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Treatment Options for Multidrug-Resistant *Acinetobacter* Species

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Abstract

Multidrug-resistant *Acinetobacter* spp. are emerging nosocomial pathogens and have become a leading cause of Gram-negative infections in many parts of the world. *Acinetobacter* spp. are commonly implicated in bloodstream infection, hospital-acquired pneumonia, and wound and other surgical-site infections. They are difficult to treat, thus often leading to adverse patient outcome. Group II carbapenems (imipenem/cilastatin and meropenem) are the agents of choice for the treatment of severe infections caused by *Acinetobacter* spp. isolates susceptible to this antimicrobial group, but infection with carbapenem-resistant strains is increasingly encountered. Therapy of such infections necessitates the use of old drugs (e.g. colistin), unusual drugs (e.g. sulbactam) or drugs with which there is

presently little clinical experience (e.g. tigecycline). Case reports, case series and small comparative observational studies suggest that these regimens are efficacious and demonstrate lower-than-expected toxicity, but there is substantial variation between these reports. Combination antimicrobial therapy is often used to treat infections caused by such multidrug-resistant strains. This article summarizes the cumulative experience with and the evidence for treating infections caused by multidrug-resistant *Acinetobacter* spp. infections. Special emphasis is placed on the use of 'non-traditional' antimicrobial agents, various aspects of combination therapy, alternative routes of drug administration, and discrete entities such as ventilator-associated pneumonia and postsurgical meningitis.

Acinetobacter species are among the most challenging bacterial pathogens that clinicians are currently facing. These non-fermentative Gram-negative bacilli are increasingly implicated in nosocomial infections worldwide. *Acinetobacter* spp. demonstrate high rates of resistance to multiple antimicrobial agents and strains resistant to most, if not all, commercially available agents are increasingly being documented. The aim of this article is to review current evidence on treatment options of nosocomial *Acinetobacter* infection caused by multidrug-resistant (MDR) strains. The medical literature was searched using PubMed with the following keywords: acinetobacter, baumannii, calcoaceticus, nosocomial, bloodstream infection, colistin, tigecycline, carbapenem, resistance, sulbactam, meningitis, ventilator, contamination, colonization.

1. Scope of the Problem

1.1 Epidemiology and Clinical Features

Acinetobacter spp. are low-virulence organisms that opportunistically cause infection in susceptible patient populations, mostly critically ill or immunocompromized individuals. Acquisition of *Acinetobacter* spp. commonly occurs after 2–3 weeks of hospital stay.[1] A variable portion of acquisition represents colonization rather than infection, but differentiation between these conditions is frequently difficult since many of the affected patients are debilitated and severely ill.[2] Nonetheless, environmental contamination, patient colonization and clinical infection commonly represent a continuum, and therefore each of these components merits consideration in an effort to prevent nosocomial morbidity and mortality.

While most *Acinetobacter* spp. rarely cause infection, *A. baumannii* is most frequently implicated in nosocomial infections. It may be difficult to interpret the literature on *Acinetobacter* infections since speciation using credible methods was not performed in most studies. Moreover, even strains of *A. baumannii* differ substantially from each other. Substantial genomic differences were recently observed between MDR *A. baumannii* and a reference *A. baumannii* strain associated with human body lice.[3] Thus, conflicting results from various studies may actually represent the study of different species or, alternatively, differences between *A. baumannii* strains. It is of great importance that future studies enhance the definitions and characterisation of the studied isolates.

Acinetobacter spp. can survive for long periods in the hospital environment, in both moist or dry conditions,[4] and thus fomites are frequently involved in the chain of nosocomial transmission beyond the inherent role of contaminated hands of healthcare workers. Indeed, contaminated fomites, such as medical equipment, have been implicated in nosocomial outbreaks of *Acinetobacter* infection; even personal staff equipment (e.g. cell phones) could be the culprit.[5] The reported success of infection control measures involving environmental decontamination in preventing transmission or halting *Acinetobacter* spp. outbreaks emphasizes the importance of the environmental persistence of the organism.[6] Patients themselves also serve as a res-

ervoir,[7,8] and this should be accounted for when designing an infection-control intervention.

The most common types of infections involving *Acinetobacter* spp. are pneumonia (especially ventilator-associated pneumonia [VAP]), urinary tract infection, surgical site infection including postsurgical meningitis (PSM), and catheter-related bloodstream infection.[9] VAP, surgical site infection or catheter-related bloodstream infection are reported be the dominant types of infection in various settings.[2,6,10] The distribution of these distinct infectious foci varies greatly, most likely to be the result of differences in the hospital environment, the case mix and the nature of the local epidemiology.

Risk factors for *Acinetobacter* spp. infection found in a number of studies include mechanical ventilation, urinary instrumentation, major surgery (especially in the context of trauma or burns and neurosurgery) and indwelling vascular catheters. The presence of these risk factors, a high burden of *Acinetobacter* spp. in a given setting (referred to as the 'colonization pressure'), breaks in infection control and selective antimicrobial pressure all favour *Acinetobacter* spp. infection. Among the various antimicrobial agents that have been implicated in selective pressure that promotes the emergence of MDR strains are third-generation cephalosporins, carbapenems and fluoroquinolones.[11-14] However, establishing risk factors for the emergence of resistance requires appropriate methodology and, particularly, using a control group that represents the population at risk;[15] many of the published studies from the literature search failed to meet these criteria and therefore may have yielded biased results.

The use of molecular tools has broadened our understanding of the epidemiology of *Acinetobacter* spp. In hospitals where *Acinetobacter* spp. are endemic, they may originate from a single clone or, more commonly, from several clones that circulate in hospitals, of which one or more may dominate. Within this complex epidemiology, the source of emergence and dissemination is not always evident.[16] Occasionally, *Acinetobacter* spp. clones may be involved in inter-institution and even interstate outbreaks.[17] Such complex epidemiology and intercontinental spread of resistant strains are also evident from the ongoing investigation in the US and UK of *Acinetobacter* infection among repatriated casualties from the military conflict in Iraq. In all, >100 nosocomial outbreaks with *Acinetobacter* spp. have been reported to date and they have been extensively summarized elsewhere.[18,19]

1.2 Impact on Patient Outcome

The outcome of patients with nosocomial *Acinetobacter* spp. infection, including measures of morbidity (e.g. the development of severe sepsis, septic shock or prolonged mechanical ventilation) and mortality, may be difficult to measure. While crude (all-cause) inhospital mortality is easy to assess, mortality attributed specifically to the infection is much more difficult to appreciate, since patients at risk for acquiring *Acinetobacter* spp. often have poor prognosis due to underlying conditions. Moreover, severity of infection and resultant patient outcome may be influenced not only by the patient's underlying condition, but also by differences between infecting strains, the site of infection, and appropriateness of empiric and definitive therapy.[20,21] Specifically, inappropriate empirical therapy has been shown to result in a 3-fold increase in therapeutic failures and a 2-fold increase in mortality.[22]

The reported mortality of nosocomial *Acinetobacter* spp. infection is estimated at being 5–50%, a range which reflects the heterogeneity of the studies. In a national study conducted in Spain, patients with *Acinetobacter* spp. infection had an odds ratio of 1.5 for mortality compared with patients colonized with this organism.[2] Comparison of mortality attributable to infection has been shown to be higher for *Acinetobacter* infection than for other nosocomial pathogens, such as *Klebsiella pneumoniae*.[23] Nevertheless, debate on the importance of *Acinetobacter* infections in leading to excess mortality continues, with several studies[24,25] not having found increased mortality in these patients, and others reporting increased mortality in the presence of MDR isolates, including *Acinetobacter*.[26] A recent systematic review of the subject concluded that

nosocomial acquisition of *Acinetobacter* (colonisation or infection) did result in excess attributable mortality,[27] supporting the hypothesis that many patients 'die with *Acinetobacter*', although the proportion of those who 'die due to *Acinetobacter*' is difficult to estimate. Our own interpretation of the literature is that conflicting findings may reflect the fact that various strains of *Acinetobacter* differ in virulence, and thus patient outcomes may be related to the virulence of the dominant infecting strain in a given institution. We have no doubt that *Acinetobacter* infections lead to severe adverse outcomes in our institution as well as in others.[28]

2. Definitions

There are >30 distinct genomo-species within the genus *Acinetobacter*. The vast majority of human infection cases are caused by antimicrobial-resistant species that belong to the *calcoaceticus-baumannii* complex, including *A. calcoaceticus*, *A. baumannii*, and genomo-species 3 and 13TU.[29] Other genomospecies have been implicated in human infection less commonly but these are relatively susceptible to various antimicrobials.

Differentiation between members of the *calcoaceticus-baumannii* complex is difficult with routine manual or automated microbiological methods. While most published papers to date simply refer to '*A. baumannii*', molecular identification was not sought in most of them, and so data on specific members of this complex are scarce. Nevertheless, *A. baumannii* is by far the most common species encountered in clinical practice. In this review, we use the term *Acinetobacter* spp. to denote all species likely to express MDR (most of which are truly *A. baumannii*).

Various terms have been used (sometimes interchangeably) to denote antimicrobial-resistant phenotypes of *Acinetobacter* spp., the most common of which are 'MDR', 'pan-drug resistance' (PR), and less commonly 'totally', 'highly', 'almost completely' or 'fully' resistant strains. Since a standard definition is currently lacking, 'MDR' has been used to describe strains resistant to at least two or three major antimicrobial classes or a varying number of individual drugs; however, other authors have used MDR as a synonym for carbapenem-resistant (CR) strains. Contrary to nosocomial pathogens, such as *Pseudomonas aeruginosa*, CR-*Acinetobacter* spp. are usually resistant to most other β-lactams, β-lactamase inhibitors, aminoglycosides and fluoroquinolones.[30] Strains that are susceptible to at least one of these 'traditional' agents are believed to be less of a challenge to treat (despite being 'MDR' according to some definitions), but comparative data are sparse. Treatment difficulties are even more pronounced when co-resistance to all of these agents is encountered because 'non-traditional' agents are to be considered. Therefore, for the sake of convenience, we refer to 'MDR' strains as those that are co-resistant to all agents conventionally recommended for the treatment of infections caused by *Acinetobacter* spp. ('traditional drugs'), and the term 'PR' to describe strains that are resistant to all commercially available agents, including 'non-traditional' ones. At the time of writing, the latter group of 'non-traditional' antimicrobials mainly includes the polymyxins, sulbactam, minocycline and tigecycline.

Nonetheless, occasional strains that are susceptible to at least one 'traditional' agent *in vitro* can be considered as being MDR from a practical point of view according to the above definition in certain clinical situations in which the use of that particular agent may prove problematic. Such situations may include drug hypersensitivity or intolerable adverse effects necessitating discontinuation, clinical treatment failure, development of non-susceptibility during therapy, temporary or permanent market unavailability of certain antimicrobials, or inappropriateness for a given infectious focus or anatomical compartment (e.g. aminoglycosides as monotherapy for the treatment of VAP).

3. Antimicrobial Resistance

Acinetobacter spp. have the propensity of rapidly acquiring resistance genes due to selective antimicrobial pressure, thereby leading to MDR, in addition to intrinsic resistance mechanisms that are typical to this genus. The frequency of resistance to

major antimicrobial classes, as well as the prevalence of MDR or PR strains, varies greatly between geographical regions, institutions and even hospital wards, and this is further complicated by the differences in methodology and definitions between published studies. Therefore, establishing and continuously monitoring local resistance rates is mandatory in settings vulnerable to a high incidence of *Acinetobacter* spp. infection.

3.1 Antimicrobial Resistance Mechanisms

Central to the development of resistance is the acquisition of resistance genes through plasmids, integrons or transposons, and most of *Acinetobacter* spp. may carry either. Integrons are of particular interest among the mobile genetic elements. Of the three known integron classes, class 1 is by far the most prevalent in *Acinetobacter* spp. Such integrons may be transferred between unrelated strains and even between species.[31,32]

Resistance to β-lactams in *Acinetobacter* spp. involves a myriad of genetic mechanisms that may coexist and/or be co-expressed. Most strains carry intrinsic β-lactamase activity mediated through chromosomally encoded genes, namely the Amp-C type cephalosporinase and OXA-51/69-type oxacillinase.[33,34] Both are characterized by a basal expression level that may be altered by genetic events, such as the introduction of an upstream insertion sequence to the bla_{AmpC} gene, resulting in an extended-spectrum β-lactamase (ESBL) phenotype.[35] Moreover, a variety of other β-lactamases have been described in *Acinetobacter* spp., such as TEM-1, SHV, CTX-M and, more recently, the ESBL enzyme VEB-1,[36] but their role is difficult to assess in the presence of β-lactamase hyper-production.[37]

Carbapenems are the preferred treatment for serious *Acinetobacter* spp. infection, although carbapenem resistance has been increasingly reported in recent years with varying frequency.[29] Carbapenem resistance is conferred by acquired β-lactamases, but not naturally occurring enzymes. These enzymes belong to either Ambler class B (metallo-β-lactamases [MBL]) or class D (oxacillinases). MBL are efficient carbapenemases (extensively reviewed elsewhere[38]) and three groups of this enzyme class have been found in *Acinetobacter* spp., mainly the IMP-like MBL and, to a much lesser extent, the VIM-like MBL or SIM-1. IMP and VIM confer high-level resistance to carbapenems and most other β-lactams with the exception of aztreonam. MBL are located in class-1 integrons, and may be transferred and expressed along with resistance genes to other antimicrobials such as aminoglycosides.

The other group of enzymes (carbapenem-hydrolysing oxacillinases [CHOs]) consists of oxacillinases with intrinsic carbapenemase activity that is 1/100th to 1/1000th that of MBL.[30] Such enzymes in *Acinetobacter* spp. (in contrast to other bacteria) do not confer ESBL properties. Nearly ten different CHOs have been described in *Acinetobacter* spp., with OXA-58 being especially common,[39] but their mode of acquisition is less clear. Recent retrospective analyses revealed that CHO have been around (and gone undetected) for at least one decade in diverse geographic locations.[40] OXA genes may occur on plasmids, chromosomes or mobile genetic elements, and complex genetics may be involved in their expression, i.e. in the form of mobile insertion sequences or genetic recombination. Phenotypically, these enzymes may be associated with differences in the minimal inhibitory concentration (MIC) of imipenem and meropenem; however, the therapeutic implications of these differences have not been studied.

A third mechanism of carbapenem resistance involves porins, which are outer-membrane proteins that allow antimicrobials, such as β-lactams, to permeate into the bacterial cell. Loss (i.e. reduced expression) or modification of porin proteins has been shown to confer carbapenem resistance and, not uncommonly, high-level resistance is observed in the presence of both loss of porin function and expression and production of carbapenemases (especially CHO).[41] Additional mechanisms that contribute to carbapenem resistance, especially in the presence of carbapenemases, include the loss of certain penicillin-binding proteins (PBPs)[42] or presence of nonspecific efflux protein pumps, such

as the AdeABC.[43] There are additional putative mechanisms that have not yet been elucidated.[44]

Resistance to aminoglycosides is mainly conferred by aminoglycoside-modifying enzymes. A high diversity of aminoglycoside-modifying enzymes have been shown in *Acinetobacter* spp. and these enzymes have been linked to class I integrons as well.[45] Moreover, identical aminoglycoside-modifying enzymes have been found in different *Acinetobacter* clones, suggesting horizontal gene transmission. Inactivation by acetylases, adenylases and phosphotransferases has been reported, notably AAA(3)-Ia, ANT(3″)9 and APH(3′)VI, respectively.[46,47] Other mechanisms may include target site modification or efflux pumps.[48] Regardless of aminoglycoside resistance, it should be kept in mind that these agents may not be effective in respiratory infection (one of the most common sites of *Acinetobacter* infection) and are not reliable as single agents in most infections other than those of the urinary tract.

Resistance to other drug classes includes: (i) mutations in the *gyrA* or *parC* genes, which lower the affinity of fluoroquinolones to their respective targets; (ii) DNA gyrase or topoisomerase IV,[49,50] which have been demonstrated in both *A. baumannii* and genomo-species 3; (iii) synthesis of chloramphenicol acetyltransferase I, which confers chloramphenicol resistance;[29] and (iv) presence of TetA and TetB (and rarely TetM), which confer resistance to tetracyclines.[51,52] All of these and other agents (e.g. trimethoprim) are also influenced by efflux pumps present in *Acinetobacter* spp.

3.2 Antimicrobial Susceptibility Testing

Accurate susceptibility determination is crucial for appropriate selection of antimicrobial therapy. Most clinical laboratories rely on one or more standard antimicrobial susceptibility testing (AST) method, usually disk diffusion, MIC determination by commercial automated systems or MIC by agar diffusion (e.g. Etest® [1], AB biodisk, Solna, Sweden), since broth microdilution is too cumbersome for routine use. Results should be interpreted according to official breakpoints designated specifically for *Acinetobacter* spp., such as those issued by the Clinical and Laboratory Standards Institute (CLSI).[53]

In general, essential and categorical agreement between these methods is more than acceptable, but there are several limitations that ought to be considered. Colistin susceptibility requires a MIC method because of poor performance of disk diffusion.[54] Using the colistin E-test is a reasonable alternative to broth dilution, although agreement rate is suboptimal in certain MIC values.[55] It should be taken into account that *in vitro* testing utilizes colistin sulfate, while colistimethate sodium is the active drug usually administered systemically; therefore, the correlation between AST and outcome is somewhat theoretical.

No breakpoints have yet been formulated by the CLSI for tigecycline and therefore manufacturer's recommendations or, alternatively, the recently published breakpoints of the European Committee on AST may be followed.[56] Disk diffusion breakpoints for tigecycline have also been proposed.[57] Tetracycline is not a good surrogate marker for its class[53] and, therefore, minocycline susceptibility should be tested specifically against *Acinetobacter* since tetracycline-resistant minocycline-susceptible phenotypes are common.

Occasional isolates may exhibit hetero-resistance to carbapenems that may result in false susceptibility when automated AST is performed. A clue for hetero-resistance in our experience is a relatively high MIC within the susceptible range, in which case performance of the Etest® may reveal resistant subpopulations, similar to those previously described.[58] Hetero-resistance has recently been described with colistin as well, but its impact on efficacy has not yet been established.[59]

Automated AST methods also require ancillary manual testing of *Acinetobacter* spp. For example, the VITEK®-2 system does not include colistin or minocycline in certain AST cards, so these agents should be tested manually. Furthermore, results for

1 The use of trade names is for product identification purposes only and does not imply endorsement.

specific antimicrobials require manual validation, such as imipenem non-susceptibility, due to high rates of false resistance[60] or amikacin in the MIC range of 16–32 μg/mL. These ancillary tests that require both disk diffusion and the Etest® may be combined in a single plate, a feature which may be convenient for laboratories that process large numbers of *Acinetobacter* spp. isolates.[61]

Other methods may be considered in special situations in which individualized therapy is warranted, but these are seldom supported by evidence. Such methods include determination of the minimal bactericidal concentration (MBC), serum bactericidal titres and synergy testing (discussed in section 5). There is little clinical experience in the application of MBC assessment in *Acinetobacter* spp. infection.

Searching for genetic resistance mechanisms is, of course, not routinely carried out in nonspecialized laboratories. The presence of MBLs can be simply established based on their inhibition by EDTA, using an Etest® strip that measures imipenem MIC with and without EDTA.[38] However, this method may yield false-positive results in MBL-negative CHO-positive strains with phenotypic carbapenem resistance.[62] Specialized selective agar media that contain carbapenems may preferentially grow carbapenem-resistant strains.[63] In addition, certain phenotypes correlate well with genotypic resistance and may be used as surrogate markers, such as evidence of ceftazidime resistance that may predict the presence of TEM-1, and of gentamicin and cotrimoxazole resistance that may predict the presence of the integrase 1 gene,[64] or of disk synergy and disk EDTA that correlate with MBL expression.[65] Molecular analysis of certain strains may reveal the presence of a resistance gene but not phenotypic resistance; the clinical significance of such findings is unknown.

4. Specific Antimicrobial Agents

The optimal regimen for treating *Acinetobacter* spp. infection has not yet been established because of the lack of comparative clinical trials. By consensus, therapy with a β-lactam agent with or without an aminoglycoside is most commonly recommended, but there are insufficient data on the relative efficacy of dual and monotherapy.[66] Group II carbapenems (imipenem/cilastatin and meropenem) are the most widely used agents for treatment of *Acinetobacter* spp. infection, especially in areas where carbapenem susceptibility rates are still high. Group I carbapenems (ertapenem) have only limited activity against *Acinetobacter* spp. and should not be used to treat infections caused by these pathogens.[67] A new group II carbapenem, doripenem, appears to have efficacy comparable to imipenem/cilastatin and meropenem.[68] Finally, a new oral penem, faropenem, has recently been made available but is not US FDA approved. However, this drug shows poor activity against nonfermentative Gram-negative bacilli.[69]

Until the last decade, carbapenem resistance was rare among *Acinetobacter* spp. isolates worldwide,[70] but the rates of carbapenem resistance are growing alarmingly.[71] With increasing carbapenem resistance, other 'non-traditional' drugs ought to be considered, such as those discussed in sections 4.1 to 4.4.

Isolates commonly show similar susceptibility to both imipenem and meropenem. Occasional discrepancies in MIC may be observed *in vitro* between these agents, but these do not necessarily imply categorical disagreement. Among discrepant isolates at certain geographical locations, imipenem may have either lower or higher MIC values than meropenem.[72,73] While the clinical impact of such discrepancies is still considered unclear, there are anecdotal reports of patient death secondary to inappropriate therapy caused by discordant susceptibility results.[74] Our recommendation is to consider resistance to any of the group II carbapenems as evidence of resistance to the entire class.

4.1 β-Lactamase Inhibitors

Of the β-lactamase inhibitors, sulbactam is the most efficacious and most studied agent in the context of *Acinetobacter* infection. Sulbactam shares many pharmacological similarities with aminopenicillins and exerts direct bacteriostatic activity against *Acinetobacter* spp. through binding to PBP2.

It has been administered as ampicillin/sulbactam (2 : 1 ratio), since pure sulbactam is not available in many countries, although the two agents are not synergetic.[75] Ideally, the dose of sulbactam should be 1 g every 3–4 hours (corresponding with a daily dose of ampicillin of up to 24 g). Sulbactam, alone or in combination, shows significant activity against both *A. baumannii* as well as genomo-species 3.[76] Experimental data also support the role of sulbactam in the treatment of *Acinetobacter* spp. infection. Sulbactam has shown greater efficacy than that of imipenem in a mouse pneumonia model involving a susceptible strain, but it was inferior to imipenem in a rabbit endocarditis model involving a non-susceptible strain.[77] These experimental findings should be interpreted with caution, given the significantly different pharmacokinetics of imipenem in mice compared with humans.

Most data on sulbactam therapy in humans come from retrospective analyses or case series. Cure rates of 80–90% have been reported by several authors in both bacteraemic and non-bacteraemic patients,[75,78,79] and ampicillin/sulbactam has been reported to have similar efficacy to that of imipenem/cilastatin.[80,81] Of 94 patients with nosocomial *Acinetobacter* spp. bacteraemia, 33 patients infected with carbapenem-resistant strains and treated with ampicillin/sulbactam had mortality rates almost identical to 38 patients infected with susceptible strains and treated with adequate standard therapy (42% vs 40%). Moreover, ampicillin/sulbactam was associated with reduced mortality among patients with high Acute Physiology and Chronic Health Evaluation (APACHE) II scores.[10] In another study, of 40 patients with different types of infection caused by carbapenem-resistant strains, 67.5% were improved or cured with ampicillin/sulbactam (even at relatively low doses).[82]

Of note, another sulbactam-containing preparation exists in several countries, namely cefoperazone/sulbactam. Despite the *in vitro* susceptibility of many MDR strains, clinical data on this combination are limited.[83]

4.2 Polymyxins

Two polymyxin compounds have been used with MDR organisms: polymyxin B and polymyxin E (colistin). Colistin is more widely used and is available in two forms – colistin sulfate, which is administered orally or topically, and colistin methanesulfate (or colistimethate sodium), which is administered systemically. The latter preparation is less potent and less toxic. Colistin is a cationic lipopeptide that acts by interacting with anionic lipopolysaccharide moieties on the bacterial cell membrane, thereby leading to increased membrane permeability.[84]

The intravenous dosage of colistin is problematic and differs between the US and Europe. Colistin 1 mg is equivalent to 12 500 IU with colistimethate and 30 000 with colistin base, and a call for standardisation of dosage regimens has recently been issued.[85] US dose administration regimen consist of 2.5–5 mg/kg/day of colistin base in two to four divided doses (75 000–150 000 IU/kg/day), while the recommended dosage in the UK is 4–6 mg/kg/day in three divided doses for adults with ≤60 kg bodyweight (50 000–75 000 IU/kg/day) and 80–160 mg (1–2 million IU) every 8 hours for adults weighing >60 kg.[86] Administration of higher dosages (3 000 000 IU every 8 hours) has also been reported.[87] The bactericidal activity of colistin is concentration dependent, therefore administering large doses in less frequent intervals may be a favourable approach.[84] Continuous colistin infusion has been reported anecdotally as well.[88] Dose adjustment is required in the presence of renal failure. Moreover, different polymyxin dose administration schedules have been proposed for patients undergoing haemodialysis.[89]

Colistin had been abandoned years ago because of high rates of nephro- and neurotoxicity. Since its revival during the last decade, it has been widely used in *Acinetobacter* spp. infection. However, most available data are uncontrolled and largely heterogeneous, and therefore its efficacy is difficult to estimate, especially if given as salvage therapy after standard therapy has failed. Surprisingly, recent data suggest that the incidence and magnitude of nephro-

toxicity is much lower than that previously reported, and even prolonged therapeutic courses are associated with nonsignificant increases of serum creatinine without frank renal dysfunction.[90] This issue has been recently subject to systematic review,[91] which showed that while older studies have reported nephrotoxicity rates of 20–30% and even as high as 50%, higher doses of colistin were administered compared with those used today. Moreover, no standard definition of toxicity was employed and studies did not control for other possible causes of nephrotoxicity such as aminoglycoside use or preexisting renal dysfunction. Not unexpectedly, nephrotoxicity correlates well with the cumulative colistin dose.[92] Fewer toxicity data are available for polymyxin B, but an incidence of renal failure of 15% has recently been reported.[93] In that uncontrolled study, polymyxin B resulted in a microbiological cure rate of 88%, with mortality being significantly higher among patients with drug-induced renal failure.

Resistance to colistin may involve mutations or adaptive mechanisms that affect both colistin and polymyxin B. These may include outer membrane alterations (reduced lipopolysaccharide levels, reduction in cation content or reduced levels of specific proteins) or even efflux pumps. However, enzymatic resistance has not been reported.[86] A recent study evaluating a collection of 115 clinical strains has found a resistance rate of 19.1% (MIC at which 50% of bacteria are inhibited = 0.06 μg/mL and MIC at which 90% of bacteria are inhibited = 16 μg/mL).[55] Nevertheless, resistance rates to polymyxins at most locations are reported to be lower, and range between 2.1% among isolates in general and up to 3.2% among MDR isolates.[94]

There are limited published data on polymyxin therapy for MDR or PR *Acinetobacter* infection. Most reports refer to treatment of bloodstream infection, or VAP and PSM, which are further discussed in sections 7.1 and 7.2. Other types of infection have been rarely studied and experimental data are not favourable for some (e.g. endocarditis).[95] Most reports are uncontrolled case series that involve a heterogeneous patient population with various infectious foci and causative pathogens, but support the reasonable clinical efficacy of intravenous colistin.[96-98] The use of polymyxins in MDR Gram-negative infection has been extensively reviewed elsewhere.[86,99]

4.3 Tetracyclines and Glycylcyclines

Tetracycline resistance is common among MDR *Acinetobacter* spp. Tetracycline resistance is mediated by genes such as *tet(A)* or *tet(B)* that encode specific efflux pumps. The latter also affects minocycline, and therefore Tet(B)-positive strains may demonstrate resistance to tetracycline and intermediate resistance to minocycline in *Acinetobacter*.[100] Tetracycline-resistant minocycline-susceptible isolates are not uncommon. High rates of minocycline susceptibility have been reported in *Acinetobacter* spp., even when the carbapenem resistance rate is substantial. Although minocycline susceptibility has been evaluated by many *in vitro* studies, data on its *in vivo* efficacy are nearly nonexistent.

Tigecycline is a new glycylcycline agent (tetracycline derivative) recently approved for use. Similar to tetracyclines, tigecycline is a bacteriostatic agent that interferes with bacterial protein synthesis through ribosomal binding and thus exhibits time-dependent bactericidal activity. Tigecycline is eliminated via biliary excretion and dose adjustment is unnecessary with renal failure. Notably, tigecycline has an excellent safety profile. It has been reviewed in several recent publications.[101,102]

Common tetracycline resistance determinants are unable to inhibit tigecycline and natural resistance to tigecycline is unusual. Nevertheless, several unique multidrug efflux pumps have been shown to reduce organism susceptibility to tigecycline.[103] Tigecycline has a wide spectrum of activity and has low MIC values (<2 μg/mL) for almost all *Acinetobacter* spp. studied thus far.[104] Tigecycline susceptibility has also been shown in polymyxin-resistant strains.[105] Strains resistant to tigecycline have already been described, although their prevalence is still low:[106] resistance was recently shown to be 6% in an international collection of European and

American isolates.[107] Interestingly, the resistance rate of imipenem among the latter was only 3%.

Tigecycline has been studied mainly in complicated skin and skin structure infections (compared with vancomycin) and in complicated intra-abdominal infection (compared with imipenem/cilastatin), and has been shown to be non-inferior to its comparators.[103] However, data in the context of MDR *Acinetobacter* are limited. Tigecycline has been reported to result in cure of severe MDR *Acinetobacter* infection after failure of combined therapy with meropenem plus colistin,[108] although at least two cases (one fatal) have been described in which carbapenem-susceptible tigecycline-resistant *Acinetobacter* strains were acquired during tigecycline therapy for other indications. Preliminary data suggest a role of efflux pump mechanisms in causing tigecycline resistance.[109] Thus, tigecycline appears to be a promising drug for treatment of *Acinetobacter* infections, but it should be used with caution until more clinical data are available.

4.4 Fluoroquinolones

Fluoroquinolones are important agents in the treatment of Gram-negative infection. Among this group, levofloxacin (the L-isomer of ofloxacin) has been shown to yield a lower MIC compared with ciprofloxacin and ofloxacin against *Acinetobacter* spp. Levofloxacin has shown a wide MIC range against *A. baumannii* (0.06–0.64 μg/mL), with a substantial difference in the modal MIC between nalidixic acid-susceptible and -resistant strains.[110]

Overall, resistance rates to ciprofloxacin and levofloxacin among *Acinetobacter* spp. clinical isolates are around 50%.[111] *In vitro* selection of resistance to fluoroquinolones has been shown to increase in *Acinetobacter* spp. by means of mutations, but this phenomenon was largely prevented when fluoroquinolones were combined with β-lactams or aminoglycosides.[112] Several other fluoroquinolones, such as gemifloxacin[113] and clinafloxacin or gatifloxacin,[114] have been shown to have enhanced activity against *Acinetobacter* spp. *in vitro* compared with older members of this class.

Data on the clinical efficacy of fluoroquinolones in nosocomial *Acinetobacter* spp. infection are sparse. Moreover, occasional MDR strains exhibit a levofloxacin-susceptible ciprofloxacin-resistant phenotype. Although the clinical implications of this discrepancy are unknown, it may represent a pre-existing mechanism of resistance that will eventually lead to fluoroquinolone treatment failure.

5. Antimicrobial Combination Therapy

The importance of combination therapy has been widely shown for other nonfermentative Gram-negative bacilli, such as *Pseudomonas aeruginosa* (especially with bloodstream infection or febrile neutropenia), but it has not been given much attention in relation to *Acinetobacter*. Combination therapy of susceptible strains is directed at improving outcome (relative to monotherapy) via a synergistic effect. Secondary goals of combination therapy are the prevention of adverse effects by lowering drug doses and the prevention of emergence of resistance during therapy.[115] In the setting of PR strains, combination therapy aims at producing additive or subadditive effects, such as the enhancement of the effect of one agent by another inactive drug. The emergence of PR *Acinetobacter* strains has prompted the study of various antimicrobial combinations, most commonly in *in vitro* studies or experimental models, while clinical experience with combination therapy is quite limited.

Several drug combinations have been tested against *Acinetobacter* spp., mostly involving colistin, carbapenems, rifampin, azithromycin, fluoroquinolones and sulbactam. Synergistic effects may have plausible explanations, such as increased β-lactam activity as a result of the effect of colistin on the cell membrane, but specific mechanisms have not been elucidated for most drug combinations.

The two most common methods for assessing synergistic effects are the checkerboard microdilution method and the time-kill assay. In checkerboard synergy studies, the fractional inhibitory concentration (FIC) index (FICI) is calculated, as the sum of the FIC of each drug. FIC equals the MIC of a certain drug in a drug combination divided by the

MIC of the same drug if administered alone. A FICI <0.5 represents synergy, FICI = 1 is an additive effect and FICI >4 indicates antagonism. A 0.5 < FICI < 1 is regarded as partial synergy by some and as an additive effect by others, while 1 < FICI < 4 may be considered indifferent. Classic checkerboard studies utilize a standard microdilution plate that contains the various concentrations of each of the two tested antimicrobials (*x* and *y* axes) and their combinations, yielding a checkerboard matrix. In triple-synergy studies, the same method is employed except that the microdilution plate is replicated as necessary, each time with a different concentration of a third antimicrobial (*z* axis), thereby creating a '3-dimensional' matrix.

With time-kill assays, synergy is usually defined as a decrease of at least 2 $\log_{10}$ in the viability count at 24 hours with a drug combination, compared with that of the more active of the drugs alone. Time-kill synergy studies may also employ two or more antimicrobials. Discrepancies between the two methods often occur and agreement depends on the method of interpretation of checkerboard results.[116] Synergy may also be tested using the Etest®.

Various studies of *in vitro* synergy against *Acinetobacter* spp. are summarized in table I; the significant variability between studies in relation to strain selection, testing methods and studied combinations is easily appreciated. Moreover, the FICI breakpoints differed widely between studies, so that no drug combination has consistently exhibited synergy. Despite these limitations, combining drugs that have previously been shown to produce synergy is reasonable when faced with MDR or PR strains. In addition, synergy studies may assist in eliminating the administration of combinations that have been shown to produce antagonistic effects. Standardization of *in vitro* synergy studies in order to establish better clinical correlates is undoubtedly warranted. Of note, strain-to-strain variation does exist in regard to synergy, probably due to differences in resistance mechanisms, and thus synergy studies may be applicable only to studied isolates.

Combination therapy has also been evaluated in several experimental models, some of which are summarized in table II. Interestingly, *in vitro* synergy often does not translate to improved outcome in experimental models. Methodology issues are the most likely explanation for these discrepancies, for example, effect of high versus low inocula, differences in pharmacokinetics/pharmacodynamics in mouse models, or the site of infection. Moreover, *in vitro* synergy may not always translate to clinical outcome in human studies. For example, in one retrospective study of MDR Gram-negative infection (including but not limited to *Acinetobacter*), colistin monotherapy resulted in a better outcome than a colistin plus meropenem combination and the authors concluded that monotherapy is not inferior to combination therapy,[139] with response rates (improvement or cure) for both being high, ranging between 68% and 86%.

With other combinations, emergence of resistance is an issue; for example, resistance to rifampin develops rapidly during treatment despite promising *in vitro* data. While experimental data suggest that this may be obviated by the addition of a β-lactam agent, such as carbapenem,[142] this finding is not supported by clinical data.[143]

We believe that combination therapy has now become the preferred practice in the treatment of infections by MDR *Acinetobacter*. Since there is strain-to-strain variation in response to different combinations, synergy tests are warranted in order to direct therapy. Further studies in this context are urgently needed.

6. Adjunctive Measures

6.1 Surgery

Similar to infections caused by other bacteria, antimicrobials alone may not always be sufficient to treat *Acinetobacter* spp. infection, and surgical interventions may be required in order to achieve better source control. This is especially true for situations like PSM with ventriculitis, mediastinitis or deep sternal wound infection following open-heart surgery, thoracic empyema, infection of traumatic wounds or orthopaedic implants, or in the event of tertiary peritonitis. Commonly, surgical

Table I. Summary of *in vitro* data regarding the effect of antimicrobial combinations against *Acinetobacter* spp.

Reference (year)	Resistance pattern	No. of isolates	Methods	Combinations tested	Results	Comments
Bajaksouzian et al.[117] (1997)	NR	101	Checkerboard	LEV-AMK	Synergy rate 1%, partial synergy rate 57%	Synergy and partial synergy found mainly in isolates with LEV MIC ≤2 μg/mL
				OFL-AMK	Synergy rate 2%, partial synergy rate 54%	
				CIP-AMK	No synergy, partial synergy 55%	
		15	Time-kill	LEV-AMK	Synergy rate 46.7%	Synergy found in isolates
				OFL-AMK	Synergy rate 46.7%	with LEV MIC ≤2 μg/mL
				CIP-AMK	Synergy rate 46.7%	
Owens et al.[118] (1997)	Various, CR NR	15	Checkerboard	PTZ-TOB	Synergy rate 100%	
				T/C-TOB	Synergy rate 100%	
				CAZ-TOB	Synergy rate 73%	
				CRO-TOB	Synergy rate 47%	
Tascini et al.[119] (1998)	NR; POLYB-S, A/S-S	5	Checkerboard	RIF-POLYB	Synergy rate 60%; partial synergy rate 40%	Old polymyxin breakpoints used
				RIF-A/S	Synergy rate 40%; partial synergy rate 60%	
				POLYB-A/S	Indifferent 100%	
Hogg et al.[120] (1998)	MDR; CR-R; COL-S	13	Checkerboard	RIF-COL	Synergy rate 84.6%; additive/indifferent 15.4%	Colistin sulphate tested; initial testing with disk diffusion
Manikal et al.[121] (2000)	MDR	24	Checkerboard	RIF-POLYB	Synergy rate 50%; additive 50%	
				POLYB-AZI	Synergy rate 83.3%; additive 16.7%	
				FOS-AMK; FOS-A/S; POLYB-MER; POLYB-TMP/SMX	Additive 100%	
Appleman et al.[122] (2000)	Various	4	Checkerboard	A/S-RIF	Synergy rate 25%	Bactericidal/bacteriostatic effects were predetermined by time-kill assays
				A/S-AZI	Synergy rate 25%	
				A/S-TVX	No synergy	
				A/S-DOX	No synergy	
Rodriguez-Hernandez et al.[123] (2000)	CR-S	1	Time-kill	IPM-AMK	No synergy (24 h)	Combination therapy not superior in an experimental model.
				DOX-AMK	Synergy rate 100% (24 h)	
Giamarellos-Bourboulis et al.[124] (2001)	MDR	39	Interactive time-kill	COL (1× MIC) -RIF	Synergy rate 15.4% (6 h); 51.3% (24 h)	10% CR-R; 15.2% RIF-S; 100% COL-S
				COL (4× MIC) -RIF	Synergy rate 15.4% (6 h); 66.7% (24 h)	
Fernandez-Cuenca et al.[125] (2002)	MDR	5	Checkerboard	AZI-IPM	No synergy	
				AZI-CAZ	Synergy rate 20%; partial synergy rate 20%	
				AZI-CIP	No synergy	

Continued next page

Table I. Contd

Reference (year)	Resistance pattern	No. of isolates	Methods	Combinations tested	Results	Comments
				AZI-AMK	No synergy	
Jung et al.[126] (2004)	NR	7	Time-kill	MOX-FEP	Synergy rate 100% (24 h)	Synergy rate lower at 8 h; both combinations tested at 0.5× and 1× MIC, yielding slightly different results
				MOX-PTZ	Synergy rate 100% (24 h)	
Drago et al.[127] (2004)	Non-MDR	10	Checkerboard	10 regimens, including CIP/LEV and IPM/CAZ/AMK/FEP/PTZ	Synergy in 27% of experiments	
		2	Time-kill		Synergy in 35% of experiments	
Yoon et al.[128] (2004)	PR; CR-R	8	Checkerboard (3D) and time-kill.	POLYB-IPM	Bactericidal rate 87.5% (24 h); synergy at various dilutions	Time-kill assays utilized 0.25× MIC of each agent
				POLYB-RIF	Bactericidal rate 87.5% (24 h); synergy at various dilutions	
				POLY-B-IPM-RIF	Bactericidal rate 100% (24 h); synergy at various dilutions	
Ko et al.[129] (2004)	MDR	1	Time-kill	A/S-MER	Synergy observed in 1 × MIC (48 h)	In an experimental model, combination therapy resulted in improved outcome
Montero et al.[130] (2004)	MDR; low level CR-R	1	Time-kill	20 regimens containing IPM, A/S, TOB, RIF	Synergy with IPM-A/S, IPM-TOB, IPM-RIF and A/S-TOB	In an experimental model, combination therapy resulted in improved response
	MDR; high level CR-R	1		28 regimens containing IPM, A/S, TOB, RIF, COL	Synergy with RIF-IPM, RIF-TOB, RIF-A/S and A/S-TOB	
Kiffer et al.[131] (2005)	MDR	48	Checkerboard	A/S-MER	Synergy rate 29.2%; partial synergy rate 47.9%; additive 10.5%; indifferent 6.2%; antagonism 6.2%	
Sader and Jones[132] (2005)	MDR	34	Checkerboard	A/S-FEP	Synergy rate 26.5%; partial synergy rate 61.8%; additive 11.8%; no antagonism	Full/partial synergy rate among CR-R isolates 84.2%
Bernabeu-Wittel et al.[133] (2005)	MDR; IPM-S	1	Checkerboard	IPM-AMK	Synergy rate 100%	Synergy not observed in an experimental model
	MDR; IPM-R	1		IPM-AMK	Indifferent	
Haddad et al.[134] (2005)	Mostly CR-R	10	E-test	IMP-COL	Synergy rate 40%	
				IMP-AMK	Synergy rate 30%	

Continued next page

Table I. Contd

Reference (year)	Resistance pattern	No. of isolates	Methods	Combinations tested	Results	Comments
Tong et al.[135] (2006)	CR-R	24	Checkerboard	FEP-A/S	Synergy 33.3%; partial synergy 58.3%; additive 4.2%; indifferent 4.2%	
Wareham and Bean[136] (2006)	CR-R (OXA-23); COL-S	5	E-test (double strip) and	POLYB-IPM	Borderline synergy in 1/5 of isolates	
			combined E-test-	POLYB-RIF	No synergy	
			agar-dilution	POLYB-AZI	No synergy	
Timurkaynak et al.[137] (2006)	MDR	5	Checkerboard	COL-RIF	Synergy rate 80%; partial synergy rate: 20%	
				COL-MER	Synergy rate: 60%; partial synergy rate: 20%	
				COL-DOX	Synergy rate: 0%; partial synergy rate 80%	
				COL-AZI	Synergy rate 60%; partial synergy rate 0%	
Biancofiore et al.[138] (2007)	MDR; COL-S	1	Checkerboard	COL-RIF	Synergy rate 100%	This triple-drug regimen
				MER-RIF	Synergy rate 100%	resulted in clinical cure
				COL-MER	Additivity	

AMK = amikacin; **A/S** = ampicillin/sulbactam; **AZI** = azithromycin; **CAZ** = ceftazidime; **CIP** = ciprofloxacin; **COL** = colistin; **CR** = carbapenem; **CRO** = ceftriaxone; **DOX** = doxycycline; **FEP** = cefepime; **FOS** = fosfomycin; **IPM** = imipenem; **LEV** = levofloxacin; **MDR** = multidrug-resistant; **MER** = meropenem; **MIC** = minimum inhibitory concentration; **MOX** = moxifloxacin; **NR** = not reported; **OFL** = ofloxacin; **PTZ** = piperacillin/tazobactam; **POLYB** = polymyxin B; **R** = resistant; **RIF** = rifampicin; **S** = susceptible; **T/C** = ticarcillin/clavulanic acid; **TOB** = tobramycin; **TMP/SMX** = trimethoprim/sulfamethoxazole; **TVX** = trovafloxacin.

interventions are either open or percutaneous drainage of fluid collections or frank abscesses, although definitive surgical procedures may be needed for resolution of underlying pathologies. There are no data on the surgical management of *Acinetobacter* infection specifically, and clinicians should obtain a surgical consultation in the appropriate circumstances, based on sound clinical judgment.

6.2 Novel Anti-Infective Agents

While *Acinetobacter* spp. appear to have exhausted the current antimicrobial armamentarium, development of novel antibacterial compounds still holds some promise. Antimicrobial peptides have gained much interest in recent years, although only a few have been experimented upon *in vivo*. Several anecdotal reports have demonstrated enhanced *in vitro* activity of synthetic peptides against *Acinetobacter*. For example, rBPI21 (recombinant N-terminal domain of human bactericidal/permeability protein) and cecropin P1 (a porcine antibacterial peptide) have shown significant *in vitro* efficacy against polymyxin-resistant strains.[144] In addition, a cecropin A-melitin hybrid peptide has also demonstrated good *in vitro* efficacy against polymyxin-susceptible *Acinetobacter* spp. and even pharmacodynamic advantages over polymyxin B.[145] Later data using several derivatives of this antimicrobial peptide have yielded promising *in vitro* results against colistin-resistant strains,[146] but clinical experience with these compounds is limited.

Other novel antibacterial compounds relevant to *Acinetobacter* spp. may be inhibitors of fatty acid biosynthesis enzymes (Fab I and Fab K) or even bacteriophages.[147] These agents have not yet reached the industrial antimicrobial pipeline.

6.3 Prevention

Prevention of nosocomial infection with MDR *Acinetobacter* spp. is, of course, no less important than adequate treatment of established infection with the micro-organism. Preventive modalities may include judicious antimicrobial use, meticulous infection control with emphasis on hand hygiene

Table II. Summary of selected *in vivo* experimental data regarding the effect of antimicrobial combinations against *Acinetobacter* spp. respiratory infection

Reference (year)	Resistance pattern	No. of isolates	Model type	Combinations tested	Comparators	Results	Comments
Wolff et al.[140] (1999)	MDR	1	Mouse pneumonia	IPM-RIF; IPM-A/S; A/S-RIF; TIC-A/S; T/C-A/S	IPM; A/S; TIC; T/C; RIF	Best survival rate with RIF-containing combinations (A/S-RIF better than IPM-RIF)	No direct comparison of mono- and dual
	Cephalosporinase-producer	1				Best survival rate with T/C-A/S	therapy
Rodriguez-Hernandez et al.[123] (2000)	CR-S	1	Mouse pneumonia	IPM-AMK	IPM; AMK; DOX	Survival rate, lung and blood sterility rate and lung bacterial counts similar to that of IPM alone	DOX-AMK showed *in vitro* synergy but IPM-AMK did
				DOX-AMK		Survival rate, blood sterility rate and lung bacterial counts similar to that of IPM alone. Lung sterility rate higher than with AMK alone	not
Joly-Guillou et al.[141] (2000)	LEV-S	1	Mouse pneumonia	LEV-IPM; LEV-AMK	LEV alone	Similar bactericidal activity and mortality	
	LEV-R	1					
Ko et al.[129] (2004)	MDR	1	Mouse pneumonia	A/S-MER	A/S; MER	Survival rate 87% with A/S-MER, 34.8% with MER and 30.4% with A/S	A/S-MER also showed *in vitro* synergy
Montero et al.[130] (2004)	MDR; low level CR-R	1	Mouse pneumonia	IPM-A/S; IPM-TOB; IPM-RIF; A/S-TOB; A/S-RIF; RIF-TOB; RIF-COL	IPM; A/S; TOB; RIF; COL	Best reduction of lung bacterial count with IPM-TOB	Combinations also shown to be synergic *in vitro*
	MDR; high level CR-R	1				Best reduction of lung bacterial count with IPM-RIF and RIF-TOB	
Bernabeu-Wittel et al.[133] (2005)	MDR; IPM-S	1	Guinea-pig pneumonia	IPM-AMK	IPM; AMK	IPM-AMK inferior to IPM in reduction of lung bacterial count	*In vitro* synergy observed
	MDR; IPM-R	1		IPM-AMK	IPM; AMK	IPM-AMK inferior to AMK in reduction of lung bacterial count	No *in vitro* synergy

AMK = amikacin; **A/S** = ampicillin/sulbactam; **COL** = colistin; **CR** = carbapenem; **DOX** = doxycycline; **IPM** = imipenem; **LEV** = levofloxacin; **MDR** = multidrug-resistant; **MER** = meropenem; **R** = resistant; **RIF** = rifampicin; **S** = susceptible; **T/C** = ticarcillin/clavulanic acid; **TIC** = ticarcillin; **TOB** = tobramycin.

and environmental cleansing, prevention of VAP, surgical site infection and catheter-related bloodstream infection via adequate clinical practices, antimicrobial prophylaxis, and skin or mucosal decontamination. The issue of prevention is beyond the scope of this review. However, there is a vast amount of literature on this subject, including guidelines issued by the Centers for Disease Control and Prevention, Infectious Disease Society of America, and other internationally known organisations. Most publications do not address *Acinetobacter* spp. specifically, but the guidelines are applicable to this organism.

7. Management of Specific Syndromes

7.1 Nosocomial Meningitis

Acinetobacter spp. are increasingly implicated in nosocomial meningitis, especially PSM. A decade ago, strains causing PSM were uniformly carbapenem susceptible[148] or showed very low carbapenem resistance rates,[149] and drugs, such as high-dose meropenem, have become the standard of care in empirical and definitive therapy of PSM. However, the rates of resistance have been on the increase. *Acinetobacter* spp. accounted for 29 of 35 PSM cases in one hospital during an 8-year period and nearly one-half of the isolates were carbapenem resistant.[150] Although most cases are sporadic, outbreaks of PSM have also occurred.[151]

There is limited experience with sulbactam in *Acinetobacter* PSM, and published reports may suffer from a publication bias (i.e. positive results are frequently published, whereas negative results are not). Seven of eight patients with nosocomial meningitis reported by Jimenez-Mejias et al.[152] were infected with carbapenem-resistant strains, and sulbactam therapy (1 g every 6 hours) resulted in the cure of most of them. Another case of PSM and shunt infection was cured with sulbactam 300 mg/kg/day, although the specific route of administration was not specified.[153] Notably, carbapenem resistance had emerged in the latter case during imipenem/cilastatin therapy and the initially used lower sulbactam doses had failed.

Nosocomial MDR *Acinetobacter* meningitis has also been successfully treated with colistin. Intravenous colistin methanesulfonate (5 mg/kg/day) resulted in cure in one case when cerebrospinal fluid colistin concentrations were roughly 25% of serum concentrations.[154] A recent literature review of 14 patients with MDR *Acinetobacter* meningitis treated with intravenous, intrathecal, intraventricular or intravenous plus intrathecal colistin has documented a 93% cure rate.[155] Colistin may be given via the intrathecal or intraventricular routes in doses of 125 000–500 000 IU/day.

Reports of colistin therapy for *Acinetobacter* PSM are summarized in table III. Caution should be exercised in the interpretation of these data, in addition to all the limitations mentioned earlier, given the variability of published cases (regarding host and therapeutic factors) as well as lack of relevant information in some of them. Host risk factors differed between cases given a wide range of patient age (paediatric patients vs adults), the events preceding the onset of PSM (recurrent craniotomies, especially in patients with malignancy vs a single procedure, usually with trauma), and type of infection (meningitis vs ventriculitis, presence of prosthetic material, presence of bacteraemia, and mono- vs poly-microbial infection). Differences in therapeutic factors included different dose administration schedules of colistin and different routes (intravenous, intrathecal, intraventricular), number of antimicrobials given (monotherapy vs dual therapy) and their routes, surgery (retention vs removal of prosthetic material, drug vs surgical therapy) and length of therapy. Moreover, specific outcome data were not always present (microbiological vs clinical cure, functional neurological outcome) and the volume of distribution of colistin was not always estimated if given intraventricularly (volume of distribution changes as a result of the volume drained by external ventricular drainage, if present). Lastly, a publication bias might have occurred with colistin as well. Therefore, on the basis of available data, we suggest that colistin is a viable option for the treatment of PSM, but an evidence-based recommendation regarding the dose, route, addition of other

Table III. Colistin (COL)-based therapy of multidrug-resistant (MDR) *Acinetobacter* spp. nosocomial meningitis

Reference (year)	Resistance pattern	No. of cases	Diagnosis	Agents used	Route	Outcome	Comments
Fernandez-Viladrich et al.[156] (1999)	CR-R, COL-S	2	PSM, EVD infection	COL 5 mg q12h	IVR	Cure	Failure of IVR TOB
				TOB 5 mg/kg/day	IV		
			EVD infection	COL 5–10 mg q12h	IVR	Cure	Failure of IVR COL 5 mg
				TOB 5 mg/kg/day	IV		
Vasen et al.[157] (2000)	CR-R, COL-S	1	PSM, EVD infection	COL 5–10 mg/day	IT	Cure	Bactericidal titre of CSF 1 : 8
Jimenez-Mejias et al.[152] (1997)	CR-R; COL-S	1	PSM, VPSI	COL 5 mg/day	IV	Cure	Bactericidal titre measured in CSF
Benifla et al.[158] (2004)	COL-S; A/S-S	1	Infected dural patch and shunt, CSF leak	COL 40 000 IU/day	IT	Cure	Polymicrobial infection
Fulnecky et al.[159] (2005)	CR-R	1	PSM	AMK 600 mg q12h	IV	Cure	
				AMK 10 mg/day	IT		
				COL 1.25 mg/kg q12h	IV		
Bukhary et al[160] (2005)	MDR	1	PSM	COL 125 000 IU q12h	IVR	Cure	Concomitant bacteraemia; failure of IV IPM/CIP/COL
Sueke et al.[161] (2005)	MDR; COL-S	1	VPSI	COL 75 000 IU q12h	IT	Cure	Higher COL dose resulted in seizures
				COL[a]	IV		
Kasiakou et al.[162] (2005)	MDR; COL-S	2	Recurrent PSM	COL 1 000 000 IU q8h	IV	Cure	Recurrent PSM in a single patient; IVR therapy
				COL 20 000–40 000 IU q24h	IVR		commenced after IV therapy failed; duration of therapy 3–6 weeks
				AMK 500 mg q12 h	IV		
				AMK 5–10 mg q24h	IVR		
				TPL 400 mg q24h	IV		
				TPL 10 mg q24h	IVR		
Ng et al.[163] (2006)	MDR	5	Recurrent EVD infection	COL 10 mg/day	IVR	Cure	
				AMK[a]	IV		
			EVD infection	COL 10 mg/day	IVR	Cure (poor functional status)	Failure of IV COL alone
				AMK[a]	IV		
				COL 150 mg q12h	IV		
			EVD infection	COL 10 mg/day	IVR	Cure	Chemical meningitis
				AMK[a]	IV		
				COL[a]	IV		
			EVD infection	COL 10 mg/day	IT	Cure	Chemical meningitis
				AMK[a]	IV		
				COL[a]	IV		
			PSM	COL 1–4 mg/day	IT	Cure (poor	Chemical meningitis at

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Table III. Contd

Reference (year)	Resistance pattern	No. of cases	Diagnosis	Agents used	Route	Outcome	Comments
				AMK[a]	IV	functional status)	4 mg/day; paediatric case
				COL 2.5 mg/kg q12h	IV		
Motaouakkil et al.[164] (2006)	MDR; COL-S	1	PSM	COL 10 mg/day	IT	Cure	COL dose 5 mg on day 1
				RIF 10 mg/kg q12h	IV		
Karakitsos et al.[165] (2006)	MDR; COL-S	6	VPSI	COL 10–20 mg/day	IVR	Cure	

a Dosage not reported.

AMK = amikacin; **A/S** = ampicillin/sulbactam; **CIP** = ciprofloxacin; **COL** = colistin; **CR** = carbapenem; **CSF** = cerebrospinal fluid; **EVD** = external ventricular drainage; **IT** = intrathecal; **IV** = intravenous; **IVR** = intraventricular; **PSM** = postsurgical meningitis; **q*x*h** = every *x* hours; **R** = resistant; **RIF** = rifampicin; **S** = susceptible; **TOB** = tobramycin; **TPL** = teicoplanin; **VPSI** = ventriculo-peritoneal shunt infection.

drugs, surgical therapy and treatment duration cannot be made at the moment.

7.2 Hospital-Acquired/Ventilator-Associated Pneumonia

Acinetobacter spp. are a major cause of VAP and are associated with mortality rates of up to 50–70%.[166] The impact of *Acinetobacter* VAP on patient outcome is far from clear.[25] Current data suggest that the most prominent risk factor for *Acinetobacter* VAP is previous antimicrobial use, and that the outcome of this condition is similar to VAP caused by other Gram-negative bacteria if it is adequately treated.[21]

The treatment of *Acinetobacter* VAP has been influenced by experimental data (table II). In an animal model of pneumonia, imipenem combined with amikacin was inferior to imipenem alone when tested against carbapenem-susceptible strains or to amikacin alone when tested against carbapenem-resistant strains, despite an earlier demonstration of *in vitro* synergy.[133] Combining imipenem and aminoglycosides in another animal model yielded positive results.[130]

Another mouse pneumonia model evaluated the role of sulbactam in combination with one or two other agents.[140] Best survival rates were achieved with a ticarcillin/clavulanic acid plus sulbactam regimen in the presence of a cephalosporinase-producing strain and sulbactam plus rifampin against MDR strains. Colistin monotherapy has also been evaluated experimentally and was found to be inferior to imipenem or sulbactam, even with isolates non-susceptible to the latter.[167]

Sulbactam treatment of VAP caused by carbapenem-resistant strains in 14 patients resulted in outcomes similar to those of 63 comparable patients treated with carbapenems for VAP caused by carbapenem-susceptible strains.[168] Sulbactam may also be administered to mechanically ventilated patients via aerosol. One small randomized controlled study employed aerosolized sulbactam (3 g every 8 hours) in combination with intravenous sulbactam (3 g every 8 hours) and found a significant decrease in *Acinetobacter* colony counts in bronchial secretions compared with intravenous therapy alone.[169] However, the clinical importance of this observation is not clear.

Colistin treatment of VAP caused by carbapenem-resistant strains resulted in similar efficacy to imipenem/cilastatin therapy of susceptible strains.[170] Both treatment groups had cure rates of 57%, inhospital mortality rates of 62–64%, and VAP-related mortality of 36–38%. Another study analysed a heterogeneous group consisting of patients infected with both *Acinetobacter* spp. and *P. aeruginosa*, most of whom had VAP; the clinical cure and mortality rates were similar for patients treated with colistin as well as other drugs (mainly carbapenems).[171] Similar findings have been reported by others,[87] although lower cure rates have also been reported.[172]

Colistin and rifampin demonstrated both *in vitro* and *in vivo* synergy against *Acinetobacter* spp. in

experimental models such as the neutropenic rat thigh infection model.[173] This combination was subsequently investigated in the treatment of 14 patients with VAP caused by carbapenem-resistant strains; intravenous colistin (2 000 000 IU every 8 hours) and rifampin (600 mg/day) were administered to them all, and sulbactam was administered to five infected by sulbactam-susceptible strains. Despite a high mortality rate (due to various causes), the combined regimen resulted in microbiological clearance of infection in nine patients.[174] In another study, 26 patients infected with MDR strains susceptible only to colistin (19 of whom had VAP) were treated with a colistin plus rifampin combination, and all had a favourable outcome.[164] Notably, non-bacteraemic VAP was treated with aerosolized colistin (1 000 000 IU every 8 hours) and intravenous rifampin (10 mg/kg every 12 hours), while nine bacteraemic patients (including three with VAP) received intravenous colistin (2 000 000 IU every 8 hours) plus rifampin.

Colistin may also be administered by inhalation. The dose of aerosolized colistin may range between 500 000 IU every 12 hours and 2 000 000 IU every 8 hours. Treatment of VAP with nebulized colistin for 14 days was recently reported in a small case series, with a notable response rate.[175] Intravenous colistin was not coadministered, although other parenteral agents were given, but isolates were resistant to them. In another series, seven patients with *Acinetobacter* pulmonary infection (mostly VAP) were treated with aerosolized colistin and concomitant intravenous therapy with colistin and/or other antimicrobials, resulting in cure among six patients.[176]

Although most reports have focused on colistin, recent data on polymyxin B has been accumulating. In a case series involving 16 patients with *Acinetobacter* nosocomial pneumonia, most were critically ill and being treated in the intensive care unit. Isolates were carbapenem resistant in 13 patients and resistant to all drugs except polymyxin B in seven patients. Polymyxin susceptibility was reported to be 100% but only disk diffusion was utilized for determining susceptibility. Patients were treated with intravenous polymyxin B and/or aerosolized polymyxin B. Since this study also analysed cases of *P. aeruginosa* infection, the efficacy of polymyxin B for *Acinetobacter* alone is difficult to extract, but it appears that about two-thirds of cases clinically improved with polymyxin B therapy.[177]

There are only few data on tetracycline therapy for *Acinetobacter* VAP. In one case series of VAP caused by carbapenem-nonsusceptible strains, therapy with minocycline or doxycycline was successful in six of seven cases.[178] Of note, most patients received additional drugs to which clinical isolates were resistant, but *in vivo* synergy was not evaluated, making the net effect of tetracycline difficult to estimate.

8. Future Prospects

The incidence of infections caused by MDR *Acinetobacter* spp. is expected to continue rising, leading to the spread of MDR and PR strains to virtually all large hospitals worldwide, causing millions of infections. Moreover, MDR and PR strains will be increasingly encountered, rendering drug treatment even more difficult. Tigecycline has been recently introduced and may be an important addition to the existing armamentarium against these resistant strains. Nevertheless, no additional new class of antimicrobials with activity against MDR *Acinetobacter* spp. is expected to become available in the near future.

Thus, it is of utmost importance that new antimicrobial agents are developed. It is also essential to explore less traditional options, such as virulence-attenuating agents, agents that influence the transmissibility of the micro-organisms, phage therapy and immune therapy. These efforts will require investment from pharmaceutical consortia, biotechnology companies and the academia. To make this possible, national and international agencies should increase the funds dedicated to research and provide the economical incentives to the development of new classes of antimicrobials.

Until new agents are available, we need to optimize the use of existing ones, for example by tailoring the use of combination therapy based on more

accurate combination testing methods and examination of clinical correlates. Better understanding is required of the activity of available agents, given the existing pharmacokinetic/pharmacodynamic data and the implicated mechanisms of resistance. Clinical studies for examining the effects of 'old' agents, new delivery methods, and various routes of administration are warranted.

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