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Therapies for multidrug resistant and extensively drug-resistant non-fermenting gram-negative bacteria causing nosocomial infections: a perilous journey toward “molecularly targeted” therapy

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Abstract

Introduction: Non-fermenting Gram-negative bacilli are at the center of the antimicrobial resistance epidemic. *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are both designated with a threat level to human health of “serious” by the Centers for Disease Control and Prevention. Two other major non-fermenting Gram-negative bacilli, *Stenotrophomonas maltophilia* and *Burkholderia cepacia* complex, while not as prevalent, have devastating effects on vulnerable populations, such as those with cystic fibrosis, as well as immunosuppressed or hospitalized patients.

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Declaration of interest

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Areas covered: In this review, we summarize the clinical impact, presentations, and mechanisms of resistance of these four major groups of non-fermenting Gram-negative bacilli. We also describe available and promising novel therapeutic options and strategies, particularly combination antibiotic strategies, with a focus on multidrug resistant variants.

Expert commentary: We finally advocate for a therapeutic approach that incorporates *in vitro* antibiotic susceptibility testing with molecular and genotypic characterization of mechanisms of resistance, as well as pharmacokinetics and pharmacodynamics (PK/PD) parameters. The goal is to begin to formulate a precision medicine approach to antimicrobial therapy: a clinical-decision making model that integrates bacterial phenotype, genotype and patient's PK/PD to arrive at rationally-optimized combination antibiotic chemotherapy regimens tailored to individual clinical scenarios.

Keywords

Gram-negative bacteria; glucose-non-fermenting; antimicrobial resistance; nosocomial infections; mechanisms of resistance; combination therapy, precision medicine

1. Introduction

During the past decade, the scientific, public health, and political communities realized the alarming public health crisis that antimicrobial resistance (AMR) represents. Based on a landmark report from the Centers for Disease Control and Prevention (CDC) published in 2013, we now know that AMR affects more than 2 million people every year, resulting in a minimum estimate of 23,000 deaths per year in the United States (U.S.) and 25,000 deaths per year in the European Union [1,2]. These figures pale in comparison to the estimate put forth by the British Government in May 2016 where authorities predict that by 2050, approximately 10 million people would die every year globally as a result of AMR, more people than currently die from cancer [3]. The problem has therefore reached proportions of significant importance for both human health and the economy, enough to propel the issue of AMR to the forefront of national and global health concerns. The Infectious Disease Society of America (IDSA) and the World Health Organization (WHO) regard AMR as one of the three greatest threats to human health worldwide [4,5]. National and world health leaders describe antibiotic-resistant bacteria as “nightmare bacteria” that “pose a catastrophic threat” to people in every country in the world [1].

Among such bacterial pathogens, two lactose- and glucose non-fermenting Gram-negative bacteria (GNB) are described by the Centers for Disease Control and Prevention (CDC) report as microorganisms with a threat level of serious: multidrug resistant (MDR) *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Two other groups of non-fermenting GNB did not make the list, probably due to their relatively lower incidence of infection: *Stenotrophomonas maltophilia* and *Burkholderia cepacia* complex (Bcc). Despite their lower incidence, these two groups of organisms also represent growing concerns, particularly to vulnerable hospitalized and immunosuppressed patients. Of particular concern, non-fermenting GNB are intrinsically resistant to a wide array of antibiotics, diminishing available therapies to only a few active antibiotics. In recent years, acquired resistance to many of these active agents has reduced therapeutic options even further, straining our

resources in combating their rise. Note that the CDC and the European CDC define MDR as acquired non-susceptibility to at least one agent in three or more antimicrobial categories, and extensive-drug resistance (XDR) as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories) [6].

In this review, we offer a general summary of the clinical impact and mechanisms of resistance of the four major groups of non-fermenting GNB: *P. aeruginosa*, *A. baumannii*, *S. maltophilia*, and *Bcc* organisms. We also present available and promising novel therapeutic options and strategies, particularly combination antibiotic strategies, with a focus on multidrug resistant variants.

2. Clinical impact and mechanisms of resistance

2.1 *Pseudomonas aeruginosa*

2.1.1 Clinical impact—Since their discovery by Professor Migula of the Karlsruhe Institute in Germany at the end of the 19th century, *Pseudomonas* spp. have proved to be formidable pathogens, efficiently adapting to and colonizing the environments they inhabit, resulting in serious and devastating infections [7,8]. Owing to these qualities, in addition to its intrinsic resistance to many antibiotics, *P. aeruginosa* is successful as a nosocomial and opportunistic pathogen in vulnerable populations, namely the immunosuppressed, critically ill, and burn patients [9,10]. Infections caused by *P. aeruginosa* are also notorious in patients with severe structural lung disease and cystic fibrosis, in whom rates of multidrug resistance are even higher [8,11–13]. The clinical impact of *P. aeruginosa* is as such the most significant among non-fermenting bacteria in the Western world, with converging epidemiologic data from the U.S. and Europe [14,15].

In the U.S., among healthcare-associated infections reported to the National Healthcare Safety Network (NHSN) in its latest report between 2011 and 2014, *P. aeruginosa* represented 7% of pathogens, ranking sixth overall but second and third for ventilator-associated pneumonias (VAP) and catheter-associated urinary tract infections, respectively [16]. Carbapenem resistance in that report averaged 26% for catheter-associated bloodstream infections (2011–2014) and 28% for VAP (2011–2012) [16].

National and global trends of infections caused by carbapenem-resistant *P. aeruginosa* are alarming, knowing that such infections portend a significantly worse prognosis than infections caused by susceptible strains. A meta-analysis of 17 studies comprising 6660 patients with *P. aeruginosa* infections indicated that infections caused by carbapenem-resistant *P. aeruginosa* are associated with a significantly higher mortality than those caused by carbapenem-susceptible *P. aeruginosa* (adjusted OR=2.38; 95% CI=1.53, 3.69) [17]. Similarly, in a prospective cohort of 709 consecutive episodes of bloodstream infections caused by *P. aeruginosa*, Morata et al. observed a 32% mortality rate for episodes caused by MDR *P. aeruginosa* vs. 17% for those caused by non-MDR isolates ($p<0.0001$) [18]. Overall mortality rate in a Korean cohort of 100 episodes of bacteremic pneumonias due to *P. aeruginosa* reached 51% at 28 days, a rate comparable to death from Ebola virus disease [19,20]. Finally, data from a 13-year prospective cohort of bloodstream infections from

Duke University Medical Center (2002–2015), *P. aeruginosa* bloodstream infection was associated with the highest mortality relative to *S. aureus* or other GNB, even after adjustment for patient and treatment factors [21].

2.1.2 Mechanisms of resistance—In general, resistance to β -lactam antibiotics in *P. aeruginosa* is due to mutations that lead to hyperproduction of AmpC cephalosporinases (*Pseudomonas*-derived cephalosporinases, PDC). In the case of carbapenem-resistant strains, there usually is an interplay of mutations in the OprD porin (sufficient to exclude imipenem), up-regulation of drug-efflux pumps (usually needed to exclude meropenem), mutations in the penicillin-binding-proteins (PBP) and decrease in PBP expression [22–24]. These mutational mechanisms are involved in *in vivo* emergence of pan- β -lactam resistance. Fortunately, many such strains retain susceptibility to the new antipseudomonal cephalosporin, ceftolozane, which is co-formulated with the β -lactamase inhibitor tazobactam [25]. Similarly, the combination of ceftazidime with avibactam, the novel β -lactamase inhibitor against ESBLs, class A, some class D β -lactamases, and AmpC class C enzymes, also has significant activity against these types of strains resistant to all other β -lactams. Of note, neither ceftazidime-avibactam nor ceftolozane-tazobactam are active against *P. aeruginosa* with acquired carbapenemases, such as metallo- β -lactamases (MBLs). Nevertheless, pre-existent resistance against ceftazidime-avibactam is not infrequent in *P. aeruginosa*, likely due to changes in membrane permeability and drug efflux [26]. Resistance to ceftolozane-tazobactam can occur prior to treatment, and is associated with therapeutic failure [27]. Emergence of resistance during treatment has been observed, and attributed to mutations resulting in AmpC or PDC overexpression [28]. MBLs are only detected sporadically in the U.S. [24,29]. In a recent survey of 290 meropenem non-susceptible *P. aeruginosa* from 34 US hospitals, an extensive genotypic characterization revealed the presence of VIM (an MBL) among only 4% of the subset of isolates non-susceptible to ceftazidime-avibactam, ceftolozane-tazobactam or both. MBL-producing *P. aeruginosa* have with VIM-7 and VIM-2 have been detected in cancer patients in Houston and VIM-2 producing *P. aeruginosa* have caused outbreaks in Chicago and Northeast Ohio [30,31]. In contrast, VIM-2 mediated carbapenem-resistance in *P. aeruginosa* has long been observed in the Mediterranean basin [32]. Indeed, among 529 isolates of *P. aeruginosa* collected from 2009–2011 from 14 European and Mediterranean countries, there was increasing prevalence of MBL producers, from 12% in 2010 to 31% in 2011 [33]. *P. aeruginosa*-harboring *Klebsiella pneumoniae* carbapenemase (KPC) has been detected in Puerto Rico and other Latin American locales [34]. Note that the major mechanisms of resistance for *P. aeruginosa* as well as the other organisms discussed are summarized in **Table 1**.

2.2 *Acinetobacter baumannii*

2.2.1 Clinical impact—The genus *Acinetobacter* contains more than 55 species, most of which are non-pathogenic and are recovered from soil, water, and even hydrocarbon sludge [35,36]. In the 1970s, several members of the species, collectively named *Acinetobacter baumannii-calcoaceticus* complex (ABC), emerged as serious pathogens, involved in numerous nosocomial outbreaks. The ABC complex includes *A. baumannii*, *A. nosocomialis* and *A. calcoaceticus* [37].

Initially susceptible to several classes of antibiotics, *A. baumannii* isolates are now routinely XDR, including resistance to carbapenems [38]. A pooled analysis of patients with carbapenem-resistant *A. baumannii* revealed that they face a significantly higher risk of mortality than patients with carbapenem-susceptible isolates, with a crude OR of 2.22 (95% CI = 1.66, 2.98). The risk of mortality is perhaps increased because patients with carbapenem-resistant *A. baumannii* are more likely to have severe underlying illness and receive inappropriate antimicrobial treatment than patients with carbapenem-susceptible isolates. [39].

In the U.S., *A. baumannii* is a cause of less than 2% of all healthcare-associated infections reported to the NHSN. In the latest NHSN report spanning 2011–2014, it was no longer in the top 15 most prevalent species reported across all hospital-associated infections [16]. Whether there is indeed a “secular trend” towards lower rates of infections caused by *A. baumannii* in the US healthcare system requires confirmation. Nonetheless, *A. baumannii* displays the highest carbapenem-resistance rates relative to all the other reported pathogens: 52% and 64% for isolates causing catheter-associated bloodstream infections and catheter-associated urinary tract infections respectively (for 2011–2014), and 60% for isolates causing VAP (2011–2012) [16].

2.2.2 Mechanisms of resistance—*A. baumannii* demonstrates low permeability to antibiotics and constitutive efflux which allows it to inherently evade a broad array of antibiotics [38]. The former is the result of reduced outer membrane porin content compared to other Gram-negative organisms, and the latter is caused by constitutive low expression of one or more active efflux systems [38,40].

In addition to these inherent characteristics, acquired resistance mechanisms include numerous β -lactamases (most commonly AmpC or *Acinetobacter*-derived cephalosporinases, ADC), OXA type-carbapenemases (intrinsic OXA-51, and the acquired OXA-type enzymes belonging to the OXA-23, OXA-24/40, OXA-58, OXA-143, and OXA-235 subfamilies), efflux pumps, as well as alterations of outer membrane proteins and alteration in expression of penicillin binding proteins (PBP). Reports of isolates containing KPC, and MBLs such as the New Delhi MBL (NDM-1) also exist [41].

A. baumannii acquires resistance genes from other organisms via horizontal gene transfer [42]. Globally, two clones labeled global clones 1 and 2 (GC1 and GC2) currently account for the majority of MDR isolates of *A. baumannii* and were first identified in the 1970s. Hall and colleagues recently dissected the evolutionary history of these clones, particularly GC1. The Australian team revealed a high mutation rate, coupled with extensive horizontal gene transfer and homologous recombinations that overtime have resulted in a diversity of MDR subclones [43]. Fournier *et al.* described a remarkably resistant strain of *A. baumannii*, the AYE epidemic strain. This strain had an 86 kilobase genomic island (AbaR1) containing 88 open reading frames (ORF) likely acquired from other Gram-negative organisms such as *Salmonella*, *Escherichia coli* and *Pseudomonas* spp. Of the 52 resistance genes found in this strain, as many as 45 were localized to this resistance island alone [44]. This and other examples illustrate the outstanding ability of the Species to diversify and lead to new resistant and versatile pathogens [42].

2.3 *Stenotrophomonas maltophilia*

2.3.1 Clinical impact—*Stenotrophomonas maltophilia* is an emerging pathogenic non-fermenting Gram-negative rod most commonly encountered among immunocompromised hosts in the hospital setting. Risk factors for infection in non-cystic fibrosis patients include malignancy (especially hematologic), treatment with corticosteroids or immunosuppressant medications, exposure to broad spectrum antibiotics, prolonged hospitalization, intensive care unit admission, mechanical ventilation, presence of an indwelling central catheter, and hemodialysis [45]. Recent surveillance studies estimate its prevalence among isolates from all sources at 1.3% to 1.7% [46]. *S. maltophilia* is an environmental pathogen found in water and soil, and has also been isolated in multiple medical devices and products. Most common infectious syndromes are pneumonia, including hemorrhagic pneumonia, bloodstream infection, including catheter-associated bloodstream infections, and urinary tract and wound infections. Other less common syndromes include post-neurosurgical meningitis, endocarditis, sinusitis, eye infections and septic arthritis [47]. Although difficult to ascertain, in a systematic review, Falagas *et al.* estimated attributable mortality of *S. maltophilia* infections at up to 38% [48]

Mortality is even higher in patients with malignancy, in whom it can reach more than 50% [49,50].

2.3.2 Mechanisms of resistance—*S. maltophilia* is intrinsically resistant to β -lactams including carbapenems, as well as aminoglycosides. Like *A. baumannii*, it possesses a relatively impermeable membrane, and like *P. aeruginosa*, it expresses efflux pumps and acquires additional resistance determinants in class 1 integrons. Key mechanisms of resistance include the production of inducible β -lactamases, and aminoglycosides-modifying enzymes, listed in **Table 1** [45,51,52]. The *S. maltophilia* chromosome harbors two β -lactamases: L1, an MBL with carbapenemase activity that does not hydrolyze aztreonam, and L2, a serine cephalosporinase that can be inhibited by clavulanic acid [51,53]. Trimethoprim-sulfamethoxazole is left as the main antibiotic option to reliably treat infections caused by *S. maltophilia*, although resistance has emerged, associated with the genes *sul1* and *sul2*. These have been linked to the presence of class 1 integrons in plasmids in the main, but also in the chromosomal genome [51]. Fluoroquinolones, colistin, and especially tigecycline and minocycline may offer activity [54].

2.4 *Burkholderia cepacia* complex

2.4.1 Clinical impact—*B. cepacia* complex (*Bcc*) organisms are ubiquitous environmental pathogens found worldwide in water, soil and plants. *Bcc* were originally described by Burkholder in 1950 as the causative agents of the bacterial rot of onion bulbs. While agents from this group, particularly *B. multivorans*, are important pathogens in patients with cystic fibrosis and chronic granulomatous disease, they remain infrequent and their epidemiology poorly defined in other populations [55]. Information about clinical characteristics and outcome of patients with *Bcc* bloodstream infections is mostly derived from small cohorts in the context of outbreaks. These cohorts indicate that patients with *Bcc* bloodstream infections are critically ill older adults with serious underlying diseases, receive intensive care, and have undergone invasive procedures [56–58]. When sources of infection

were identified, the respiratory tract and intravascular catheters were the most common portals of entry [56–60].

Bcc organisms are also remarkable in their ability to contaminate environmental surfaces and drug solutions and cause outbreaks in vulnerable populations including hospitalized and intensive care unit patients, cancer patients and transplant recipients [61–69]. A recent report describes a multi-state outbreak related to oral liquid docusate sodium, a common stool softener [70,71]. Owing to lifestyle-specific chlorhexidine tolerance mechanisms via efflux pump mutants, *Bcc* organisms can also contaminate disinfecting solutions such as the widely used chlorhexidine and can be a cause of outbreaks in that context [72,73].

In addition to their outbreak and contamination potential, these organisms have bioenvironmental and agricultural applications. While they are no longer used for these purposes, prior use has raised concerns for selective pressure and resistance promotion through human environment contamination, including water reservoirs, food supply and household plants [74–76]. This, in addition to tolerance to chlorhexidine, render *Bcc* an under-recognized potential public health threat.

2.4.2 Mechanisms of resistance—*Bcc* organisms are intrinsically resistant to multiple antimicrobial classes, and acquired resistance is prevalent. Mechanisms of resistance are varied and selection of mutant clones is favored by the propensity of these organisms to cause long-standing and difficult-to-eradicate colonization and infections in patients exposed to frequent antibiotic courses, such as cystic fibrosis patients [77]. Antimicrobial treatment of infections caused by *Bcc* is more difficult due to their ability to form biofilms, particularly in patients with cystic fibrosis and those with intravascular catheters [78].

Resistance to β -lactams in *Bcc* is attributable to the production of inducible or constitutively expressed chromosomal or plasmid-mediated β -lactamases. One major β -lactamase is *PenA*, a chromosomally-encoded inhibitor-resistant class-A-carbapenemase that structurally resembles *Klebsiella pneumoniae* carbapenemase (KPC) [77,79]. Others are also described in the literature (*PenB*, *AmpC*), as well as efflux pumps and mutations in the cell-wall recycling enzyme AmpD, but the role of these mechanisms with treatment failure in clinical practice is not well understood and their relative impact may be differentially represented in individual *Bcc* species [55,77,80–86].

The main mechanisms of fluoroquinolones resistance occur through efflux transporter systems and through the accumulation of mutations in the quinolone resistance-determining region of the topoisomerase genes. Efflux systems are also implicated in resistance to aminoglycosides and trimethoprim. A modification of the dihydrofolate reductase enzyme also contributes to trimethoprim resistance, and changes in outer membrane affecting the binding sites on the lipopolysaccharide layer is related to intrinsic resistance to the polymyxins and aminoglycosides [83,85,87,88].

3. Implications for present and future antibiotic therapy

3.1 Introduction of concepts of therapy: monotherapy vs. combination antibiotic chemotherapy

The rise of MDR Gram-negative organisms and the dwindling pipeline of new agents and novel therapies have led to renewed interest in combination antibiotic regimens for MDR and XDR GNB, particularly carbapenem-resistant, polymyxin-only-susceptible isolates [89]. The supporting data for such use is mixed and mostly based on retrospective or nonrandomized prospective cohorts of clinically heterogeneous populations using a large number of different combinations [89,90]. With few exceptions [91], these studies so far point to an advantage of combination schemes over monotherapy only for carbapenem-resistant *Enterobacteriaceae* (CRE) but not for other MDR GNB infections [89,92].

Combination therapy seems beneficial in two instances in particular: i) for isolates that show a meropenem or imipenem Minimum Inhibitory Concentration (MIC) of < 16 mg/ L [93]; ii) for patients with CRE bloodstream infections and a high mortality score as measured by the validated mortality score INCREMENT-CPE, in whom combination therapy was associated with improved survival [94].

Despite limited data and concerns that combination chemotherapy is more expensive and potentially more toxic, it remains appealing for many reasons. Combination chemotherapies have proven their utility for various viral, mycobacterial and parasitic infections (HIV, MTB, malaria, filariasis etc.). The rationale for its use in MDR and XDR Gram-negative infections is based on maximizing bacterial killing and minimizing the emergence of resistance through synergistic combination of antibiotics [92]. Monotherapy with agents like polymyxins and fosfomycin, in many cases the only agents carbapenem-resistant Gram-negative organisms remain susceptible to, has been shown to lead to the development of resistance during therapy [8,89,92]. Additionally, we know that multidrug resistance has been associated with patients being more likely to receive inappropriate antimicrobial therapy and Micek *et al.* found that appropriate initial antimicrobial therapy was more likely to be administered in patients receiving combination chemotherapy. Hence combination chemotherapy might increase the likelihood of administering initial appropriate empiric therapy [8,95]. Further research is still needed to confirm whether the microbiologic rationale for combination chemotherapy translates into clinical benefit, but in the setting of multidrug resistance limiting effective options, careful consideration is warranted. So far three published randomized controlled trial (RCT) studied combination antibiotic chemotherapy for MDR GNB infections, and the three addressed the treatment of MDR *A. baumannii* alone (Table 2).

Two RCTs are currently ongoing to compare combination chemotherapy to monotherapy. They compare colistin and meropenem vs. colistin alone; one in patients with XDR *A. baumannii* and *P. aeruginosa*, and CRE (NCT01597973), the other in carbapenem-resistant, colistin-susceptible GNB (NCT01732250). While the former is still recruiting, we are awaiting the results of the latter which the authors, led by Mical Paul from Israel, completed in February 2017 (Table 2).

The results of these trials will shed further light on the clinical benefit of combination chemotherapy or lack thereof for infections caused mostly by *A. baumannii*, but the question remains for other non-fermenters such as *P. aeruginosa*, as well as *Bcc* and *S. maltophilia*. Indeed, these last two organisms present extraordinary challenges. *Bcc* are intrinsically resistant to both carbapenems and polymyxins and *S. maltophilia* is intrinsically resistant to multiple antibiotics including carbapenems; however, they are not the target of current studies or drug development efforts. These unfortunate realities underscore the urgent need to study combinations of agents active against these two organisms.

3.2 *P. aeruginosa*

3.2.1 Monotherapy—Traditionally, the anti-pseudomonal antibiotics include ceftazidime, cefepime, piperacillin/ tazobactam, aztreonam, carbapenems (except ertapenem), fluoroquinolones (ciprofloxacin, levofloxacin), aminoglycosides, and polymyxins. These agents should always be administered at the appropriate higher dosages described in the literature [96]. Of note, *in vitro* data demonstrate a lower MICs for doripenem against *P. aeruginosa*, followed by those of meropenem and imipenem [97]. However, the superior clinical efficacy of doripenem is not borne out by clinical studies.

Since the introduction of ceftolozane-tazobactam, several case reports and case series of MDR *P. aeruginosa* infections treated with ceftolozane-tazobactam have demonstrated the clinical efficacy of this formulation, including its use to treat infections in critically ill patients, and those with cystic fibrosis [98,99]. In contrast, experience with ceftazidime-avibactam in the management of *P. aeruginosa* infections is more limited, although adding avibactam to ceftazidime is successful in lowering MICs of many XDR *P. aeruginosa* isolates [100,101]. When considering XDR *P. aeruginosa*, an important concept is that although ceftolozane-tazobactam is more likely to be active than ceftazidime-avibactam, there are some ceftolozane-tazobactam-resistant strains that can be susceptible to ceftazidime-avibactam [102]. Therefore, *in vitro* susceptibilities to ceftazidime-avibactam should be obtained.

MBL-producing *P. aeruginosa* strains demonstrate resistance against all anti-pseudomonal β -lactams, including ceftazidime-avibactam and ceftolozane-tazobactam. The monobactam aztreonam is unique in demonstrating stability to hydrolysis by MBLs and MBL-producing *P. aeruginosa* may retain susceptibility to aztreonam [103,104]. Many strains of MBL-producing *P. aeruginosa* will also contain mechanisms of resistance against aztreonam, such as increased expression of PDCs. Nevertheless, aztreonam is an attractive component for rationally optimized combination with ceftazidime-avibactam for the treatment of infections caused by MBL-producing *P. aeruginosa* [105], as well as by MBL-producing *S. maltophilia* [53,106], and MBL-producing *Enterobacteriaceae* [107].

Analyses of PK/PD characteristics and clinical outcomes demonstrates that anti-pseudomonal β -lactams ought to be administered as an extended infusion, as this dosing strategy likely results in lower mortality relative to intermittent infusions, particularly for *P. aeruginosa* strains with higher MICs [108]. This strategy is based on the possibility of attaining longer periods of free drug exposure above the isolates' MICs [89]. In one study of patients with invasive *P. aeruginosa* infections admitted to the hospital between 2008 and

2010, mortality was significantly lower in the group that received extended cefepime infusion compared to those who were administered intermittent infusion (1/33 or 3% vs. 11/54 or 20%, $p=0.03$) [109]. The same group also observed a significant reduction in 14-day mortality in patients treated with extended infusions of piperacillin-tazobactam compared to intermittent infusions. Other studies have corroborated these findings [108], including large, double-blind placebo-controlled randomised controlled trials, as long as patients were not undergoing renal replacement therapy [110,111].

The anti-pseudomonal fluoroquinolones, ciprofloxacin and levofloxacin, when active, are important options against *P. aeruginosa* [112], especially because of their high oral bioavailability. Similarly, among aminoglycosides, tobramycin and amikacin offer reliable activity against *P. aeruginosa*, even MDR strains. Reservations about the efficacy and toxicity of monotherapy with aminoglycosides remain, but may be overcome with careful dosing guided by therapeutic drug monitoring, with special attention to peak and trough levels, and fluctuations in renal function [113].

The polymyxins, colistimethate-sodium and polymyxin B, have become a mainstay in the treatment of carbapenem-resistant and other MDR *P. aeruginosa*, as agents of “last resort”. Unfortunately, our confident use of polymyxins is hampered by evolving definitions of their different pharmacologic characteristics and nephrotoxic potential. Nonetheless, consensus is emerging regarding the superiority of colistin *versus* polymyxin B for treatment of urinary tract infections, but inferiority in all other infections, in addition to increased nephrotoxicity of colistin relative to that of polymyxin B [89]. Interestingly, case series and retrospective comparisons validate the efficacy of monotherapy with this class of agents against *P. aeruginosa*. Nevertheless, *in vitro* studies raise concerns about the reliability of polymyxins as monotherapy against *P. aeruginosa*, in terms of attaining requisite PK/PD targets and succumbing to resistance.

3.2.2 Combination chemotherapy—Both intrinsic and acquired resistance frequently result in delays before an appropriate antimicrobial regimen is initiated for *P. aeruginosa*. Such delays correlate with worse outcomes and higher mortality [114]. Therefore, there is a strong argument to support combination therapy for serious infections caused by *P. aeruginosa*, aiming to deliver effective empiric therapy. A multicenter retrospective study of 183 monomicrobial *P. aeruginosa* VAP cases in Spain showed that the administration of two empiric antipseudomonal antibiotics resulted in improved survival and fewer microbiological failures [115]. Conversely, a meta-analysis of 11 *P. aeruginosa* VAP clinical trials comprising 1,805 patients comparing monotherapy to combination chemotherapy, demonstrated no significant differences in either efficacy or treatment failure between both regimens, albeit the overall quality of the studies was low [116]. Similarly, a multicenter randomized trial conducted by Heyland and colleagues [117] among critically ill patients with late onset VAP found no statistically significant difference between combination chemotherapy and monotherapy. Although the trial revealed enhanced microbiologic clearance and shorter intensive care unit stays for patients receiving combination antimicrobials, the differences were not statistically significant. Neutropenic patients infections caused by *P. aeruginosa* may be more vulnerable to ineffective empiric therapy

[118]. Nevertheless, it is firmly established that there is no additional benefit of aminoglycosides to β -lactams monotherapy, and that they augment nephrotoxicity [119,120].

An additional theoretical argument for combination therapy is to achieve antimicrobial synergy, but this is difficult to demonstrate clinically [121]. The checkerboard technique has emerged as a means to examine various combinations and test for possible synergy in the management of MDR *P. aeruginosa* infections. Combination chemotherapy with piperacillin-tazobactam and tobramycin as well as ceftazidime and tobramycin displayed the highest synergy ratios [122]. The following combinations also displayed synergy: ceftazidime and colistin [123], clarithromycin and tobramycin [124], polymyxins and rifampin [125], meropenem and levofloxacin [126], and prolonged infusion fosfomycin (16 to 24 g) in combination with a carbapenem [127]. A concept that is invoked to support the use of combination therapy against *P. aeruginosa* is the potential suppression of the emergence of resistance. For example, the mechanistic analysis of a combined regimen of β -lactams and tobramycin demonstrated resistance suppression in *P. aeruginosa*, through reduction of AmpC β -lactamase expression due to inhibition of protein synthesis by tobramycin [128,129]. Furthermore, it is the antibiotic exposure achieved during the first dose that may be relevant for predicting the microbial response and prevention of resistance to a therapeutic intervention, and the likelihood of achieving this may be increased with combination therapy [130].

A special category is the use of polymyxins-containing combination “salvage regimens” for patients with serious infections caused by XDR *P. aeruginosa*. There is a considerable number of in vitro studies supporting the use of polymyxins in combination with carbapenems (i.e. doripenem) and other agents (e.g., fosfomycin). Unlike CRE, observational evidence demonstrating the value of combination therapy with polymyxin-based regimens (usually with carbapenems) against *P. aeruginosa* is scarce. In contrast with *Acinetobacter*, there are no published randomized controlled trials comparing polymyxin monotherapy vs. combination therapy. Nevertheless, clinicians treating patients with these challenging infections would be wise to carefully evaluate combinations on an individual basis. A suggested approach to interpretation of susceptibility testing and treatment of *P. aeruginosa* is presented in **Figure 1**.

3.2.3 Novel therapies—As discussed above, the recently introduced antibiotics ceftolozane-tazobactam and ceftazidime-avibactam offer activity against some carbapenem-resistant *P. aeruginosa*, but MBL producing isolates are categorically excluded. Although aztreonam-avibactam (currently in phase II studies) offers activity against MBL-producing *Enterobacteriaceae*, the MIC₉₀ against a large collection of *P. aeruginosa*, which included MBL-producing isolates, was 32 μ g/mL [131]. Meropenem-vaborbactam, also recently approved, is a combination with a β -lactams with a novel boronic acid β -lactamase inhibitor; unfortunately, its activity is similar to that of meropenem alone against *P. aeruginosa* [132]. In contrast, rates of susceptibility of *P. aeruginosa* to imipenem were improved from 70.3% to 94.2% with the addition of relebactam, a diazabicyclooctane similar to avibactam [133]. Imipenem-relebactam (MK-7655A) is currently in a phase III study to compare its efficacy against colistimethate-sodium in patients with infections caused by imipenem-resistant Gram-negative bacteria, including *P. aeruginosa* (NCT03293485).

Cefiderocol (S-649266), the novel siderophore cephalosporin able to penetrate the outer cell membrane through bacterial iron transporters, is stable against all β -lactamases and very potent against *P. aeruginosa*. Among 82 carbapenem-resistant *P. aeruginosa* from Greek hospitals, the MIC₉₀ of cefiderocol was 0.5 mg/L [134], similar to those from a global survey; however, isolates with higher MICs were also reported [135]. The recently announced results of a multicenter randomized controlled trial in patients with complicated urinary tract infections (APEKs-cUTI) demonstrated superiority against imipenem/cilastatin (clinical cure and microbiologic eradication of 72.6 % vs. 54.6 %) (NCT02321800). Additional trials vs. meropenem for hospital-acquired and ventilator-associated pneumonia (NCT03032380) and against “best available therapy” for resistant Gram-negative bacteria (NCT02714595) are underway.

There are anti-pseudomonal products that are not traditional antibiotics such as monoclonal antibodies [136] and bacterial phages. Aerubumab is an anti-*P. aeruginosa* IgG1 monoclonal antibody that binds to surface polysaccharide alginate to enhance immune response, with a prolonged half-life of 3–4 weeks. It is currently in phase-2 trials as adjunct treatment in addition to standard of care antibiotics for pneumonia caused by *P. aeruginosa* (NCT03027609). Similarly, MEDI-3902 is an anti-*P. aeruginosa* IgG monoclonal antibody that targets virulence factors Psl and PcrV and is in clinical trials for the prevention of ventilator-associated pneumonia in colonized patients (NCT02696902). The use of monoclonal antibodies beyond adjunctive of pre-emptive therapy, as an alternative to traditional antibiotics remains to be proven. A trial evaluating phage therapy for the treatment of wound infections, including those caused by *P. aeruginosa*, in burn patients (PHAGOBURN: NCT02116010) might offer more insight on use in humans although considerable work remains to be done before clinical development for systemic therapy is underway. Antimicrobial peptides [137] are also in development but remain in early stages.

3.3 *A. baumannii*

3.3.1 Monotherapy—Polymyxins (polymyxin B and polymyxin E or colistin, administered as colisthimetate sodium) are the backbone antibiotics for the treatment of carbapenem-resistant *A. baumannii*. However, high rates of renal injury, and, in the case of colistin, difficulty in achieving adequate and consistent plasma levels, as well as poor lung penetration, make their use challenging [138,139]. Resistance to polymyxins is also increasing, mostly mediated by preventing drug binding through modification of the lipid A moiety of lipopolysaccharide [140].

Sulbactam, in addition to being a β -lactamase inhibitor, also acts as a β -lactams by binding to PBP2, and is as such an active agent against *A. baumannii*. When susceptible, sulbactam-based therapies are a viable option to treat carbapenem-resistant *A. baumannii*, or even as a carbapenem-sparing option for carbapenem-susceptible strains [141]. Sulbactam is available only as ampicillin/sulbactam or cefoperazone/sulbactam in certain locations. A small meta-analysis of four studies suggest that sulbactam-based therapies are similarly efficacious to various comparator drugs (e.g., fluoroquinolones, tetracyclines, polymyxins, carbapenems) [141–143].

Minocycline and doxycycline are tetracycline antibiotics that are currently being investigated for the treatment of MDR *A. baumannii* infections. Most of the data is from small retrospective studies, where these agents were used in combination with other therapies. A systematic review by Falagas *et al.* summarized ten retrospective studies regarding doxycycline and minocycline for the treatment of 185 *A. baumannii* infection. In this review, tetracyclines in combination with other antibiotics (notably ampicillin-sulbactam, cefoperazone-sulbactam, aminoglycosides, carbapenems, tigecycline, and colistin) for the treatment of several infections caused by *A. baumannii* were successful in about 77% of patients with an observed mortality of 22% [144]. Tigecycline, a derivative of minocycline, is bacteriostatic and achieves low plasma concentrations. Levels in urine and different lung compartments might also not be sufficient to eliminate bacteria in patients with pneumonia [145,146]. Resistance has also emerged, in addition to breakthrough *A. baumannii* bacteremia during treatment with tigecycline. All these limitations, in addition to a black box warning about increased risk of death based on multiple systematic reviews [147], make tigecycline a last resort therapeutic option when no other alternative is available. High dose tigecycline-based regimens might overcome these limitations in MDR GNB including *A. baumannii* [148,149]. Fosfomycin does not have activity against *A. baumannii*. However, it demonstrated *in vitro* synergy with colistin and sulbactam [150]. Finally, use of rifampicin as monotherapy is limited by rapid development of resistance. However it has shown some promise as a part of combination chemotherapy.

3.3.2 Combination chemotherapy—Multiple studies have compared monotherapy to combination chemotherapy for the treatment of *A. baumannii*, but many are retrospective and propose heterogeneous combinations, precluding firm conclusions. A high-quality prospective observational study conducted in 28 Spanish hospitals did not find an association of combination therapy with improved mortality in infections caused by *A. baumannii* [151].

Polymyxin-carbapenem combinations are commonly used for the treatment of MDR *A. baumannii*, driven by evidence of *in vitro* synergy. In a systematic review and meta-analysis of *in vitro* synergy between the two classes comprising 1,054 bacterial isolates, Zusman *et al.* showed synergy rates as high as 77% in time-kill studies for combination chemotherapies for *A. baumannii*. This was the highest observed synergy rate when compared to other organisms such as *P. aeruginosa* (50%) or *K. pneumoniae* (44%). All had low antagonism rates [152].

Clinically, a number of prospective studies have examined polymyxin-based combination chemotherapies for the treatment of *A. baumannii* and share similar conclusions: i) a small, prospective randomized study of treatment of carbapenem-resistant *A. baumannii* VAP with colistin or colistin and rifampicin, showed improved time to microbiologic eradication in the combination treatment group (4.5 vs 3.1 days), but improvement in mortality was not evident [153]; ii) a RCT of colistin alone compared to colistin and rifampicin for the treatment of serious infections caused by *A. baumannii* showed improved microbiologic eradication with combination chemotherapy (60.6 vs 44.8) but again, significant differences in mortality were not seen [154]; iii) a study of colistin versus colistin plus fosfomycin for the treatment of carbapenem-resistant *A. baumannii* infections showed significant

microbiologic eradication in favor of the combination (87.8% vs 65.7%), but no significant difference in clinical response [155]. **Table 2** provides a summary of available and ongoing RCTs studying combination chemotherapies for *A. baumannii* infections.

In contrast to these studies, a prospective multicenter observational study showed increased mortality associated with a colistin-tigecycline combination (when the MIC of tigecycline exceeded 2 mg/L) compared to the colistin-carbapenem combination [156]. Another polymyxin-based combination that has shown synergistic killing *in vitro* as well as in animal models is colistin-glycopeptides but clinical data is inconclusive [157–159]. Lastly, Lenhard *et al.* recently demonstrated additivity or synergy against two clinical isolates of *A. baumannii* using triple therapy with polymyxin B, high-dose ampicillin-sulbactam, and meropenem in a 14-day hollow-fiber infection model. The isolates were resistant to all 3 antibiotics yet the combination resulted in rapid (96-hour) eradication of *A. baumannii* in 24-hour time-kill experiment [160].

Finally, none of the studies reviewed here show significant mortality benefit as a primary outcome with using combination chemotherapy, only improved microbiologic eradication with different combinations. These and others are presented in the **figure 2**. A suggested approach to interpretation of susceptibility testing and treatment of *A. baumannii* is also presented in **Figure 3**.

3.3.3 Novel therapies—Since the approval of tigecycline in 2005, no new antibiotics with activity against *A. baumannii* spp. were approved for clinical use. Fortunately, several drugs are currently in Phase 2 and 3 trials that show some activity against *A. baumannii*. Eravacycline, a novel fluorocycline of a tetracycline class, is currently in phase 3 development. In *in vitro* experiments with collection of 158 *A. baumannii* isolates, eravacycline showed to be 4-fold more active than tigecycline by comparison of MIC₉₀ values (1 mcg/mL vs 4 mcg/mL). However, the study also included isolates with MICs reaching 2 and 4 mcg/mL, attributable to increased expression of efflux pump AdeABC [161]. Similarly TP-6076, another synthetic tetracycline more potent than tigecycline against *A. baumannii*, has elevated MICs against isolates overexpressing the adeABC pump [162].

A next generation aminoglycoside, plazomicin has been the subject of *in vitro* studies, alone and in combination with other Gram-negative agents against 69 carbapenem-resistant *A. baumannii* obtained from clinical samples in Spain. MIC₉₀ values were 16- and 32-fold lower than those of amikacin and gentamicin. Studies also looked at plazomicin's performance in combination with imipenem or meropenem and showed improved synergistic killing compared to amikacin combinations [163]. Cefiderocol, a novel parenteral siderophore cephalosporin, which is currently in Phase 3 development, has shown *in vitro* activity against *A. baumannii*, including carbapenem-resistant strains. Cefiderocol was tested against two types of global isolate collections of *A. baumannii*. One included 104 randomly collected clinical isolates of *A. baumannii* and another included 99 β -lactam-resistant strains, including carbapenem-resistant and multidrug resistant strains containing IMP-1, OXA-23, OXA-24/40, OXA-51/ISAba, and OXA-58 enzymes. For the clinical isolates MIC₅₀ and MIC₉₀ were 0.125 mcg/mL and 2 mcg/mL respectively. Among the 99 β -lactam-resistant strains, only two had an MIC of >32 mg/L and seven strains with MIC of

8mg/L [164]. Though *in vitro* results look promising for these new agents, how they will perform in the clinical setting remains to be seen. The presence of clinical strains that are already non-susceptible to these new drugs is also discouraging.

Neither avibactam, vaborbactam or relebactam inhibit the class D or OXA-type β -lactamases that confer resistance to carbapenems in *A. baumannii*. Another diazabicyclooctane β -lactamase inhibitor, ETX2514 does inhibit such enzymes and promises activity against *A. baumannii* in combination with other agents, but is only in early stages of development [165].

In addition to these new agents, several antibiotic alternatives, adjuvant therapies and vaccines are currently in development. Schooley *et al.* recently achieved a successful clinical outcome with personalized bacteriophage-based therapy in a patient with necrotizing pancreatitis complicated by MDR *A. baumannii* infection [166]. As with phage therapy for *P. aeruginosa*, this case supports the merits of studying phage-based therapies further for MDR and XDR infections with limited therapeutic options.

Another potential adjuvant therapy is inhibition of LpxC, a zinc-dependent deacetylase that catalyzes the first committed step in the biosynthesis of lipid A. Garcia-Quintanilla and her team from the University of Sevilla were recently able to show that the LpxC inhibitor PF-5081090 significantly increased cell permeability and significantly potentiated the activity of existing antibiotics including rifampin, vancomycin, azithromycin, imipenem and amikacin against MDR *A. baumannii* [167].

3.4 *S. maltophilia*

3.4.1 Monotherapy—Antibiotics potentially active against *S. maltophilia* include trimethoprim-sulfamethoxazole, piperacillin-tazobactam, ticarcillin-clavulanate, fluoroquinolones, minocycline, tigecycline, colistin and chloramphenicol. High dose trimethoprim-sulfamethoxazole is the preferred treatment, supported by clinical experience [55]. Some cephalosporins have also been reportedly used successfully. Similar to carbapenems, treatment with the same cephalosporins (especially ceftazidime and cefepime) is also a risk factor for the emergence of *S. maltophilia* infections. Clinical experience with tetracycline derivatives is limited, but these agents have shown reliable *in vitro* activity and are an alternate option. The use of colistin is limited by the lack of experience and toxicity.

3.4.2 Combination chemotherapy—Combination chemotherapy is a necessary strategy when *S. maltophilia* is resistant to trimethoprim-sulfamethoxazole. Data supporting this approach are lacking but the high-level intrinsic resistance and the emergence of acquired resistance under antibiotic pressure makes combination chemotherapy the only available option, especially in severe invasive infections.

Proposed combinations include trimethoprim-sulfamethoxazole with any second-line agent, including ceftazidime, ticarcillin-clavulanate, aztreonam, or a fluoroquinolone, provided both agents used are active against the particular pathogenic strain on *in vitro* testing [47,55,168–170]. A noteworthy and recent case report describes a MDR *S. maltophilia* bloodstream infection in a young immunosuppressed renal transplant patient [53]. The

organism was resistant to trimethoprim-sulfamethoxazole, ceftazidime, meropenem, and levofloxacin. The authors used PCR to confirm the presence of a L1 MBL and L2 cephalosporinase, both inducible β -lactamases. Disc diffusion susceptibility testing showed resistance to the novel agent ceftazidime-avibactam and aztreonam but the authors demonstrated *in vitro* synergy between these agents. The patient eventually responded to a “triple combination” of ceftazidime-avibactam and aztreonam with clearance of his bacteremia. This approach is promising, both for *S. maltophilia* infections as well as infections caused by other Gram-negative organisms with a MBL. However, more studies are needed to confirm the efficacy and safety of such approach. Finally, a suggested approach to interpretation of susceptibility testing and treatment of *S. maltophilia* is presented in **Figure 4**.

3.4.3 Novel therapies—Similar to other MDR organisms, there is a lack of promising agents in development that appear to be available in the near future for clinical use. Parenteral fosfomycin and polymyxins, alone or in combination, are considered possible last-resort agents in desperate situations. However, this is hindered by the variability and difficult interpretation of *in vitro* testing. Novel agents at different stages of development carry some hope, although it is difficult to predict the outcome of such efforts at this early stage [45,171]. The *in vitro* efficacy of aztreonam-avibactam against selected clinical strains of *S. maltophilia* due to the inhibition of the L2 β -lactamase by avibactam has been demonstrated [106]. Also, the novel siderophore cephalosporin cefiderocol is stable against both serine β -lactamases and MBLs harbored by *S. maltophilia*. The MIC₉₀ of cefiderocol against *S. maltophilia* were 0.5 μ g/ml for North American isolates (n = 152) and 0.25 μ g/ml for European isolates (n = 276); none of the isolates had an MIC >4 μ g/ml [135].

3.5 *Burkholderia cepacia* complex

3.5.1 Monotherapy—*Bcc* are remarkable for being intrinsically resistant to a wider range of antibiotics compared to other non-fermenting GNB. They are inherently resistant to penicillins, cephalosporins (with the exception of ceftazidime), monobactams, carbapenems (with the exception of meropenem), polymyxins, aminoglycosides (with the exception of *B. vietnamiensis*), and fosfomycin. Additionally, *Bcc* are resistant to all antimicrobial classes that are usually inactive against non-fermentative GNB. Antibiotics that may be active include: ticarcillin-clavulanate, piperacillin-tazobactam, ceftazidime, meropenem, minocycline, ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, and chloramphenicol. Clinical Laboratory Standards Institute (CLSI) provides interpretative criteria for susceptibility reporting for trimethoprim-sulfamethoxazole, ticarcillin-clavulanate, ceftazidime, minocycline, levofloxacin, and chloramphenicol [172].

Although trimethoprim-sulfamethoxazole is often recommended, high-quality evidence to guide treatment in cystic fibrosis patients and other settings is lacking [173]. The recommendation is nonetheless based on susceptibility profiles reported in retrospective clinical studies. These susceptibility profiles are most favorable for trimethoprim-sulfamethoxazole followed by ceftazidime and meropenem [56–58,174–176], albeit recent studies found elevated resistance to the latter (25%–35% non-susceptibility to ceftazidime) [58,85]. Readers are referred to Avgeri *et al.* for a compilation of some of these papers [168].

The authors summarized more than fifty studies and concluded that ceftazidime, meropenem and piperacillin are appropriate choices in monotherapy or in combination with other antibiotics when the administration of trimethoprim-sulfamethoxazole is inappropriate or ineffective. In a cohort of 248 bacteremic cases, overall <20% were treated with trimethoprim-sulfamethoxazole, with no effect on clinical outcome [58]. This and other major studies of bloodstream infections caused by *Bcc* are summarized in Table 3 and a suggested approach to interpretation of susceptibility testing and treatment of *B. cepacia* complex is presented in **Figure 5**.

3.5.2 Combination chemotherapy—The above listed first and second-line agents may also be used in combination of two or more active antibiotics, particularly for salvage treatment. However, as of this writing, reliable data on combination chemotherapy for *Bcc* infections for either cystic fibrosis or non-cystic fibrosis patients are not yet available.

3.5.3 Novel therapies—The novel non- β -lactam β -lactamase inhibitor avibactam has potent activity against the PenA β -lactamase present in *Bcc* and as such, the administration of ceftazidime-avibactam may serve as an option in cases where first-line agents are not active. *In vitro* assays demonstrate that the addition of avibactam to ceftazidime resulted in a 4 fold reduction in MIC among 35 of 49 ceftazidime-resistant *Bcc* strains [177]. In another study, addition of avibactam to ceftazidime also restored susceptibility to ceftazidime in all ceftazidime-resistant *B. multivorans* isolates from cystic fibrosis patients [178]. Ceftolozane-tazobactam possesses *in vitro* activity against some organisms from this group. However, the MIC range was broad (0.5 to >64 μ g/ml), there were differences between species, and clinical efficacy has not been evaluated [179]. Cefiderocol had MICs ≤ 4 μ g/ml against all but one of 12 strains of *Bcc* included in a recent global survey [135]. Unfortunately, only few agents in development, of which information is currently available to the public, seem to target or be collaterally active against pathogens of the *Bcc* group.

4. Expert commentary

The challenges presented by non-fermenting GNB infections are remarkable. In addition to their intrinsically resistant nature, the rise in recent years of acquired resistance, particularly to carbapenems, has propelled *A. baumannii* and *P. aeruginosa* to the center of the epidemic of AMR. Our experience in treating these and other carbapenem-resistant bacterial infections, such as CRE, is limited to less than a decade and the evidence is scarce, mostly derived from observational cohort studies. Last, but not least, the progress in the development of new antibiotics remains slow.

As a result, infectious disease clinicians have resorted to strategies that utilize basic principles of microbiology and PK/PD against infections caused by MDR and XDR GNB. These include inhalation antibiotic therapy for respiratory infections, reviewed elsewhere [180], in addition to the use of combination antibiotic chemotherapy or the prolonged infusion of antibiotics. The study of such strategies, particularly combination antibiotic chemotherapy, is challenging owing to difficulties in recruitment but also in design. For example, combination chemotherapy has so far consisted of two agents but skeptics have raised the specter of possible resistance selection with only two agents [181–183].

Therefore, should study protocols for the treatment of MDR GNB include three or more agents such as is the case for the treatment of HIV or *Mycobacterium tuberculosis*? Another challenge concerns which backbone agent to use, should we include a carbapenem in combination chemotherapies for carbapenem-resistant organisms and if we should, what cutoff MIC would we use in such trials? What other agents should we use in combination?

A central notion in attempting to answer these questions is that there is no single set of combination of agents that is effective for individual MDR and XDR GNB, whether fermenters or non-fermenters. This is the result of the multitude of mechanisms of resistance that make up each observed resistance phenotype and the genetic heterogeneity that underlies it. Unfortunately, available therapeutic studies do not address the genetic makeup of the organisms they study and its impact on treatment. While the geographic diversity of these studies is remarkable, it is important to understand that the treatment of carbapenem-resistant *A. baumannii* or *P. aeruginosa* originating from the Mediterranean basin is not necessarily the same as for those from the U.S. or Southeast Asia. Molecular characterization of the organisms and the identification of mechanisms of resistance are essential to precisely formulate a choice of combination chemotherapy that would be effective against the epidemiologically predominant strains in a particular location, in what we call “molecularly-targeted” therapy. Similarly, Zavascki *et al.*, have advanced the notion of “rationally-optimized combination regimens” [92]. These regimens ought to be designed based on thorough *in vitro* antibiotic susceptibility testing including combination testing, screening for resistance genes, including β -lactamases and others, in addition to PK/PD parameters. Such an approach is illustrated in the *S. maltophilia* case report of Mojica *et al.* described previously, where the clinicians and microbiologists went from “the bench to the bedside and back”, using genetic and *in vitro* testing of various combinations to arrive to an effective “rationally-optimized” and “molecularly-targeted” regimen for that individual patient [53].

Unfortunately, the systems currently in place do not, most of the time, allow us in practice to obtain such information in a timely fashion. Yiying Cai and his team have nonetheless proven that this bench-to-bedside approach is feasible [184]. In a pragmatic and effectively designed study, the Singaporean team put in place an “*in vitro* antibiotic combination testing service” with the catchy acronym “iACT”. The service provided clinicians with the information they needed, based on the parameters we detailed above, to select a rationally-optimized combination antibiotic regimen for the precise treatment of XDR GNB with a rapid turnover of 48 hours. While their study lacked a control group, their prospectively-determined outcomes compared very favorably to historical cohorts, with a low 30-day infection-related mortality of 15% and high clinical response and microbiologic eradication of approximately 80%.

While we await further much needed novel agents, this individualized methodical, rational scheme is the sound alternative to approaches to combination therapy that are otherwise based on generalizations that ignore the marked molecular heterogeneity in resistant bacteria. Despite our optimism about rational, molecularly targeted combinations, we are not naïve to the fact that the current body of clinical evidence does not support the use of combination therapy for non-fermenter GNB. The gap between the existing anecdotal

experiences and high quality evidence needs to be filled with systematic studies that rely on the molecular characterization of isolates to determine therapy. We acknowledge that this is not feasible today, but advances in whole genome sequencing promise to rapidly deliver interpretable data to the bedside, allowing for the identification and selection of subjects to be enrolled in such studies. Such breakthroughs will be crucial to bridge the extraordinary obstacles that prevent the development and implementation of molecularly-targeted and rationally-optimized combination therapies.

5. Five-year view

There is an urgent need for further novel antibiotic agents to address the growing epidemic of AMR in general and MDR and XDR non-fermenting GNB in particular. In addition to traditional antibiotic development, other novel therapies are showing promise as adjuvants to antibiotic agents. These include biotherapeutics like monoclonal antibodies or small molecules that target certain bacterial virulence factors such as toxins, biofilms and adherence, and signaling pathways [185]. Other agents that could be used as adjuvants are target immune receptors, which allow for the modulation of host immunity and the enhancement of protective antimicrobial immunity [186].

As these new agents become available, we need to build evidence towards a systematic, standardized approach for the use of rationally-optimized and molecularly-targeted combination antibiotic chemotherapies for the treatment of MDR and XDR GNB. In order to achieve this in the near future, we need to not only develop our rapid diagnostic capabilities geared towards the detection of resistance mechanisms, but to incorporate such information into clinical decision making regarding therapy of infections caused by GNB. This approach will take into consideration the genotypic makeup of resistant isolates, together with their phenotype, in order to make the best therapeutic decisions. Beyond the logistical and technological aspects, this new clinical practice model represents a cultural shift in the way we approach these infections. In other areas such as cancer chemotherapy, this new paradigm has been referred to as “precision medicine”, a term that we think should be applied to antibiotic chemotherapy [89]. We will need this and other innovative approaches as we persevere on our perilous journey to fight infections caused by MDR and XDR GNB. This is particularly true for non-fermenters, which cause serious infection in some of the most vulnerable patients in our healthcare system, are tenaciously resilient in the nosocomial environment, and for which the therapeutic options are limited due to broad intrinsic resistance.

6. Key issues

Non-fermenting Gram-negative bacteria, especially *P. aeruginosa* and *A. baumannii*, are critically important in the epidemic of antimicrobial resistance due to broad intrinsic resistance to a wide array of antibiotics, in addition to growing acquired resistance patterns.

Although less prevalent, *S. maltophilia* and *B. cepacia* complex have even broader intrinsic resistance, encompassing most β -lactams, including carbapenems, and

polymyxins. They have a disproportionate impact on vulnerable populations, including immunosuppressed and hospitalized patients, and those with cystic fibrosis.

Cefiderocol is a promising agent in the antibiotic pipeline with activity against all four major groups of non-fermenters: *P. aeruginosa*, *A. baumannii*, *S. maltophilia*, and *B. cepacia* complex, but is still undergoing clinical development.

Ceftolozane-tazobactam is a new option to treat infections caused by carbapenem-resistant, XDR *P. aeruginosa* where resistance is not mediated by acquired carbapenemases or MBLs. However, the use of ceftolozane-tazobactam should be guided by susceptibility testing because it is not universally active and treatment failures occur with resistance.

Ceftazidime-avibactam has less activity against carbapenem-resistant, XDR *P. aeruginosa* than ceftolozane-tazobactam. Nevertheless, it may still be an option against some ceftolozane-tazobactam-resistant strains of *P. aeruginosa*.

No new agents targeting carbapenem and XDR *A. baumannii* have become available since the introduction of tigecycline in 2005. Given the limitations of tigecycline, polymyxin remains the backbone of antibiotic treatment of XDR *A. baumannii*.

Eravacycline has in vitro activity against *A. baumannii*, but it may be vulnerable to efflux pumps present in tigecycline resistant strains, and requires further clinical development.

Trimethoprim-sulfamethoxazole (TMP-SMX) remains the most reliable first-line agent for the treatment of infections caused by *S. maltophilia* and *B. cepacia* complex.

Ceftazidime-avibactam *B. cepacia* complex may serve as an option for strains resistant to TMP-SMX.

Aztreonam is an attractive component for rationally-optimized therapy in combination with ceftazidime-avibactam for infections caused by the MBL-producing non-fermenters *P. aeruginosa* and *S. maltophilia*. This is in part due to aztreonam's stability to hydrolysis by MBLs, a unique feature among β -lactams.

Data from randomized controlled trials demonstrate that combination therapy of *A. baumannii* polymyxins with rifampin or fosfomycin is not associated with improved survival. There is insufficient clinical data on combination antibiotic therapy against *P. aeruginosa*, *S. maltophilia* or *B. cepacia* complex.

For serious infections caused by MDR and XDR non-fermenters where there are no clear therapeutic options, we advocate a "precision medicine" approach that integrates information on the bacterial phenotype and genotype, *in vitro* assessments of antibiotic combination, and PK/PD considerations to achieve "rationally-optimized" and "molecularly-targeted" antibiotic regimens.

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* of interest

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Figure 1.
Proposed algorithm for the interpretation of antimicrobial susceptibility testing and treatment of *Pseudomonas aeruginosa*

Figure 2.
Forest plot comparing mortality for combination therapy versus monotherapy in major cohort studies of *Acinetobacter baumannii* infections (both retrospective and prospective) [151,153–155,187–193]

Figure 3.

Proposed algorithm for the interpretation of antimicrobial susceptibility testing and treatment of *Acinetobacter baumannii* UTI Urinary Tract Infection; BSI Bloodstream Infection; CNS Central Nervous System; IAI Intraabdominal Infection; OM Osteomyelitis

Figure 4. Proposed algorithm for the interpretation of antimicrobial susceptibility testing and treatment of *Stenotrophomonas maltophilia* TMP-SMX Trimethoprim Sulfamethoxazole; BSI Bloodstream Infection; IAI Intraabdominal Infection; SSI Skin and Soft Tissue Infection; OM Osteomyelitis

Figure 5.
Proposed algorithm for the interpretation of antimicrobial susceptibility testing and treatment of *Burkholderia cepacia* complex

Table 1.

Major mechanisms of resistance

	β -lactamases				Others
	Class A	Class B	Class C	Class D	
<i>Pseudomonas aeruginosa</i> [22,24]	PER-1, PER-2, VEB-1, VEB-2, VEB-3, GES-1, GES-2, GES-5, GES-8, GES-9, GES-13, GES-18, BEL-1, BEL-2, BEL-3, PME-1 Rarely identified: TEM-, SHV-, CTX-M-, KPC-, and NDM- types	IMP-1, VIM-1, VIM-2, SPM-1, GIM-1, FIM-1	AmpC overexpression	OXA-50 (naturally occurring), OXA-1, OXA-2, OXA-10, OXA-18, OXA-24/40, OXA-45, OXA-56, OXA-198 subfamilies (acquired)	OprD porin deficiency; Alterations of efflux systems (MexAB-OprM RND-type system, <i>mexCD-oprJ</i> and <i>MexEF-oprN</i> operons); PBP mutations; Aminoglycoside-modifying enzymes (RmtA and RmtD enzymes); LPS alteration (cobst resistance)
<i>Acinetobacter baumannii</i> [22]	PER-1, PER-2, PER-3, PER-7, VEB-1, VEB-3, GES-1, GES-11, GES-12, GES-14, GES-22 Rarely identified: TEM-, SHV-, CTX-M- and KPC- types	IMP-1, IMP-2, IMP-4, IMP-5, IMP-8, IMP-11, IMP-14, IMP-19, VIM-1, VIM-2, VIM-4, VIM-6, VIM-11, SIM-1, NDM-1, NDM-2	AmpC overexpression	OXA-51 (naturally occurring), OXA-23, OXA-24/40, OXA-45, OXA-58, OXA-143, OXA-235 subfamilies (acquired)	Overexpression of efflux systems (<i>adeABC</i> , <i>adeIJK</i> operons and AbeM efflux system); PBP mutations; Aminoglycoside-modifying enzymes (ArmA and RmtB enzymes); LPS alteration (cobst resistance)
<i>Stenotrophomonas maltophilia</i> [51,52]	L2 cephalosporinase Rarely identified: TEM-2, CTX-M	L1 carbapenemase Rarely identified: NDM-1			Overexpression of efflux systems (RND pumps SmeABC, SmeDEF, SmeOP-TolC, SmeYZ, SmeVWX, SmeIJK; ABC pumps MacABC, SmrA, FuaABC; MFS pumps FloR, MfsA, tetA, Ter A) FPS alteration; Aminoglycoside-modifying enzymes; Bypassing dihydropteroate synthase and dihydrofolate reductase; Presence of class I integron carrying <i>sal</i> and <i>dhfr</i> genes
<i>Burkholderia cepacia complex</i> [72,77,79,85]	PenA, PenB carbapenemases		AmpC, AmpD overexpression		Overexpression of efflux systems (RND-3, RND-4 and RND-9 systems); FPS alteration; Modification of dihydrofolate reductase; Mutation of the QRDR region of topoisomerase II; Presence of class I integron

RND Resistance-Nodulation-Division; PBP Protein Binding Proteins; LPS lipopolysaccharide

Table 2.

List of major randomized, controlled trials of combination antibiotic therapy versus monotherapy for drug-resistant Gram-negative bacteria

Name	Start date/completion date	Location	Organisms/Syndrome	Intervention*	Primary Outcome	Status or Results
For treatment of drug-resistant <i>Acinetobacter baumannii</i> alone						
- Durante-Mangoni et al, 2013 [154] - Multi-center, open-label, parallel, phase 3 randomized controlled trial - n=209	November 2008 – July 2011	Italy	- Colistin- susceptible XDR- <i>Acinetobacter baumannii</i> (resistant to carbapenems MIO 16 mg/L and all other antibiotics except colistin) - BSI, HAP, VAP, complicated intra-abdominal infections	Colistin 2 Million units IV every 8 hours and rifampicin 600 mg orally every 12 hours vs. colistin alone (same dose) for 10–21 days	30-day all-cause mortality	- Primary outcome: 45/104 (43.3%) mortality in the combination arm vs. 45/105 (42.9%) in the colistin arm (NS) - Microbiologic eradication: 63/104 (60.6%) in the combination arm vs. 47/105 (44.8%) in the colistin arm (p=0.034)
- Sirijatuphat R. and Thamlikitkul V., 2014 [155] - Single-center, open-label, parallel, phase 3, randomized controlled trial - n=94	January 2010 – March 2011	Thailand	- Carbapenem-resistant <i>Acinetobacter baumannii</i> - Pneumonia, BSI, UP, skin and soft tissue infections, intraabdominal infections	Colistin base activity 5 mg/Kg/ day and fosfomycin 4g IV every 12 hours vs. colistin alone (same dose) for 7–14 days	- Favorable clinical outcome defined as “cure or improvement at 28 days”	- Primary outcome: 62.8% favorable outcome in the combination arm vs. 56.4% in the colistin arm (NS) Microbiologic eradication: 100% in the combination arm vs. 84.5% in the monotherapy arm (p=0.023)
- Aydemir H. et al. [153] - Single-center, open-label, parallel, phase 3, randomized controlled trial - n=43	March 2011 – March 2012	Turkey	- Carbapenem-resistant <i>Acinetobacter baumannii</i> VAP alone	Colistin base activity 300 mg daily and rifampicin 600 mg daily vs. colistin alone (same dose)	Clinical response (normothermia, normal respiratory secretions, PaO ₂ /FiO ₂ >240 or nonechanical ventilation)	- Primary outcome: 11 (52.4%) clinical response in the combination arm vs. 9 (40.9%) in the monotherapy arm (NS) - Time to microbiologic clearance: 3.1+/- 0.5 days in the combination arm vs. 4.5+/-1.7 days in the monotherapy arm (p=0.029)
For treatment of other drug-resistant Gram-negative bacteria						
- NCT01732250 (responsible party: Mical Paul, Rabin Medical Center, Israel) - Multi-center, open label, parallel, phase 4 trial,	March 2013 – February 2017	Greece, Israel, Italy	- Carbapenem-resistant, colistin-susceptible Gram-negative bacilli - BSI, HAP, VAP, UH	Colistin 9 Million units loading IV once then 4.5 Million units every 12 hours and meropenem 2g IV every 8 hours vs. colistin alone	Clinical success at 14 days (composite of: being alive, not in septic shock or improved SOFA score, stable or improved PaO ₂ /FiO ₂ in the case of HAP/ VAP, and negative blood cultures if still febrile).	Completed - pending publication of results

Name	Start date/completion date	Location	Organisms/Syndrome	Intervention*	Primary Outcome	Status or Results
For treatment of drug-resistant <i>Acinetobacter baumannii</i> alone						
randomized controlled trial				(same dose) for 10 days		
-NCT 01597973 (responsible party: Keith Kaye, University of Michigan) - Multi-center, triple-blind, parallel, phase 3, randomized controlled trial	October 2012 – September 2021	United States, Israel, Taiwan, Thailand	- XDR- Acinetobacter baumannii, XDR- Pseudomonas aeruginosa, and carbapenem- resistant Enterobacteriaceae -BSI or pneumonia	Colistin and meropenem vs. colistin and placebo	30-day all-cause mortality	Currently recruiting

* Doses renally-adjusted as needed

XDR Extensively drug-resistant; MIC Minimum Inhibitory Concentration; BSI Bloodstream Infection; HAP Hospital-Acquired Pneumonia; YAP Ventilator-Associated Pneumonia; UTI Urinary Tract Infection; SOFA Sequential Organ Failure Assessment score

Table 3.Summary of the major studies of *Burkholderia cepacia* complex bloodstream infections

Characteristics	El Chakhtoura et al. [58]	Liao et al. [174]	Bressler et al. [175]; Woods et al. and [176]	Lu et al. [56]	Huang et al. [57]
Study Population	1999-2015	2004-2007	1996-2002	1982-1995	1997-1999
Time Frame	1999-2015	2004-2007	1996-2002	1982-1995	1997-1999
Number of cases	248	95	53	70	42
Age – mean (range)	68 (22-94)	69 (55-87)	46 (24-82)	34 (median, <1-83)	70 (2-92)
Source					
Catheter-related infection	155/248 (63)	21/95 (22)	---	11/70(16)	8/42 (19)
Respiratory tract infection	49/248 (20)	47/95 (49)	---	17/70 (24)	20/42 (48)
Nosocomial	225/248 (91)	All cases	All cases	64/70 (91)	40/42 (95)
Susceptibility pattern					
Trimethoprim-sulfamethoxazole	193/205 (89)	0/73 (0)	4/53 (83)	---	36/42 (86)
Ceftazidime	152/212 (72)	71/73 (97)	37/40 (92)	41/43 (95)	40/42 (95)
Meropenem	22/32 (69)	73/73 (100)	---	---	---
Imipenem	54/136 (40)	---	5/40 (13)	23/38 (61)	32/42 (76)
Recorded outcomes					
14-day mortality	40/248 (16)	16/95 (17)	25/53 (47)	8/70(11)	---
In-hospital mortality	---	51/95 (54)	---	---	27/42 (64)

Adapted from El Chakhtoura et al. [58]

Values in No. (%) unless otherwise specified