



Review

Treatment Strategies of Colistin Resistance *Acinetobacter baumannii* Infections

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Abstract: *Acinetobacter baumannii* has emerged as a pressing challenge in clinical practice, mainly due to the development of resistance to multiple antibiotics, including colistin, one of the last-resort treatments. This review highlights all the possible mechanisms of colistin resistance and the genetic basis contributing to this resistance, such as modifications to lipopolysaccharide or lipid A structures, alterations in outer membrane permeability via porins and heteroresistance. In light of this escalating threat, the review also evaluates available treatment options. The development of new antibiotics (cefiderocol, sulbactam/durlobactam) although not available everywhere, and the use of various combinations and synergistic drug combinations (including two or more of the following: a polymyxin, ampicillin/sulbactam, carbapenems, fosfomycin, tigecycline/minocycline, a rifamycin, and aminoglycosides) are discussed in the context of overcoming colistin resistance of *A. baumannii* infections. Although most studied combinations are polymyxin-based combinations, non-polymyxin-based combinations have been emerging as promising options. However, clinical data remain limited and continued investigation is essential to determine optimal therapeutic strategies against colistin-resistant *A. baumannii*.

Keywords: *Acinetobacter baumannii*; colistin; resistance; mechanisms; treatment



Citation: Papazachariou, A.; Tziolos, R.-N.; Karakonstantis, S.; Ioannou, P.; Samonis, G.; Kofteridis, D.P.

Treatment Strategies of Colistin Resistance *Acinetobacter baumannii* Infections. *Antibiotics* **2024**, *13*, 423. <https://doi.org/10.3390/antibiotics13050423>

Academic Editor: Demosthènes A. Makris

Received: 14 April 2024

Revised: 1 May 2024

Accepted: 2 May 2024

Published: 6 May 2024



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1. Introduction

Acinetobacter baumannii infections pose a significant threat to human health, particularly within current healthcare settings. This opportunistic pathogen is one of the major causes of nosocomial infections, such as ventilator-associated pneumonia, septicemia, meningitis, wound and urinary tract infections, contributing to substantial morbidity and mortality [1]. The antibiotics that are usually effective against *A. baumannii* infections include carbapenems, polymyxins E and B, sulbactam, piperacillin/tazobactam, tigecycline and aminoglycosides [2]. Yet, multidrug-resistant strains (MDR) have become increasingly prevalent, limiting the effectiveness of conventional antibiotic therapies [3].

Antimicrobial resistance (AMR) has emerged as a globally chronic public health problem, with the forecast of 10 million deaths per year by 2050 [4]. The treatment of *A. baumannii* infections presents a formidable challenge due to its propensity for antimicrobial resistance. In contrast to Enterobacterales for which there are many options against carbapenem-resistant strains (ceftazidime/avibactam ± aztreonam, meropenem/vaborbactam, imipenem/relebactam), new β -lactam/ β -lactamase combinations are not active against *A. baumannii*'s OXA carbapenemases [4]. This has sparked interest in the revival of old antibiotics, predominantly colistin [5], which has resulted in an escalating incidence of colistin resistance in *A. baumannii* [6,7], its prevalence being as high as 85% in Greece [8]. The ability of *A. baumannii* to acquire and disseminate resistance mechanisms has profound implications for human health since resistance to last-resort antibiotics, including colistin,

has resulted in the emergence of pan-drug-resistant (PDR) strains [5], which are associated with increased mortality [3] and very limited treatment options [6,7] where new antibiotics (cefiderocol, sulbactam/durlobactam) are not yet available. Of interest is that colistin can still be used as part of combination regimens against colistin-resistant strains as it can work synergistically with other antibiotics even at subinhibitory concentrations [6,7]. Furthermore, various non-polymyxin-based combination regimens have been tried [7]. Notably, even though colistin represents a last resort treatment option for carbapenem-resistant *A. baumannii*, there is conflicting evidence on the impact of colistin resistance on clinical outcomes ranging from lower to higher mortality associated with colistin resistance [8–10].

Colistin belongs to the class of polymyxin antibiotics; possessing a positively charged L-diaminobutyric acid, that forms electrostatic bonds with the negatively charged phosphate groups of lipid A, a vital constituent of lipopolysaccharide (LPS) found in Gram-negative bacilli [11]. This interaction is pivotal as lipid A governs bacterial permeability and external exchange [12]. By competitively displacing divalent cations like calcium (Ca^{2+}) and magnesium (Mg^{2+}), colistin disrupts the structure of LPS, subsequently incorporating its hydrophobic acyl chain. Consequently, the external outer membrane (OM) undergoes expansion, leading to permeabilization and facilitating colistin entry. This process elucidates the synergistic effect observed when colistin is combined with other hydrophilic antimicrobials like β -lactams, gentamicin, rifampicin, meropenem, and tigecycline [13]. In essence, colistin acts by solubilizing the bacterial cell membrane, culminating in a bactericidal outcome [14].

This review aims to provide comprehensive insight into the colistin resistance mechanism in *A. baumannii* and summarize available treatment strategies. By elucidating the molecular mechanisms driving colistin resistance and assessing the effectiveness of different therapeutic approaches, this study aims to contribute to the development of more targeted and efficacious treatments for *A. baumannii* infections.

2. Mechanisms of Colistin Resistance

Colistin (polymyxin E) belongs to the class of polymyxin antibiotics; its primary target is the outer bacterial cell membrane and is considered bactericidal [14]. As a cationic polypeptide, colistin interacts with the cell membrane's negatively charged LPS molecules through the displacement of positively charged ions (Mg^{2+} , Ca^{2+}), destroying the integrity of the cell membrane [13].

A well-described mechanism of resistance to colistin in *A. baumannii* involves the complete loss of LPS structure due to mutations in or disruption of the LPS biosynthesis genes (*lpxA*, *lpxC*, or *lpxD*). Since colistin primarily targets the lipid A component of LPS, the absence of LPS or alterations in its structure can result in reduced susceptibility or resistance to colistin [15]. The initial study that observed this resistance mechanism involved 13 independent colistin-resistant derivatives of the *A. baumannii* type strain ATCC 19606. Various genetic alterations (nucleotide substitutions, deletions, and insertions) were observed in one of these three genes, ultimately causing frameshifts or truncated proteins impairing lipid A biosynthesis. It is noteworthy that although the mutations found varied in scale, ranging from single nucleotide mutations to large deletions spanning up to 445 nucleotides, they all led to the same outcome: disruption of the synthesis pathway of lipid A, which in turn led to the absence of or reduction in LPS production [16]. In subsequent research, the insertion of *IS* *Aba1* or *IS* *Aba11* within the *lpxC* gene has been identified as a frequent occurrence in colistin-resistant *A. baumannii*. This mutation causes the inactivation of the *lpxC* and *lpxA* genes, leading to the loss of LPS. Across different studies, the disruption of the *lpxC* gene has consistently been observed within the same region (321–420 nucleotides), leading to the proposal that this region may serve as a preferred site for the integration of insertion sequences (ISs) [17–20]. Furthermore, some colistin-resistant *A. baumannii* isolates have shown downregulation of *lpxACD* expression, resulting in reduced LPS production [21]. It should be emphasized that certain amino acid substitutions, such as N287D in *lpxC* and E117K in *lpxD*, have been identified in both

colistin-susceptible and colistin-resistant isolates. However, when these substitutions are combined with a mutation in the *pmrCAB* operon, they may exhibit a synergistic effect, contributing to colistin resistance [22–24].

Another significant resistance mechanism involves modifying the lipid A fraction of the LPS in the bacterial cell membrane. This modification includes the addition of molecules such as 4-amino-4-deoxy-L-arabinose (L-Ara4N), phosphoethanolamine (PEtN), or galactosamine to lipid A. These alterations in the structure of lipid A lead to a decrease in the net negative charge of the cell membrane. Consequently, this affects the binding of positively charged colistin to the membrane, reducing its efficacy [25,26]. Although the modification of LPS with L-Ara4N has been identified as a common and effective mechanism of colistin resistance in diverse Gram-negative pathogens such as *Salmonella enterica*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa*, this modification was found to be absent in *A. baumannii* [27]. Chin et al. revealed that mutations in *pmrB* can lead to heightened expression of the *naxD* gene. *NaxD* is responsible for modifying lipid A by adding galactosamine, thereby reducing the affinity for cationic colistin and contributing to resistance in *A. baumannii* strains [28]. The addition of PEtN to the 4'-phosphate or 1-phosphate group of lipid A in colistin-resistant *A. baumannii* is primarily mediated by the enzymatic activity of pEtN transferases encoded by *pmrC* [29]. This mechanism is mediated by mutations in genes encoding the *PmrAB* two-component system, leading to overexpression of the phosphoethanolamine transferase *PmrC* [30–33]. A systematic review found that most in vivo studies highlighted mutations within the *pmrC* AB locus, with *pmrB* mutations being the most prevalent, leading to the upregulation of *pmr* genes. Conversely, mutations in genes crucial for the synthesis of the lipid A component of LPS were more frequently observed in vitro, with only one instance identified in vivo [34]. A study involving the isolation of three colistin-resistant clinical *A. baumannii* strains from distinct patients unveiled that although non-synonymous mutations were present across all domains of *PmrB*, a significant proportion was concentrated within the histidine kinase A (HisKA) domain. This domain is crucial in facilitating autophosphorylation and transferring the phosphoryl group to the *PmrA* response regulator. *PmrA*, upon phosphorylation, serves as a transcriptional regulator capable of modulating the expression of various genes involved in LPS structural modifications, such as the addition of PEtN [35]. In addition, mutations in the receiver domain (REC) of the *PmrA* have been reported in *A. baumannii* strains resistant to colistin [23]. Furthermore, another study investigating colistin resistance in four isogenic isolate pairs of *A. baumannii* reported that *PmrB* mutations led to approximately 10–13 times higher expression of *pmrC* compared to susceptible isolates. However, it is worth mentioning that PEtN addition was also observed in susceptible isolates according to a study investigating indicating that this resistance mechanism might be strain-specific and that PEtN addition alone is not the sole factor leading to colistin resistance [29]. Except for the overexpression of *PmrC*, a mechanism of colistin resistance in *A. baumannii* was observed in some isolates and to a lesser extent the upregulation of the *pmrA* and *pmrB* [36–38]. While this observation is anticipated, given that these genes belong to the same operon as the *pmrC* gene (*pmrCAB*), there are instances where no correlation was observed between *PmrAB* and *PmrC* overexpression [39]. It is worth noting that, according to Beceiro et al. who analyzed *PmrCAB* in a diverse array of clinical isolates and laboratory mutants of *A. baumannii*, it was suggested that resistance to colistin necessitates at least two separate genetic occurrences: (i) the occurrence of at least one amino acid alteration in *PmrB* and (ii) the upregulation of *pmrA* and *pmrB* expression [33].

An alternative mechanism documented involving the addition of PEtN that consequently leads to colistin resistance in *A. baumannii* is the overexpression of another *pmrC* homolog, *eptA* (ethanolamine phosphotransferase A). While the sole presence of the *eptA* gene in the bacterial genome does not inherently result in colistin resistance, the insertion of the ISAbal sequence into the DNA preceding the *eptA* gene can enhance the expression of this enzyme. The activity of the *pmrC*-homolog *eptA* results in the modification of lipid A through the addition of PEtN [40]. In a recent investigation on *A. baumannii* isolates

collected from a patient before and after ineffective colistin therapy, genomic sequencing of the post-treatment isolate uncovered an additional instance of ISAba125 within the *H-NS* gene, which encodes a transcriptional regulator. As *H-NS* regulates the expression of genes implicated in lipid A modification, including *eptA*, the presence of this extra copy was linked to *H-NS* dysfunction, thereby contributing to colistin resistance [41].

The presence of *mcr* genes, which encode phosphoethanolamine transferases (MCR enzymes) catalyzing the attachment of phosphoethanolamine to lipid A of LPS, represents a well-known mechanism of colistin resistance in Gram-negative bacteria [42,43]. Until now, bacteria isolated from animals, food, humans, and the environment have revealed the existence of ten distinct *mcr* gene families (*mcr-1* to *mcr-10*) [44]. In the context of *A. baumannii* strains resistant to colistin, it was found that the resistance was primarily caused by specific plasmid-mediated *mrc* genes, such as *mcr-1* and *mcr-4.3* [45,46].

In addition to modifications or loss of LPS structure, *A. baumannii* can develop resistance to colistin through a different mechanism, such as alterations in outer membrane permeability. The outer membrane permeability of *A. baumannii* is notably lower, accounting for less than 5% compared to other Gram-negative bacilli. This is attributed to the relatively small number and size of porins present [47]. According to the literature, colistin resistance in *A. baumannii* mutants has been associated with either the loss or reduced expression of the OmpW porin [48]. Furthermore, specific non-lpx (lipoprotein) proteins involved in the structure and integrity of the outer membrane have been observed to contribute to colistin resistance. This hypothesis emerged from analyzing *A. baumannii* strains exposed to escalating colistin concentrations. The findings indicated that strains lacking LpsB, a non-Lpx protein known as a glycosyltransferase responsible for LPS core synthesis, exhibited heightened susceptibility to colistin. This underscores the potential role of LpsB in facilitating colistin resistance in *A. baumannii* by bolstering the stability of the outer membrane [49]. In addition to the absence of lpsB, single mutations in genes such as *H128Y* and **241K* have been documented in *A. baumannii* strains exhibiting colistin resistance [50]. Colistin resistance also correlates with amino acid substitutions in VacJ and PldA non-lpx proteins. PldA, crucial for preserving lipid asymmetry in the outer membrane, and VacJ, a component of the ABC transporter system, undergo mutations that disrupt outer membrane organization, thereby fostering resistance development [51].

Heteroresistance represents a lesser-explored and less understood concept, where a minor fraction of bacterial cells within a clonal population display resistance to an antibiotic. At the same time, the majority remain susceptible [50,51]. Li et al. were the first to define colistin heteroresistance in *A. baumannii* as the occurrence of resistance to colistin within a subpopulation despite the majority being susceptible with a minimum inhibitory concentration (MIC) of ≤ 2 mg/L [52,53]. Prior administration of colistin may pose a risk for an increased incidence of heteroresistance [54]. The identification of colistin-heteroresistant *A. baumannii* strains in clinical samples serves as a significant cautionary signal that inappropriate colistin usage could lead to rapid resistance development and treatment ineffectiveness [55].

Table 1 summarizes all the abovementioned mechanisms of resistance.

Table 1. Summary of the mechanisms of resistance to colistin in *A. baumannii*.

Mechanism of Colistin Resistance
Modification of LPS
Mutations leading to deficient or complete loss of LPS structure
Mutations in <i>lpxACD</i> genes leading to decreased LPS production
Addition of positively charged molecules
Addition of galactosamine to lipid A fraction of LPS through mutations in <i>pmrB</i>
Overexpression of <i>pmrC</i> leads to the modification of lipid A fraction of LPS through the addition of pEtN

Table 1. Cont.

Mechanism of Colistin Resistance
Overexpression of <i>EptA</i> leads to modification of lipid A fraction of LPS through the addition of pEtN
Dysfunction of <i>H-NS</i>
Horizontal gene transfer
Horizontal gene transfer enables the acquisition of <i>mcr</i> genes, encoding <i>pEtN</i> transferases that attach <i>pEtN</i> to lipid A
Alterations in outer membrane permeability
Overexpression of efflux pumps (EmrAB)–Decreased expression of OmpW porin
Expression of specific non-lpx proteins involved in the structure and integrity of the outer membrane
Heteroresistance
Occurrence of resistance within a subpopulation through spontaneous mutations or the presence of resistance genes despite majority susceptibility, leading to rapid resistance development.

Abbreviations: LPS: lipopolysaccharide, pEtN: phosphoethanolamine, lpx: lipoprotein.

3. Available Treatments of *A. baumannii* Colistin Resistance

The approach to treating colistin-resistant *A. baumannii* is similar to the approach for carbapenem-resistant *A. baumannii* [56,57], with the main difference being that colistin is not appropriate as a monotherapy and may not be the preferable backbone for combination therapy. Of note colistin resistance in carbapenem-resistant *A. baumannii* strains may result in pandrug resistance where new antibiotics (cefiderocol and sulbactam/durlobactam) are not available.

Evidence on the treatment of carbapenem-resistant *A. baumannii* is limited due to the observational (and predominantly retrospective) design of the majority of available studies, with multiple limitations (including heterogeneous patient populations, heterogeneous *A. baumannii* susceptibilities and mechanisms of resistance, heterogeneous treatment regimens, and small study populations). Multiple meta-analyses [58–61] (including network meta-analyses [62–64]) have been conducted to determine the optimal treatment regimen against carbapenem-resistant *A. baumannii*, but the results of these studies are difficult to interpret and limited by the quality of available studies. Notably, the majority of studies have been conducted in patients with infections by colistin-susceptible *A. baumannii* and most studied combinations are polymyxin-based. Guidelines have been published by both the Infectious Diseases Society of America (IDSA) [56] and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [65]; however, these were published before approval of sulbactam/durlobactam (which now represent a first-line treatment option where available) and recommendations against cefiderocol may change considering subsequent encouraging real-life data [57].

Unfortunately, cefiderocol and sulbactam/durlobactam are not yet widely available. Furthermore, sulbactam/durlobactam is not active against metallo-β-lactamase producing *A. baumannii*, which, in combination with the high prevalence of cefiderocol non-susceptibility in these strains [66,67], could prove to be a problem in the future. As these new antibiotics are increasingly being used in clinical practice, there is a risk of selection and spread of New Dehli Metallo-beta-lactamase (NDM)-producing *A. baumannii*, which is already increasingly being reported [68,69]. This leaves synergistic antibiotic combinations as the only treatment option against colistin-resistant (typically PDR) *A. baumannii* strains [6,7]. Multiple antimicrobial combination regimens have been evaluated and are being used in clinical practice, but the optimal regimen remains unclear [7]. Current guidelines recommend a sulbactam-based (ampicillin/sulbactam or sulbactam/durlobactam if the latter is available) treatment regimen. Sulbactam can be combined with several antibiotics, predominantly, colistin, tigecycline and cefiderocol [56,57]. The various treatment options and considerations for selecting a treatment regimen are summarized in Tables 2 and 3.

Table 2. Summary of treatment options for colistin-resistant *A. baumannii*.

Antibiotic	Comment
Sulbactam/durlobactam	<p>The preferred treatment option where available [57].</p> <p>Retains activity against most XDR/PDR <i>A. baumannii</i> strains [70], including strains resistant to colistin and cefiderocol [71].</p> <p>Has shown non-inferiority and lower nephrotoxicity compared to colistin in the registrational phase 3 trial [72].</p> <p>Limitations:</p> <ul style="list-style-type: none"> • Limited clinical evidence • Sulbactam/durlobactam was used in combination with imipenem/cilastatin (to cover other co-infecting pathogens) in the registrational phase 3 trial [72]. At least based on in vitro data the impact of imipenem on the activity of sulbactam/durlobactam appears to be minimal [70]. • Not active against metallo-β-lactamase-producing <i>A. baumannii</i> • Not yet widely available
Cefiderocol	<p>Retains activity against most XDR/PDR <i>A. baumannii</i> strains [66].</p> <p>Despite initial disappointing data from subgroup analyses from the randomized trials [73,74], subsequent studies and meta-analyses are more encouraging [57–59].</p> <p>Limitations:</p> <ul style="list-style-type: none"> • Not yet widely available • In available randomized trials cefiderocol performed worse than the best available therapy (CREDIBLE [73]) and similar to high-dose meropenem (APEKS-NP [74]), which is inactive alone, in subgroup analyses of patients with <i>A. baumannii</i> infections. • Subsequent real-life studies are promising but observational and mostly retrospective, and with mixed results [57–59]. • Conflicting breakpoints comparing EUCAST and CLSI [66] • High prevalence of resistance/heteroresistance in some settings [66] • Especially high prevalence of resistance and risk of treatment-emergent resistance in metallo-β-lactamase-producing strains [66]
Ampicillin/sulbactam	<p>Sulbactam is the active component. Used in high doses: 27 g/day (18 g ampicillin/3 g sulbactam) infused over 24 h or divided into three doses and infused over 4 h.</p> <p>Most XDR <i>A. baumannii</i> strains have a sulbactam MIC of 32–64 mg/L, and only a small proportion have an MIC below the CLSI-defined breakpoint for ampicillin/sulbactam [71,75]. Based on PK/PD data high-dose sulbactam may cover isolates with MICs as high as 32–64 mg/dL [76].</p> <p>Limitations:</p> <ul style="list-style-type: none"> • Breakpoints for sulbactam have not been established yet. Breakpoints for ampicillin/sulbactam underestimate the treatment potential considering that the doses used for <i>A. baumannii</i> are likely sufficient for sulbactam MICs as high as 32–64 mg/dL [76], and maybe even higher in synergistic combination regimens. Ampicillin/sulbactam is still recommended even in case of resistance to ampicillin/sulbactam, as defined based on CLSI breakpoints [56]. • Optimal dosing regimen and adjustment for kidney function not yet clear.
Colistin/Polymyxin-B	<p>Even in case of resistance, it can be useful as part of synergistic combination regimens (subinhibitory concentrations are sufficient for synergy) [6,7].</p> <p>With the exception of urinary tract infections, polymyxin-B is preferable to colistin where available due to better pharmacokinetic properties and lower risk of nephrotoxicity.</p> <p>Despite conflicting recommendations by guidelines [56,77], nebulized colistin may be a useful option when administered properly (correct nebulization technique and at high doses) [78–80], but larger well-designed studies are necessary to confirm potential benefits. Notably, nebulized colistin may achieve concentrations well above MICs [78], suggesting potential benefit even against colistin-resistant isolates.</p> <p>Limitations:</p> <ul style="list-style-type: none"> • Poor penetration in epithelial lining fluid (but promising potential for nebulized colistin). • Nephrotoxicity. • Dosing adjustment for renal function can be complicated for colistin [77], especially in patients with unstable renal function.

Table 2. Cont.

Antibiotic	Comment
Tigecycline	<p>Good penetration in skin and soft tissue infections and osteoarticular infections. Recommended dose: 200 mg loading dose followed by 100 mg twice daily.</p> <p>Limitations:</p> <ul style="list-style-type: none"> • Breakpoints not established • Nausea/vomiting/abdominal pain are common side effects and may lead to treatment discontinuation • Thrombocytopenia and hypofibrinogenemia are common with high doses used for <i>A. baumannii</i> • Poor concentration in blood and urine • Treatment with tigecycline has been associated with worse outcomes in early studies using lower doses, a finding that has not been confirmed in subsequent studies [61,81], although microbiological cure may be lower [61,81].
Minocycline	<p>Good penetration skin and soft tissue infections and osteoarticular infections. Recommended dosing for <i>A. baumannii</i> is 200 mg twice daily. Can also be given orally.</p> <p>Limitations:</p> <ul style="list-style-type: none"> • Breakpoints not established [82] • Nausea common
Eravacycline	<p>More potent (lower minimum inhibitory concentrations) than tigecycline/minocycline [83]. Can be administered orally.</p> <p>Limitations:</p> <ul style="list-style-type: none"> • Breakpoints not established • Very limited clinical evidence, predominantly from small case series and small observational studies [83–86] and potentially poor outcomes in bloodstream infections [83]
Fosfomycin	<p><i>A. baumannii</i> is considered inherently resistant to fosfomycin. However, fosfomycin can be useful as part of synergistic combination regimens based on in vitro data, as well as limited clinical data [7,87–90].</p> <p>Limitations:</p> <ul style="list-style-type: none"> • Available clinical data have severe limitations. The single randomized trial was small and assessed the combination colistin + fosfomycin vs. colistin monotherapy in colistin-susceptible isolates [88]. The two other studies are both observational, one prospective [90] and one retrospective [89]. Most isolates in the prospective study were colistin-susceptible [90], while all isolates in the retrospective study were pandrug-resistant [89]. In both studies, very heterogeneous treatment regimens were used. Furthermore, the latest study was very small [89]. Lastly, ampicillin/sulbactam, the currently preferred backbone, was used in very few patients [89,90]. • The optimal dosing regimen for fosfomycin when used as part of a combination is unclear.
Ceftazidime/avibactam	<p>Ceftazidime/avibactam is not active against carbapenem-resistant <i>A. baumannii</i>. However, where sulbactam/durlobactam is not available, the combination of ceftazidime/avibactam with ampicillin/sulbactam is promising [91,92]. The rationale is that avibactam (similar to durlobactam) may help restore the activity of sulbactam [91,92].</p> <p>Limitations:</p> <ul style="list-style-type: none"> • Virtually no published clinical data on the combination.
Trimethoprim/sulfamethoxazole	<p>Active against some XDR <i>A. baumannii</i> strains</p> <p>Limitations:</p> <ul style="list-style-type: none"> • Very limited clinical evidence, usually in combination with other antibiotics [93,94]
Aminoglycosides	<p>Active against some XDR <i>A. baumannii</i> strains</p> <p>Limitations:</p> <ul style="list-style-type: none"> • Very limited clinical evidence • Not recommended as monotherapy beyond uncomplicated urinary tract infections

Table 2. Cont.

Antibiotic	Comment
Rifabutin	<p>Using culture media more relevant to in-vivo conditions rifabutin is much more potent than rifampicin [95], and is active even against PDR <i>A. baumannii</i> strains [96], and has been shown to be effective in vivo [95].</p> <p>Rifabutin also demonstrates synergy with polymyxins and the combination may be associated with lower risk of emergent resistance [97].</p> <p>Limitations:</p> <ul style="list-style-type: none"> • Not yet recommended given lack of clinical evidence • Currently only available orally (intravenous preparation under development [98,99]) • Risk of emergence of resistance during treatment. <p>Topic reviewed by Phillips MC et al. [100]</p>
Azithromycin	<p>Similar to rifabutin, traditional culture media may underestimate azithromycin's potential. In vitro and in vivo data suggest potential to treat <i>A. baumannii</i> with azithromycin, as well as synergy potential with polymyxins [101–103].</p> <p>Limitations:</p> <ul style="list-style-type: none"> • Not yet recommended given lack of clinical evidence. Very limited clinical data, all for <i>P. aeruginosa</i> [104].
Combination vs. monotherapy	<p>Based on in vitro and in vivo synergy and limitations of monotherapy options guidelines currently suggest combination therapy over monotherapy, especially for severe infections by <i>A. baumannii</i>. Where sulbactam/durlobactam is not yet available, guidelines suggest ampicillin/sulbactam as the preferred backbone for combination therapy [56,57].</p> <p>Limitations:</p> <ul style="list-style-type: none"> • Clinical evidence is predominantly based on observational, mainly retrospective studies, and anecdotal experience. • Methodology for assessing antimicrobial combinations in vitro needs re-evaluation [105]. • There is lack of clinical evidence correlating in vitro synergy with clinical outcomes. <p>Combinations not to use:</p> <ul style="list-style-type: none"> • Colistin/meropenem has not shown benefit over colistin monotherapy in randomized clinical trials and meta-analyses [106,107]. There may be potential for triple combinations (e.g., colistin/meronem/ampicillin/sulbactam or colistin/meropenem/fosfomycin) [7,57]. However, given lack of clinical data such combinations cannot be recommended. • Colistin/rifampicin has not shown clinical benefit in randomized trials [108–110]. As discussed above, colistin/rifabutin may be a better combination, pending clinical validation and availability of an intravenous formulation. <p>A common limitation to all above options is the lack of strong clinical evidence to guide optimal treatment. Where ampicillin/durlobactam is not available, ampicillin/sulbactam is considered the preferred backbone for combination therapy. Abbreviations: XDR: extensively drug-resistant, PDR: pandrug-resistant, MIC: minimum inhibitory concentration, PK/PD: pharmacokinetic/pharmacodynamic</p>

Table 3. Summary of considerations for selecting a treatment regimen for *A. baumannii*.

Consideration	Comment
Infection vs. colonization	<p>Isolation of <i>A. baumannii</i> from a non-sterile site does not prove infection. This is especially problematic when <i>A. baumannii</i> is isolated from the respiratory tract, urine or ulcers/burns/surgical site as well as in polymicrobial cultures (which are quite common [111]). To differentiate infection vs. colonization it is useful to consider a response to empirical treatment and the patient's status at the time of <i>A. baumannii</i> isolation (in a patient already improving or asymptomatic at the time of <i>A. baumannii</i> identification, treatment escalation to better cover <i>A. baumannii</i> is unnecessary).</p>
Severity of the infection and comorbidities	<p>For high-risk patients and/or severe infections a more aggressive treatment approach is reasonable (e.g., combination therapy vs. monotherapy).</p>

Table 3. Cont.

Consideration	Comment
Antibiotic susceptibility and mechanisms of resistance	Ideally, the treatment regimen should include at least one active antibiotic (if available). If this is not an option then selecting an antibiotic with an MIC close to breakpoints (e.g., tigecycline) is reasonable. Note also that for many of the above-discussed options, breakpoints are not well-established or need revising (see Table 2). Furthermore, appropriate breakpoints for synergistic antibiotic combinations are unclear. In vitro evaluation of synergy combined with PK/PD modeling may be helpful in selecting an appropriate antibiotic combination [112–115].
Site of infection	Antibiotic selection should take into account the penetration of different options at the site of infection. For example, tigecycline/minocycline have great penetration in soft tissues/bone but low urinary excretion and low. Colistin on the other hand does not achieve sufficient concentration in the epithelial lining fluid.
Adverse effects/history of allergies	Patients often do not tolerate treatment due to adverse effects and/or history of adverse reactions.
Response to treatment	In patients not responding or with recurrent infections it may be reasonable to add a third antibiotic to the treatment regimen [57].

Abbreviations: MIC = minimum inhibitory concentration, PK/PD: pharmacokinetic/pharmacodynamic.

4. Conclusions

In understanding the mechanisms of colistin resistance in *A. baumannii*, it becomes evident that the bacterium employs a multifaceted approach to evade the antimicrobial effects of this last-resort antibiotic. Primarily, alterations in the lipid A component of the LPS structure play a pivotal role. Adding molecules like *PEtN*, or galactosamine to lipid A alters its structure, reducing the affinity for colistin. Furthermore, mutations or disruptions in LPS biosynthesis genes, such as *lpxA*, *lpxC*, or *lpxD*, lead to the loss or modification of LPS, rendering the bacterium less susceptible to colistin. Additionally, mutations affecting outer membrane permeability, such as the loss or reduced expression of porins or mutations in non-Lpx proteins contribute to colistin resistance. Heteroresistance further complicates treatment, potentially leading to failure if not addressed appropriately.

Despite colistin being a last resort treatment option for infections by carbapenem-resistant *A. baumannii*, resistance to colistin likely does not pose a major problem yet given the availability of several non-polymyxin-based regimens as well as the potential to still use colistin as part of synergistic combination regimens. The currently preferred backbone for the treatment of carbapenem-resistant colistin-resistant *A. baumannii* is sulbactam (sulbactam/durlobactam if available, or else ampicillin/sulbactam). However, the optimal combination regimen remains unclear.

Author Contributions: Methodology, R.-N.T. and D.P.K.; validation, P.I., S.K. and D.P.K.; formal analysis, A.P.; investigation, R.-N.T., A.P. and S.K.; resources, D.P.K.; data curation, A.P., D.P.K., R.-N.T. and S.K.; writing—original draft preparation, A.P.; writing—review and editing, R.-N.T., S.K., P.I., D.P.K. and G.S.; visualization, S.K.; supervision, D.P.K.; project administration, D.P.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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