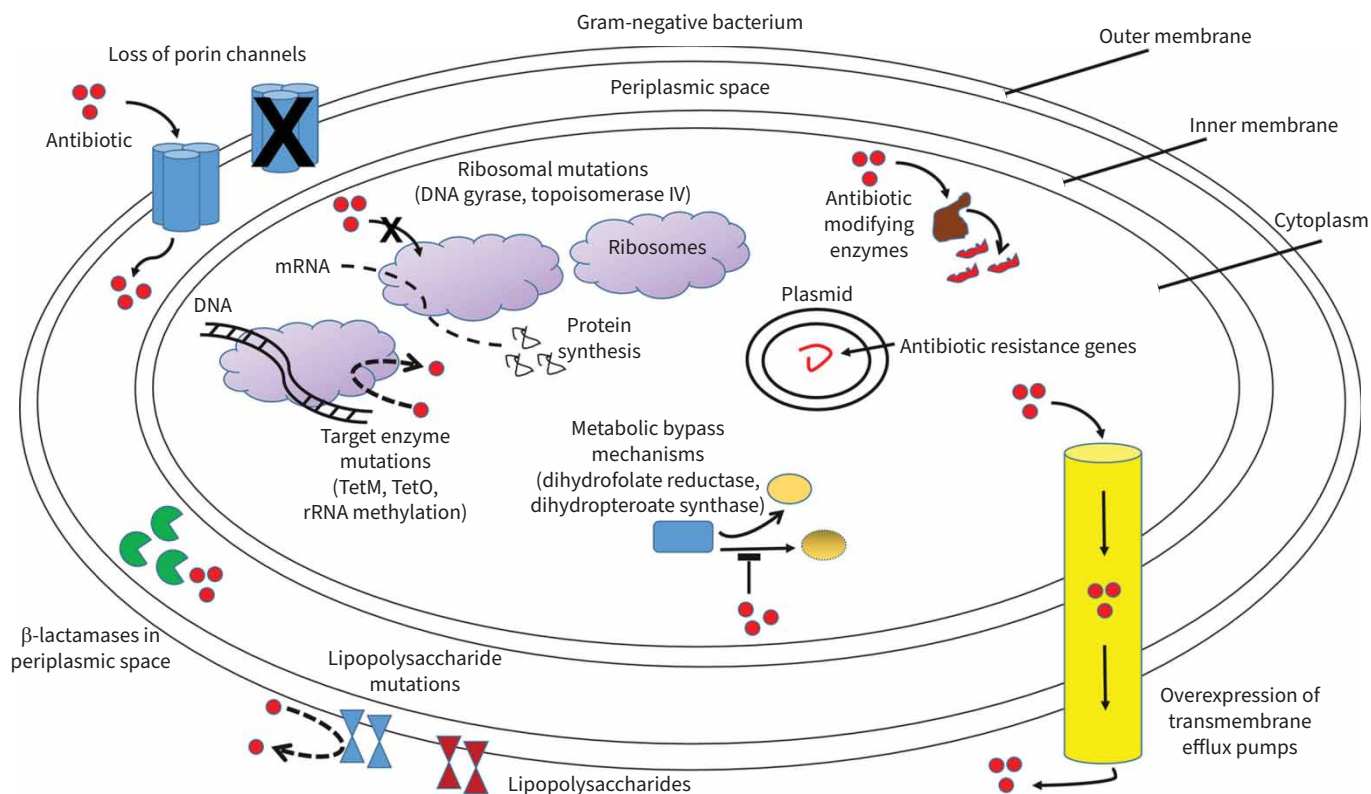


FIGURE 2 Mechanisms of antibiotic resistance in Gram-negative bacteria. Shown are loss of porin channels which reduce antibiotic movement across the bacterial membrane; β -lactamases in the periplasmic space inactivating β -lactams; increased transmembrane efflux pump expression expelling antibiotics from within the bacteria; antibiotic-modifying enzymes altering antibiotics so they cannot interact with end targets; antibiotic target and ribosomal mutations interfering with antibiotic actions; metabolic bypass mechanisms allowing alternative enzyme pathways bypassing antibiotic inhibitory effects; and lipopolysaccharide mutations limiting specific antibiotics such as polymyxins from disrupting the cell membrane.

Phenotypically, β -lactamases include extended-spectrum β -lactamases (ESBLs), AmpC cephalosporinases and carbapenemases [36]. A summary of β -lactamase classification is displayed in figure 3.

ESBLs

ESBLs confer resistance to penicillins, cephalosporins including extended-spectrum (third and fourth generations) and monobactams, and are categorised as Ambler class A and Bush–Jacoby group 2 [35, 37]. This group of β -lactamases is genetically diverse, with the most common mutations including TEM, SHV and CTX-M isolated in Enterobacterales species [32, 38]. CTX-M-15 is the most common variant worldwide, but there are nearly 500 recognised variants of the various mutations [35]. Contemporary ESBLs are reliably inhibited by newer β -lactamase inhibitors, including avibactam, relebactam and vaborbactam; however, older-generation β -lactamase inhibitors including clavulanate, sulbactam and tazobactam may succumb to the inoculum effect or may be rendered ineffective against isolates harbouring inhibitor-resistant β -lactamases [35, 39, 40]. OXA-type ESBLs (Ambler class D) are less common, but include derivations of OXA-10 and OXA-2, commonly detected in isolates of *P. aeruginosa* [35].

AmpC

AmpC β -lactamases are classified as Ambler class C and Bush–Jacoby group 1 and are often isolated in Enterobacterales species [32, 41]. These enzymes result from either the inducible or stable derepression of *ampC* regulatory protein production or from transmission of plasmid-mediated *ampC* genes [42, 43]. Susceptibility testing of an organism with stable derepressed AmpC production will demonstrate resistance to third-generation cephalosporins and cephamycins, while inducible AmpC producing organisms will initially test susceptible to third-generation cephalosporins. These inducible organisms become resistant upon exposure to certain β -lactams, which causes disabling of the negative regulator protein, AmpR, resulting in increasing production of AmpC [42]. Potent inducers of AmpC production include the aminopenicillins, first-generation cephalosporins, and cephamycins, while weak inducers include

TABLE 2 Antibiotic mechanisms of resistance of Gram-negative organisms

Resistance mechanism	Pathogens commonly harbouring mechanism	Antibiotic classes impacted by mechanism	Therapeutic options to overcome mechanism
Enzymatic inactivation			
ESBL	Enterobacterales, <i>P. aeruginosa</i> , <i>A. baumannii</i> , <i>S. maltophilia</i>	Penicillins, cephalosporins (all), aztreonam	Carbapenems non-BL based on susceptibility testing
Amp-C	Inducible: <i>E. cloacae</i> , <i>C. freundii</i> , <i>K. aerogenes</i> Stable derepressed: <i>E. coli</i> , <i>A. baumannii</i> , <i>Shigella</i> spp. Plasmid-mediated: <i>K. pneumoniae</i> , <i>E. coli</i> , <i>Salmonella</i> spp.	Strong inducers: cephamycins, aminopenicillins, first-generation cephalosporins Weak inducers: piperacillin-tazobactam, third-generation cephalosporins, aztreonam	Cefepime Carbapenem non-BL based on susceptibility testing
Carbapenemases			
KPC	Enterobacterales	Penicillins, cephalosporins (all), carbapenems, aztreonam	Newer-generation BL/BLI Cefiderocol non-BL based on susceptibility testing
MBL (NDM, VIM, IMP)	<i>P. aeruginosa</i> , <i>S. maltophilia</i> , Enterobacterales	Penicillins, cephalosporins (all), carbapenems	Ceftazidime/avibactam PLUS aztreonam cefiderocol non-BL based on susceptibility testing
OXA-48	<i>Acinetobacter</i> , Enterobacterales	Penicillins, cephalosporins (narrow), carbapenems	Ceftazidime/avibactam Cefiderocol non-BL based on susceptibility testing
Other inactivating enzymes			
AME	Enterobacterales, <i>Acinetobacter</i> , <i>Pseudomonas</i> , <i>S. maltophilia</i>	Aminoglycosides	Based on susceptibility testing
Porin mutations			
OprD protein	<i>Pseudomonas</i> , <i>Acinetobacter</i>	Aminoglycosides, carbapenems	Based on susceptibility testing
Omp proteins	Enterobacterales, <i>Acinetobacter</i>	Aminoglycosides, carbapenems, tigecycline	
Efflux pumps			
MexAB-OprM	<i>Pseudomonas</i>	β -lactams including carbapenems, macrolides, fluoroquinolones, tetracyclines, TMP/SMX	Based on susceptibility testing
MexXY-OprM	<i>Pseudomonas</i>	Aminoglycosides	
MexCD-OprJ	<i>Pseudomonas</i>	β -lactams including carbapenems	
Target site modification			
16s rRNA mutation or methylation 30S ribosomal mutation	<i>Pseudomonas</i> , Enterobacterales	Aminoglycosides	Based on susceptibility testing
Topoisomerase IV or DNA gyrase mutation	<i>Pseudomonas</i> , Enterobacterales, <i>Acinetobacter</i> , <i>S. maltophilia</i>	Fluoroquinolones	
23S rRNA mutation or methylation 50S ribosomal mutation	Enterobacterales	Macrolides	
RNA polymerase mutation	Enterobacterales	Rifampin	
DHFR overproduction or DHPS mutation	Enterobacterales	TMP/SMX	
Lipid A neutralisation	Enterobacterales, <i>Pseudomonas</i> , <i>Acinetobacter</i>	Colistin	
PBP mutation	<i>Pseudomonas</i>	β -lactams including carbapenems	

ESBL: extended-spectrum β -lactamases; KPC: *Klebsiella pneumoniae* carbapenemases; MBL: metallo- β -lactamases; NDM: New Delhi MBL; VIM: Verona integron-encoded MBL; IMP: imipenem's MBL; OXA: OXA- β -lactamases; AME: aminoglycoside-modifying enzymes; DHFR: dihydrofolate reductase; DHPS: dihydropteroate synthase; PBP: penicillin-binding protein; *P. aeruginosa*: *Pseudomonas aeruginosa*; *A. baumannii*: *Acinetobacter baumannii*; *S. maltophilia*: *Stenotrophomonas maltophilia*; BL: β -lactam; *E. cloacae*: *Enterobacter cloacae*; *C. freundii*: *Citrobacter freundii*; *K. aerogenes*: *Klebsiella aerogenes*; *E. coli*: *Escherichia coli*; *K. pneumoniae*: *Klebsiella pneumoniae*; BLI: β -lactam inhibitor; TMP: trimethoprim; SMX: sulfamethoxazole.

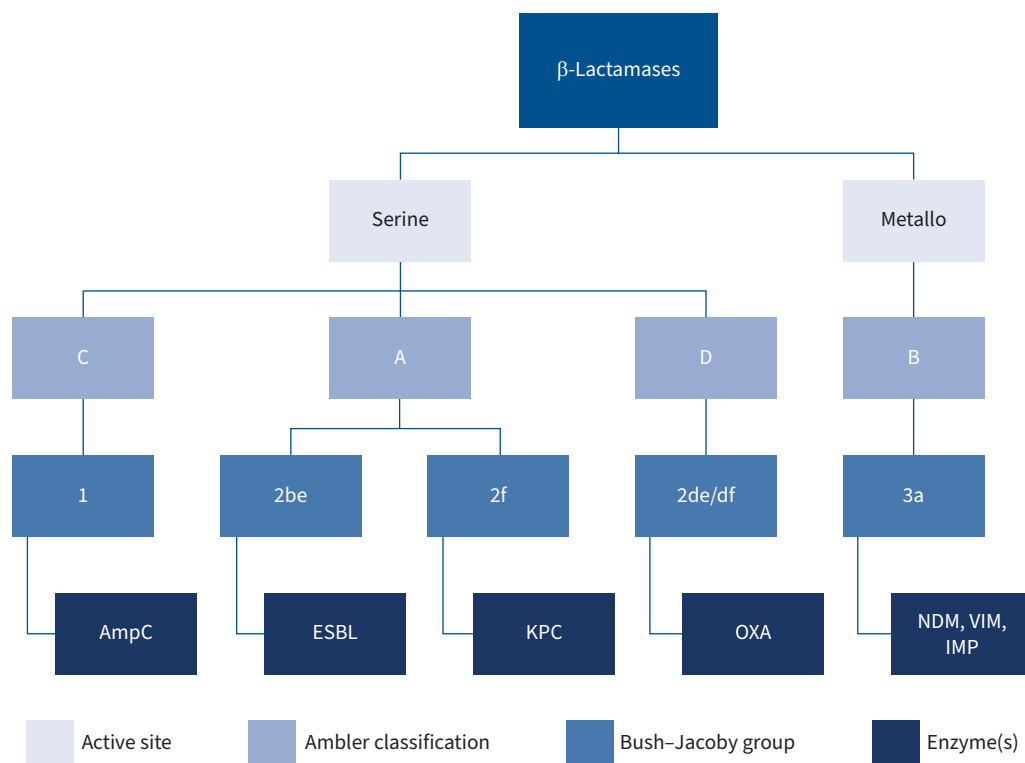


FIGURE 3 Molecular, functional and phenotypic classification of β -lactamase enzymes. ESBL: extended-spectrum β -lactamase; KPC: *Klebsiella pneumoniae* carbapenemases; OXA: OXA- β -lactamases; NDM: New Delhi metallo- β -lactamase; VIM: Verona integron-encoded metallo- β -lactamase; IMP: imipenem's metallo- β -lactamase.

piperacillin-tazobactam, aztreonam, and third-generation cephalosporins, all of which may be hydrolysed in varying levels of AmpC production. Cefepime and carbapenems are inducers of AmpC production, but withstand its hydrolysis [42].

Carbapenemases

Carbapenemases include β -lactamases from Ambler class A (*K. pneumoniae* carbapenemases (KPC)), class B (New Delhi metallo- β -lactamases (NDM), Verona integron-encoded metallo- β -lactamases (VIM) and imipenem's metallo- β -lactamases (IMP)) and class D (OXA-48 variants) [36]. Carbapenemase enzymes are isolated in Enterobacterales, *Pseudomonas* and *Acinetobacter* species [44].

KPCs are the most clinically relevant of the class A carbapenemases and have been identified across the globe [44–46]. Despite their nomenclature, these genes are found on transferable plasmids and are isolated in other Enterobacterales species, in addition to *K. pneumoniae* [47].

The three subclasses of metallo- β -lactamases (MBLs) (NDM, VIM and IMP) render resistance to carbapenems *via* hydrolysis utilising zinc, and they are not inhibited by available β -lactamase inhibitors [44, 48].

OXA- β -lactamases, specifically OXA-48 variants, have been isolated in Enterobacterales species. Because of their heterogeneity, the global prevalence of OXA-48 β -lactamases may be underestimated [44].

In addition to carbapenems, most carbapenemases also hydrolyse penicillins and cephalosporins, while only KPCs hydrolyse monobactams [45, 46]. Similar to ESBLs, KPCs are generally inhibited by traditional β -lactamase inhibitors, while OXA carbapenemases are not [45, 46]. KPCs are additionally susceptible to all of the newer-generation β -lactamase inhibitors. OXA carbapenemases are not reliably inhibited by vaborbactam, but demonstrate variable susceptibility to avibactam and relebactam [49]. Gram-negative organisms may also produce aminoglycoside-modifying enzymes (AMEs), including

acetyltransferases, nucleotidyltransferases and phosphotransferases, all of which inactivate aminoglycosides [50, 51]. Less commonly, fluoroquinolone-, macrolide- and rifampin-inactivating enzymes may be produced by various Enterobacterales, *Pseudomonas* and *Acinetobacter* species [33].

Target site modification

Although alterations in penicillin-binding proteins are commonly observed with Gram-positive organisms, *Pseudomonas* species may harbour such mechanisms, leading to reduced β -lactam susceptibility [33]. Modification of fluoroquinolone target proteins occurs by mutations of *gyrA/gyrB* and *parC/parE* genes [32, 52], while aminoglycoside binding site alteration occurs by mutation of the 30S ribosomal subunit or by production of 16s rRNA methyltransferases via organisms harbouring *armA* and various *rmt* genes [50, 51]. Additionally, resistance to colistin is observed with alterations in the negative charge of the bacterial cell membrane, which prevents binding and insertion of the positively charged drug at its target site [33].

Efflux pumps

In nonfermenting Gram-negative bacteria, such as *Pseudomonas* species, resistance to β -lactams and fluoroquinolones is often caused by overproduction of the MexAB-OprM efflux pump, whereas overproduction of MexXY-OprM transporters results in resistance to aminoglycosides [32, 52, 53]. This overproduction is mediated by mutations in the *nalB*, *nfxB* and *nfxC* genes [52].

Porin mutations

Porin channels play an important role in antibiotic uptake into Gram-negative bacteria [32]. Mutations resulting in inactivation or decreased expression of porin proteins, most notably OprD, leads to decreased permeability of several antibiotic classes including carbapenems, aminoglycosides and fluoroquinolones [32, 51, 52].

Gram-negative bacteria can harbour multiple resistance mechanisms that manifest clinically as a multidrug resistance phenotype [32]. Multiple β -lactamases may coexist, such as the combination of carbapenemases with an AmpC or ESBL, which, along with the presence of an AME-, ESBL- and AmpC-producing organism also having porin mutations results in a slowed rate of bacterial penetration, facilitating enzymatic hydrolysis of β -lactams, including carbapenems [44]. Additionally, the presence of such β -lactamases in combination with various drug efflux pumps or alterations in target sites can also confer resistance to other classes of antibiotics, and thus the manifestation of multidrug resistant organisms [44]. The growing prevalence and global impact of such multidrug resistance is of great concern.

Impact of Gram-negative antibiotic-resistant pulmonary infection on outcomes

There is a consensus that timely and appropriate antibiotic treatment, defined as an antibiotic regimen with *in vitro* activity against the causative pathogens, is a necessary first step to optimise the outcomes of patients with serious infections, especially in the ICU setting [54–58]. The guiding principle of timely appropriate antibiotic treatment of serious infections is endorsed by the most recent 2021 Surviving Sepsis Campaign International Guidelines for the management of sepsis and septic shock with a strong recommendation [59]. KUMAR *et al.* [58] demonstrated that for every hour's delay until appropriate antibiotic administration, crude mortality increased by more than 10%. VAZQUEZ-GUILLAMET *et al.* [60] studied >1000 subjects with septic shock and calculated that appropriate therapy enhanced the likelihood of survival at least three-fold. More importantly, this converted into a number needed to treat (NNT) to save one life of only 4, and the prevalence-adjusted pathogen-specific NNT to prevent one patient death was lowest for infections caused by MDR bacteria (NNT=20) [60]. Thus, both appropriate antibiotic selection and their timely administration are necessary to optimise patient outcomes.

BASSETTI *et al.* [61] summarised the data regarding appropriate early therapy of serious infections in a meta-analysis of 114 studies of appropriate therapy in severe bacterial infections including pneumonia. Appropriate initial antibiotic therapy not only significantly reduced in-hospital mortality (OR 0.44, 95% CI 0.38–0.50), but also reduced length of stay by >2.5 days [61]. Delayed appropriate antibiotic therapy has also been shown to be associated with greater mortality in VAP [62]. Moreover, several nosocomial pneumonia registration trials for agency drug approval have demonstrated that when inactive antibiotic therapy is administered to patients, primarily inactive due to inadequate dosing or antibiotic exposure, mortality is increased [63–66]. These studies confirm the importance of delivering an appropriate and adequately dosed antibiotic regimen to patients with bacterial lung infections in order to improve patient outcomes, especially hospital survival.

The strongest evidence supporting early appropriate antibiotic therapy for severe infections comes from a randomised prospective trial examining this issue. The MERINO trial compared piperacillin-tazobactam to

meropenem in patients with bloodstream infection caused by ceftriaxone-nonsusceptible *E. coli* or *K. pneumoniae*; in essence, it was a trial of appropriate versus inappropriate therapy [57]. The source of infections was primarily urinary tract and intra-abdominal with <5% being pneumonia. Noninferiority of the piperacillin-tazobactam arm could not be established, with 12.3% of 187 patients randomised to piperacillin-tazobactam dying at 30 days compared with 3.7% of 191 patients randomised to meropenem [57]. Microbiological failures were also more common among patients randomised to receive piperacillin-tazobactam when infected with Amp-C overexpressing Gram-negative bacteria [67].

MDR and XDR Gram-negative bacterial infections are more likely to initially receive inappropriate antibiotic treatment, resulting in worse outcomes. ZILBERBERG *et al.* [68] studied 1064 patients with Gram-negative bacteraemia, of whom 351 (29.2%) did not survive hospitalisation. Nonsurvivors were significantly more likely to have infection with an MDR isolate and to have received inappropriate initial antibiotic therapy. A multivariate analysis demonstrated that presence of infection with an MDR isolate was strongly associated with the receipt of inappropriate initial antibiotic therapy (adjusted OR 13.05, 95% CI 7.00–24.31). The same group of investigators also evaluated 1423 patients from United States hospitals with pneumonia or sepsis due to *A. baumannii* [69]. Harbouring MDR *A. baumannii* increased the risk of receiving inappropriate initial antibiotic therapy more than five-fold, and inappropriate initial antibiotic therapy nearly doubled hospital mortality. More recently, MARTINEZ-NADAL *et al.* [70] evaluated 1615 episodes of bacteraemia associated with neutropenia, of which 394 (24%) received inappropriate initial antibiotic therapy. Patients with MDR Gram-negative bacteria, accounting for 221 (14%) of all isolates, were more likely to receive inappropriate initial antibiotic therapy (39% versus 7%, $p < 0.001$). Overall mortality was also higher in patients with Gram-negative bacteraemia who received inappropriate initial antibiotic therapy (36% versus 24%, $p = 0.004$). Thus, it can be seen that the presence of antibiotic resistance among Gram-negative bacteria is associated with greater initial administration of inappropriate antibiotic therapy, which in turn leads to greater mortality.

The problem of antimicrobial resistance appears to be escalating. Data from the National Healthcare Safety Network from 2015 to 2017 show that among *P. aeruginosa* isolates in ICU patients, 26.3% were resistant to carbapenems, 26.5% were resistant to extended-spectrum cephalosporins and 27.1% were resistant to fluoroquinolones, with 18.6% classified as MDR [71]. Increasing resistance has led clinicians to employ antimicrobial “cocktails” in the hopes of salvaging patients with MDR/XDR infections [72, 73]. Verona integron-encoded metallo- β -lactamase-positive *P. aeruginosa* (VIM-PA) has emerged as one of the most resistant Gram-negative pathogens, along with carbapenem-resistant *A. baumannii*. In a study from the Netherlands, VIM-PA bacteraemia was associated with greater mortality compared to carbapenem-susceptible infection [74]. Thus, it is evident that increasing future infections with MDR/XDR pathogens will be associated with greater morbidity and mortality, particularly in respiratory infections. Figure 4 offers an approach to the clinical management of antibiotic-resistant Gram-negative infections in the hospital setting.

Novel and pipeline antibiotics

Several antibiotics have been introduced to combat Gram-negative resistance and expand coverage against MDR Gram-negative infections, including respiratory tract infections (table 3) [75]. Their precise role in empirical and definitive treatment is beyond the scope of this review; however, well-written reviews and guidelines highlight the importance of pertinent risk factors, current and prior culture and susceptibility data, local resistance rates, available clinical and/or *in vitro* data and other factors [75–77]. Moreover, the use of novel antibiotics as combination therapy provides a unique approach to the treatment of MDR Gram-negative infections. For example, ceftazidime/avibactam has broad activity against serine β -lactamases; however, it is hydrolysed by MBL. In contrast, aztreonam is resistant to MBL hydrolysis, but susceptible to serine β -lactamases. Available *in vitro* and *in vivo* data have demonstrated synergistic activity with this combination against MBL-producing Gram-negative organisms [78–81].

Pipeline antibiotics will provide extended Gram-negative coverage and may become useful options for the treatment of MDR Gram-negative respiratory infections (table 3). For example, the addition of the novel β -lactamase inhibitor zidebactam to the β -lactam cefepime improves activity against KPC, ESBL, OXA-48 and MBLs [82, 83]. The expanded spectrum provided by and mechanism of β -lactam/ β -lactamase inhibitor combinations differs among agents [49, 82]. Avoidance of aminoglycoside-inactivating enzymes affords the novel synthetic aminoglycoside, arbekacin, improved activity against MDR Gram-negatives and Gram-positives [84]. Murepavadin highlights a novel drug class of outer membrane protein targeting antibiotics by binding to the lipopolysaccharide transport protein D present on the outer membrane of MDR *P. aeruginosa* [85]. Initially encouraging phase I and II data have been stifled by the termination of the phase III PRISM-MDR trial due to safety concerns surrounding adjunctive use of murepavadin in

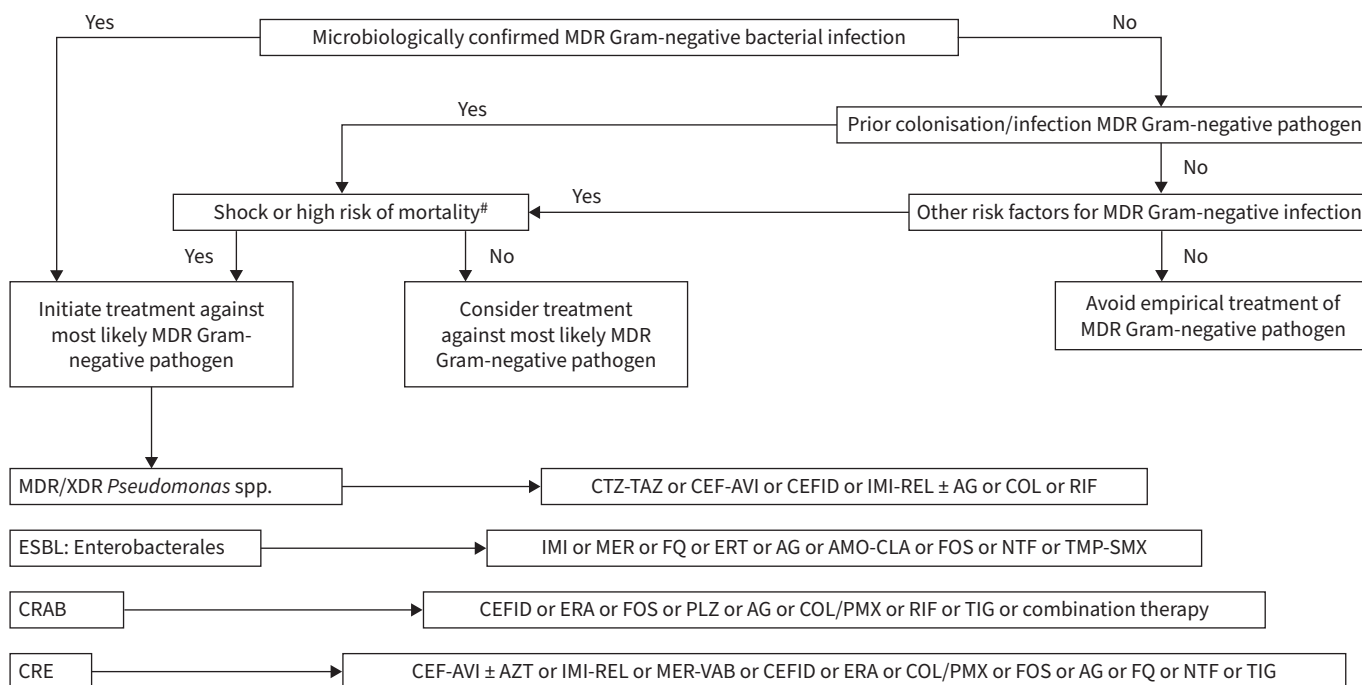


FIGURE 4 Clinical approach to the treatment of microbiologically confirmed or suspected multidrug-resistant (MDR) Gram-negative bacterial infection. XDR: extremely drug-resistant; CTZ-TAZ: ceftolozane/tazobactam; CEF-AVI: ceftazidime-avibactam; CEFID: cefiderocol; IMI-REL: imipenem-cilastatin; AG: aminoglycoside; RIF: rifampicin; ESBL: extended-spectrum β -lactamase producing; MER: meropenem; FQ: fluoroquinolone; ERT: ertapenem; AMO-CLA: amoxicillin-clavulanate; FOS: fosfomicin; NTF: nitrofurantoin; TMP-SMX: trimethoprim-sulfamethoxazole; CRAB: carbapenem-resistant *Acinetobacter baumannii*; ERA: eravacycline; PLZ: plazomicin; COL-PMX: colistin-polymyxin B; TIG: tigecycline; CRE: carbapenem-resistant Enterobacterales; AZT: aztreonam; MER-VAB: meropenem-vaborbactam. #: high risk of mortality is considered >15%.

patients with MDR *P. aeruginosa* VAP [86]. These data emphasise the need for ongoing study of all novel antimicrobials for MDR Gram-negative respiratory infections.

Monoclonal antibodies

The success of monoclonal antibodies (mAbs) for treatment and/or prevention of various diseases has reinvigorated consideration in treatment and prevention of bacterial infections. Antibacterial mAbs may disrupt bacterial infections *via* several mechanisms; however, targeting polysaccharides, proteins or toxins associated with proliferation, adhesion, host immunity protection, host cell damage and/or increased virulence are most common (table 4) [87, 88]. Encouraging results in prevention or treatment of *Clostridioides difficile*, inhalational anthrax and MRSA infections have been reported; however, data in Gram-negative respiratory infections remain preliminary [89–91].

The mAb KB001-A targets the PcrV protein on *P. aeruginosa*, reducing levels of toxin transport and lung injury/inflammation in animal models [92]. In cystic fibrosis patients, KB001-A was not associated with decreased time to need for antibiotics, but increased forced expiratory volume in 1 s and reduced inflammatory markers [92]. A randomised phase II trial of mechanically ventilated patients colonised with *P. aeruginosa* reported no difference in incidence of treatment-related adverse events, but reduced incidence of *P. aeruginosa* pneumonia development in patients receiving KB001-A [93]. The EVADE trial is assessing the ability of MEDI3902, a bivalent/multi-target mAb, to prevent *P. aeruginosa* infections in patients mechanically ventilated colonised with *P. aeruginosa* [94]. Panobacumab and AR-105 target polysaccharides produced by *P. aeruginosa* and are under investigation as adjuncts with standard-of-care antibiotics for nosocomial *P. aeruginosa* infections [95, 96]. Continued advancements in molecular modelling and bioinformatics are likely to yield additional targets for pathogens associated with MDR Gram-negative respiratory infections [97].

Antibacterial mAbs show great promise for the treatment and prevention of Gram-negative bacterial respiratory infections. Noteworthy advantages include target specificity, reduced risk of resistance

TABLE 3 Novel and pipeline antibiotic treatment options for Gram-negative respiratory infections

	Drug class and indication(s) [#]	Notable activity [¶]	Development phase	Comments
Novel antibiotics				
Ceftolozane/tazobactam	BL/BLI HABP/VABP	ESBL-E, MDR <i>P. aeruginosa</i>	FDA/EMA approved	Verify ESBL-E No CRE activity
Ceftazidime/avibactam	BL/BLI HABP/VABP	MDR <i>P. aeruginosa</i> , CRE (class A, KPC), AmpC and ESBL-E	FDA/EMA approved	No MBL activity Not reliable against <i>A. baumannii</i> Limited anaerobic activity
Imipenem/cilastatin/relebactam	BL/BLI HABP/VABP	CRE (KPC), ESBL-E, MDR <i>P. aeruginosa</i>	FDA/EMA approved	No additional activity against <i>A. baumannii</i> , compared to imipenem No MBL activity Anaerobe and MSSA activity
Meropenem/vaborbactam	BL/BLI HABP/VABP	CRE (KPC), ESBL-E, non-MDR <i>P. aeruginosa</i> and non-MDR <i>A. baumannii</i>	FDA/EMA approved	No additional activity against MDR <i>P. aeruginosa</i> or MDR <i>A. baumannii</i> compared to meropenem No MBL activity Anaerobe and MSSA activity
Cefiderocol	BL HABP/VABP	CRE (KPC and MBL), ESBL-E, MDR <i>A. baumannii</i> and <i>P. aeruginosa</i>	FDA/EMA approved	Inactive against Gram-positives and anaerobes
Delafloxacin	Fluoroquinolone CABP	ESBL-E	FDA/EMA approved	Limited <i>P. aeruginosa</i> activity Broad Gram-positive and atypical coverage
Eravacycline	Fluorocycline No indications	CRE (KPC and MBL), ESBL-E, MDR <i>A. baumannii</i>	FDA/EMA approved	Limited clinical efficacy data against MDR infections Often lower MICs than tigecycline Low rates of and <i>in vitro</i> activity against <i>C. difficile</i>
Omadacycline	Tetracycline CABP	ESBL-E, KPC, MBL, MDR <i>A. baumannii</i>	FDA/EMA approved	No <i>Pseudomonas</i> or <i>Proteus</i> spp. activity Broad Gram-positive and atypical coverage
Plazomicin	Aminoglycoside No indications	CRE (KPC and MBL), ESBL-E	FDA/EMA approved	Variable <i>P. aeruginosa</i> activity No <i>A. baumannii</i> activity Limited safety and efficacy data Consider in combination therapy regimens
Pipeline antibiotics				
Arbekacin	Aminoglycoside	Aminoglycoside-inactivating Gram-positive and Gram-negative pathogens	Phase III	Highly active against MRSA and shows activity against MDR- <i>P. aeruginosa</i> and <i>-A. baumannii</i>
Aztreonam/avibactam	Monobactam/BLI	ESBL, KPC, MBL, AmpC, OXA-48	Phase III	No increased activity to <i>P. aeruginosa</i> compared to aztreonam monotherapy No <i>A. baumannii</i> activity
Cefepime/enmetazobactam	BL/BLI	ESBL, AmpC, limited evidence of KPC and OXA-48	Phase III	No increased activity to <i>P. aeruginosa</i> compared to cefepime monotherapy No class B β -lactamase activity
Cefepime/taniborbactam	BL/BLI	ESBL, KPC, class B β -lactamases (VIM, NDM, SPM-1, GIM-1), AmpC, OXA-48	Phase III	Adds activity to cefepime against CRE and carbapenem-resistant <i>P. aeruginosa</i>
Cefepime/zidebactam	BL/BLI	ESBL, KPC, MBLs, AmpC, OXA-48	Phase III	Active against carbapenem-resistant <i>P. aeruginosa</i> Limited <i>Acinetobacter</i> spp. activity
Murepavadin	OMPTA	Highly active against MDR <i>P. aeruginosa</i>	Phase III	Showed activity against colistin, ceftolozane/tazobactam and tobramycin nonsusceptible <i>P. aeruginosa</i>
Sulopenem	Carbapenem	ESBL, AmpC	Phase III	Does not provide additional activity to current carbapenems

BL: β -lactam; BLI: β -lactamase inhibitor; HABP: hospital-acquired bacterial pneumonia; VABP: ventilator-associated bacterial pneumonia; ESBL-E: extended spectrum β -lactamase Enterobacteriales; MDR: multidrug-resistant; *P. aeruginosa*: *Pseudomonas aeruginosa*; FDA: United States Food and Drug Administration; EMA: European Medicines Agency; CRE: carbapenem-resistant Enterobacteriaceae; KPC: *Klebsiella pneumoniae* carbapenemase; MBL: metallo- β -lactamase; *A. baumannii*: *Acinetobacter baumannii*; MSSA: methicillin-sensitive *Staphylococcus aureus*; CABP: community-acquired bacterial pneumonia; MIC: minimum inhibitory concentration; *C. difficile*: *Clostridium difficile*; OXA: OXA- β -lactamases; VIM: Verona integron-encoded metallo- β -lactamases; NDM: New Delhi metallo- β -lactamases. [#]: EMA or FDA; [¶]: inclusive of *in vitro* and *in vivo* data, which may not correlate with clinical efficacy.

TABLE 4 Monoclonal antibody treatment options for Gram-negative respiratory infections

	Target	Gram-negative target(s)	Development phase	Studied place in therapy
A1102	LPS-O-antigen D-galactan-III	<i>K. pneumoniae</i>	Pre-clinical	Prevention
A1124	LPS-O-antigen o25b	<i>E. coli</i>	Pre-clinical	Prevention
AR-101	LPS 011 exopolysaccharide	<i>P. aeruginosa</i>	Phase II	Treatment
AR-105	Alginate exopolysaccharide	<i>P. aeruginosa</i>	Phase II	Prevention and treatment
Anti-Hyr1	Hyr1 peptide 5	<i>A. baumannii</i> and <i>K. pneumoniae</i>	Pre-clinical	Prevention
KB001-A	Pcrv protein	<i>P. aeruginosa</i>	Phase II/III	Prevention
MEDI3902	Pcrv protein and Psl exopolysaccharide	<i>P. aeruginosa</i>	Phase II	Prevention

LPS: lipopolysaccharide; *K. pneumoniae*: *Klebsiella pneumoniae*; *E. coli*: *Escherichia coli*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *A. baumannii*: *Acinetobacter baumannii*.

emergence, minimal disturbance of gut microbiota and unique pharmacokinetic profiles. Still, limitations related to target specificity, cost, antibody development, administration, availability and clinical data hamper use in routine clinical practice [87]. Results of ongoing clinical trials are awaited to properly assess their efficacy, safety and appropriate place in therapy.

Bacteriophage therapy

Bacteriophages (phages) are the most abundant viruses/organisms on Earth and can infect and replicate within bacterial cells, causing lysis [98]. Leveraging phages to target pathogenic bacteria has seen a resurgence due to threats of antimicrobial resistance and advancements in molecular engineering (table 5). Bacteriophages offer several presumed advantages related to their specificity and ubiquity, including minimal effects on microbiota, safety profile, administration flexibility, and self-limiting properties. However, there is a paucity of data in these regards, combined with unknowns surrounding monitoring, toxin release, antibody production and inevitable development of resistance. Considerations of the unique interplay with bacteria, antibiotics and the immune system are necessary to optimise delivery and production, minimise or leverage resistance and understand their safety.

Clinical evidence for phages is limited to case series and reports. A systematic review highlighted the potential of phages in difficult-to-treat respiratory infections [99]. One such case described success of adjunctive phage therapy for the treatment of a *P. aeruginosa* VAP and bronchopleural fistula after thoracotomy, resulting in both clinical improvement and bacterial eradication at 6-month follow-up [100]. Phage therapy has exceptional potential for patients with MDR Gram-negative respiratory infections; however, well-designed clinical trials are still necessary.

Oligonucleotides

Antimicrobial oligonucleotides are synthetic nucleic acid sequences able to silence genes vital to bacterial survival (table 6) [98]. *In vivo* and *in vitro* data suggest that oligonucleotides may serve as a future treatment modality of severe Gram-negative respiratory infections [98]. Oligonucleotides targeting the genes MexB, ^{bla}NDM-1, and CTX-M-15 have resulted in improved minimum inhibitory concentration (MIC) profiles of common antimicrobials [101, 102]. Like mAbs and phages, oligonucleotides offer a target-specific method with potentially longer-lasting effects and reduced resistance development; however,

TABLE 5 Bacteriophage therapies for Gram-negative respiratory infections

	Phage components	Bacterial target	Development phase	Administration route
AB-PA01 cocktail	Pa193, Pa204, Pa222, Pa223	<i>P. aeruginosa</i>	Pre-clinical	Intravenous ± nebulised
AB-PA01 m1	Pa193, Pa204, Pa222, Pa223, Pa176	<i>P. aeruginosa</i>	Pre-clinical	Intravenous ± nebulised
<i>Acinetobacter</i> therapies	2φ ± φAb124	<i>A. baumannii</i>	Pre-clinical	Topical or nebulised
<i>Achromobacter</i> cocktail	Not specified	<i>A. xylosoxidans</i>	Pre-clinical	Oral + nebulised
Navy Phage cocktail 1	Paφ1, PaSKWφ17, PaSKWφ22	<i>P. aeruginosa</i>	Pre-clinical	Intravenous ± nebulised
Navy Phage cocktail 2	PaATFφ1 and PaATFφ3	<i>P. aeruginosa</i>	Pre-clinical	Intravenous
Adaptive Therapeutics phage	BdPF16phi4281	<i>B. dolosa</i>	Pre-clinical	Intravenous

P. aeruginosa: *Pseudomonas aeruginosa*; *A. baumannii*: *Acinetobacter baumannii*; *A. xylosoxidans*: *Achromobacter xylosoxidans*; *B. dolosa*: *Burkholderia dolosa*.

TABLE 6 Oligonucleotides for Gram-negative respiratory infections

Gene silenced and typical function		Silencing clinical result	Development phase	Bacterial target
CTX-M-15 ASO	<i>bla</i> _{CTX-M-15} Encodes resistance to third-generation cephalosporins	Reduced MIC to third-generation cephalosporins	Pre-clinical	<i>E. coli</i> ; other Gram-negatives
MexB siRNA	<i>mexB</i> Encodes efflux pump component	Restored activity of resistant antibiotics	Pre-clinical	<i>E. coli</i> ; other Gram-negatives
NDM-1 ASO	<i>bla</i> _{NDM-1} Encodes carbapenemases	Restored activity of resistant antibiotics	Pre-clinical	<i>P. aeruginosa</i> ; other Gram-negatives

NDM: New Delhi metallo-β-lactamases; MIC: minimum inhibitory concentration; *E. coli*: *Escherichia coli*; *P. aeruginosa*: *Pseudomonas aeruginosa*.

limitations surrounding their adequate delivery, use with antibiotics and unestablished safety and efficacy profile highlight the need for continued study.

Role of stewardship in curbing MDR spread

Antimicrobial stewardship programmes (ASPs) are an essential tool in helping prevent the spread of MDR respiratory infections, and involve a multidisciplinary approach to ensure that patients receive appropriate initial antibiotic therapy, appropriate dosing and route of administration, as well as sufficient duration of antimicrobial therapy [103, 104]. The goal of ASPs is to improve clinical outcomes of patients, decrease costs associated with antimicrobial use and control the spread of resistant organisms [105–107]. It is increasingly recognised that ASPs are an essential part of management of hospitalised patients, especially those in the ICU, and its use is recommended by the Infectious Diseases Society of America and international sepsis guidelines [59, 104, 108].

The ICU is an essential area for ASPs, due to the frequent use of antibiotics, high levels of MDR organisms and implications for poor clinical outcomes in patients treated with inappropriate antibiotics [105–107, 109]. Despite more than half of patients in the ICU having suspected or confirmed infection, antibiotic use in the ICU is still frequently overly broad or too narrow [1, 106]. The consequence of overly broad antimicrobial use in the ICU leads to the development of antimicrobial-resistant organisms, which is associated with increased mortality [1, 110, 111]. Infection with an MDR organism is also associated with increased all-cause mortality and increased likelihood of hospital readmission [112].

Respiratory infections in critically ill patients represent an important area for antimicrobial stewardship, and pneumonia is the most common infection found in the ICU [1]. Initial antibiotic therapy that is inappropriately narrow has been shown to be associated with an increased risk of mortality, while initial antibiotic therapy that is inappropriately broad-spectrum has also been associated with increased risk of mortality [113]. Appropriate duration of antibiotic therapy is also an important aspect of ASPs, as unnecessarily prolonged courses of antibiotics are associated with adverse patient outcomes and the development of MDR organisms [111, 113]. TESHOME *et al.* [111] showed that each additional day of broad-spectrum antibiotic use directed against *P. aeruginosa* was associated with an increased risk of development of MDR infection. The benefits of shorter courses of antibiotics for pneumonia were shown in a systematic review and meta-analysis of >1000 patients with hospital-acquired pneumonia (HAP) and VAP found that a shorter course of antibiotics resulted in increased 28-day antibiotic-free days as well as a reduction in recurrent VAP due to MDR organisms [114].

In a retrospective cohort analysis of >17 000 patients admitted to the hospital with sepsis and positive cultures, RHEE *et al.* [113] found that overly broad empirical antibiotic therapy was associated with increased mortality, with an estimated 20% increase in the odds of death. The adverse effects of overly broad antibiotic therapy were also seen in a retrospective study of over 1900 patients admitted to the hospital with pneumonia, which showed that the use of broad-spectrum antibiotics in community-onset pneumonia was associated with longer hospital stays, increased rates of *Clostridium difficile* infection and increased mortality [115]. Unnecessarily broad antibiotic therapy has the unfortunate consequence of disrupting the microbiome, which refers to the numerous bacteria, fungi and viruses that exist in a symbiotic relationship with a human body [116, 117]. The use of broad-spectrum antibiotics has been shown to alter the beneficial bacteria that make up the microbiome, leading to dysbiosis and placing the patient at risk for colonisation with MDR organisms and subsequent opportunistic infections [116].

ASPs can be beneficial in preserving the host microbiome by limiting unnecessary antimicrobial use and limiting length of therapy to an appropriate duration. The importance of appropriate timing, duration and spectrum of antimicrobial activity is detailed in figure 5.

The success of an ASP is dependent on several key elements and must include a multidisciplinary approach that utilises the expertise of ICU physicians, infectious disease physicians, pharmacists and microbiologists [104, 106]. Several of the key elements that are recommended by the United States Centers for Disease Control and Prevention for a successful ASP are detailed in table 7 [104]. Prospective audit and feedback of antibiotic use is an effective aspect of an ASP, which functions as a review of broad-spectrum antibiotic therapy leading to antibiotic de-escalation when appropriate [103, 104]. It has been shown to be associated with a reduction in use of broad-spectrum antibiotics in critically ill patients, reduction in resistance of Gram-negative organisms, with no adverse consequences on mortality or ICU length of stay [103, 108, 118].

Clinical decision support systems are another important part of an effective ASP, which are designed to incorporate numerous clinical and patient-specific data in order to provide more information to clinicians so that they can make more appropriate decisions regarding antimicrobial therapy. Previous studies have shown that clinical support tools that make antibiotic recommendations using patient data and antibiogram information can decrease overall use of antibiotics [119] as well as improve initial antibiotic therapy in patients with sepsis [120].

Rapid diagnostic testing to identify a source of infection remains an area of need for ASPs in the ICU. Earlier identification of causative organisms, as well as rapid diagnostics that are sensitive in ruling out specific organisms that are treated with broad-spectrum antimicrobials can lead to rapid de-escalation of antibiotics [103]. A randomised controlled trial of 45 mechanically ventilated patients with suspected pneumonia showed that testing with a PCR of bronchoalveolar lavage fluid for MRSA resulted in significant reduction in vancomycin and linezolid use when MRSA was not detected compared to the control group [121]. PCR-based assays for detection of Gram-negative organisms remains a challenging area, but recent studies have demonstrated good sensitivity of PCR-based assays in detecting respiratory

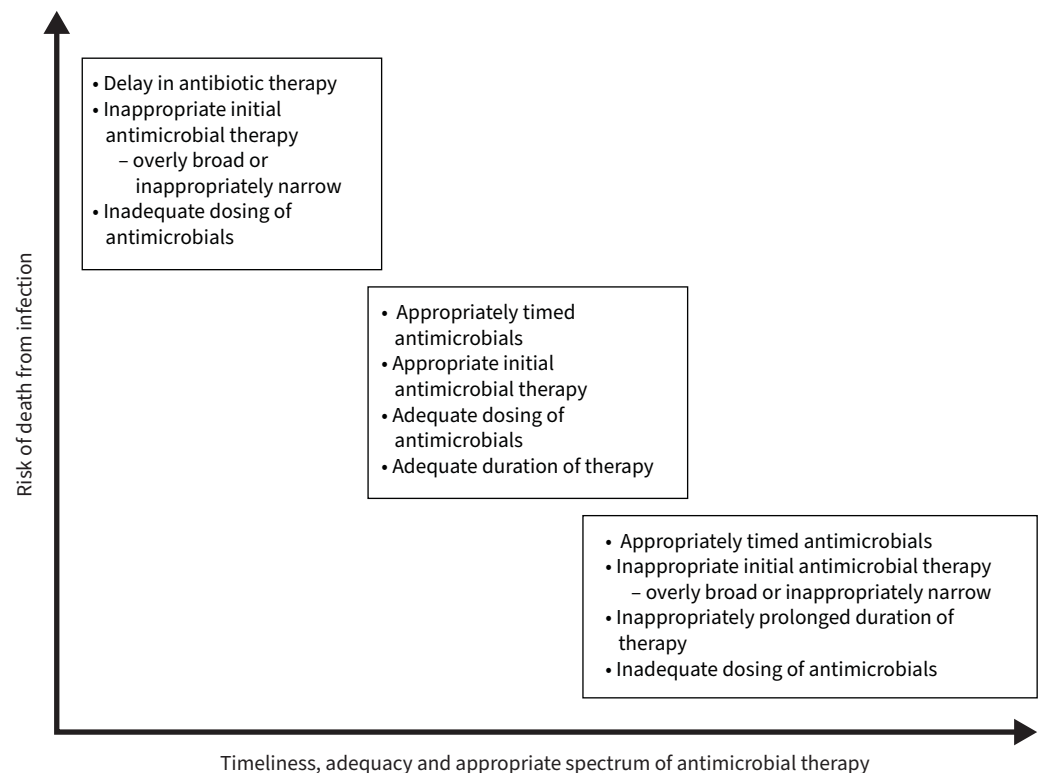


FIGURE 5 The importance of appropriate timing, duration and spectrum of antimicrobial activity.

TABLE 7 Key components of an effective antimicrobial stewardship programme

Description		Outcomes
Pre-authorisation	Prescribers are required to gain approval prior to use of certain antimicrobials	Ensures appropriate antibiotic selection and dosing Prevents unnecessary initiation of antibiotics
Prospective audit and feedback	External review of antibiotics after initiation, with suggestions from experts on optimal use	Reduction in unnecessary use of broad-spectrum antibiotics
Facility-specific treatment guidelines	Specific treatment guidelines for common conditions, such as community-acquired pneumonia, UTI and surgical prophylaxis, taking into account national guidelines and local susceptibilities and formulary options	Simplifies antibiotic prescribing for common conditions Allows for consensus between stewardship team and prescribers
Antibiotic time-outs	Provider-led reassessment of the continuing need for antibiotics after additional clinical information has returned	Improves the appropriateness of antibiotic use Encourages antibiotic de-escalation when appropriate
Pharmacy-based interventions	Prescribing interventions by pharmacy to optimise antibiotic use May be incorporated into electronic health record	Dose optimisation, dose adjustments based on renal function, changing intravenous antibiotics to oral formulation
Rapid diagnostics	Early pathogen identification using technology such as PCR to identify bacterial infection prior to awaiting culture results	Earlier identification of causative organism can lead to antibiotic de-escalation and optimisation of antibiotics
Clinical decision support system	Incorporation of clinical and patient-specific data into electronic health record to provide providers with relevant information prior to prescribing antibiotics	Decreased overall antibiotic use and improved use of antibiotics in patients with sepsis

UTI: urinary tract infection

pathogens, including detection of potential resistant organisms, which could lead to improvements in antimicrobial prescribing [122, 123].

One alternative to empiric broad-spectrum antibiotics for critically ill patients with a suspected HAP/VAP is to utilise surveillance cultures to guide initial antimicrobial therapy. If MDR pathogens are found on surveillance cultures, initial antibiotic therapy can be directed towards that pathogen, while more narrowed antibiotics could be used in a patient without MDR colonisation. Multiple studies have investigated the use of surveillance cultures, with varying degrees of sensitivity and specificity, depending on the sites of surveillance as well as the frequency of surveillance cultures [124]. A prospective observational cohort study investigated the role of surveillance cultures for identifying MDR *P. aeruginosa* by performing daily tracheal aspirates on patients mechanically ventilated for >48 h, and found 75 patients with newly colonised *Pseudomonas*, 27% of whom had MDR *P. aeruginosa* and 45% of whom went on to develop VAP, which the authors argued emphasised the importance of early detection of MDR colonisation to guide antibiotic therapy [125]. A systematic review and meta-analysis investigated whether surveillance cultures of lower respiratory tract specimens accurately predicted VAP organisms, and they found a pooled sensitivity of 75% and specificity of 92% in culture-positive VAP, showing that surveillance cultures may be able to accurately predict MDR VAP [126]. Cultures may need to be taken more than twice weekly, which contributes to the main limitation of the surveillance strategy, which is its high cost [124, 126].

Selective oropharyngeal decontamination (SOD) and selective digestive decontamination (SDD) are additional methods used to reduce the burden of MDR pathogens in ICUs. SOD/SDD refers to prophylactic treatment with antibiotics, often involving a paste in the oropharynx, enteral suspension of antimicrobials and an intravenous antibiotic, typically early on after ICU admission [127]. There have been numerous studies looking into the effect of SOD/SDD on development of MDR infections and ICU outcomes, with previous studies in ICUs with low levels of antibiotic resistance showing benefits of SOD/SDD, including lower levels of development of MDR pathogens and improved mortality [127, 128]. The use of SOD/SDD in ICUs with high endemic levels of MDR pathogens is more controversial, although a recent prospective observational cohort study found that implementation of an SDD programme in an ICU in Spain with high endemic levels of bacterial resistance led to a reduction of infections caused by MDR organisms, while also being associated with lower rates of VAP and bloodstream infections [129]. The most recent guidelines from the European Respiratory Society suggest utilising SOD but not SDD in areas with low levels of antimicrobial resistance for patients who are mechanically ventilated for >48 h [130].

There have been several studies demonstrating the benefits of ASPs in reducing the development of MDR organisms. A large systematic review and meta-analysis of 26 studies investigating the effects of implementation of an ASP on hospitalised patients showed a pooled percentage change of total antibiotic use of -19% , which increased to -39% in ICU patients [131]. Additionally, implementation of an ASP was associated with a reduction of infection with MDR organisms such as MRSA, carbapenem-resistant *P. aeruginosa* and ESBL *Klebsiella* [131]. A separate systematic review and meta-analysis included 32 studies that investigated development of infection and colonisation with MDR organisms, finding that ASP led to a 51% reduction in the development of an infection or colonisation with an MDR Gram-negative bacteria, a 48% reduction in ESBL Gram-negative bacteria and a 37% reduction in MRSA infection and colonisation [132].

Conclusions

The rising tide of antibiotic resistance leading to endemic spread and infection with MDR/XDR Gram-negative bacteria is a cause for great alarm. Greater research and clinical efforts now and in the future need to be directed towards improved methods for the diagnosis, prevention and treatment of MDR/XDR Gram-negative bacteria, as well as respiratory infections attributed to these pathogens. Only in this way can we prevent a future pandemic of infection attributed to MDR/XDR respiratory infections. The importance of this goal is highlighted by the future possibility of having converging respiratory infection pandemics, one caused by a respiratory virus and the other by MDR/XDR Gram-negative bacteria.

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