**Combined therapy for multi-drug-resistant *Acinetobacter baumannii* infection – is there evidence outside the laboratory?**

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*Acinetobacter* are among the most common bacteria isolated in hospital infections, especially in developing countries. Multi-drug, extended-drug or pan-drug resistance makes treatment a real medical challenge. In the present review, the authors describe clinical and experimental data in order to present different current and potential future strategies to treat infections caused by multi-drug-resistant *Acinetobacter*. The therapeutic options for carbapenem-resistant *Acinetobacter* are scarce, and the current options have poor pharmacokinetic aspects and severe side effects. Combined therapy has been an alternative for multi-drug-resistant *Acinetobacter*. However, this issue is always controversial. In some studies combined therapy has shown superiority for some strains of *Acinetobacter* in animal models and in vitro studies. However, studies with humans are scarce and too poor quality to suggest the best approach for the treatment of infections caused by multi-drug-resistant *Acinetobacter baumannii*.

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**Introduction**

The genus *Acinetobacter* is commonly associated with hospital-acquired infections or healthcare-associated infections (HAI), mainly in developing countries (Baumgart et al., 2010; Cieslinski et al., 2013). The *Acinetobacter* genomic species emerged as a major problem in the 1990s, and it has even become the micro-organism most frequently associated with pneumonia, catheter infections and meningitis in some public and private hospitals (Toledo et al., 2012). The emergence of *Acinetobacter* has been attributed to not only bacterial characteristics such as survival for long periods on surfaces and medical equipment but also its association with person-to-person transmission (Pilonetto et al., 2004; Raka et al., 2009; Medell et al., 2012).

In the 1980s, imipenem (previously called N-formimidoylthienamycin) was a promising drug for the treatment of hospital infection (Cullmann et al., 1982; Chang et al., 1995). In an article published by Giamarello et al., the last phrase was: 'imipenem provides the possibility of treating successfully multi-resistant and polymicrobial infections with a single antimicrobial' (Giamarello et al., 1986). However, in the same year cases of imipenem-resistant *Acinetobacter* were reported (Joly-Guillou et al., 1990) and outbreaks in North America and Europe were described some years later (Urban et al., 1993; Wood & Reboli, 1993; Go et al., 1994; Tankovic et al., 1994).

Emergence of resistance in *Acinetobacter* genomic species is a major problem, which makes *Acinetobacter* spp. difficult to treat. Carbapenem were the first treatment option for HAI caused by *Acinetobacter* (Sader et al., 1999, 2000, 2001) but susceptibility rates decreased year after year (Rossi et al., 2008; Sengstock et al., 2010). Such increment in carbapenem resistance may have been associated with abusive prescription of these drugs (Romanelli et al., 2009). Improvement in *Acinetobacter* susceptibility to carbapenems has been attributed to stewardship programmes, but with weak strength of evidence (Lima et al., 2011).

Carbapenem were replaced by polymyxins as the first choice in the therapeutic arsenal against *Acinetobacter*, despite possible severe side effects: mainly acute renal failure and neurological disorders. Furthermore, polymyxins have a poor pharmacokinetic profile regardless of the infection site (Zavascki et al., 2008). This pharmacokinetic
profile could be the cause of current polymyxin resistance in several hospitals (Choi et al., 2014).

Global mortality associated with Acinetobacter baumannii infections is higher than 50% in some series, which may be attributed to inadequate therapy (Tuon et al., 2010b, 2011).

Combined therapy for multi-drug-resistant (MDR) Acinetobacter baumannii was hypothesized as beneficial despite the lack of evidence (Metan et al., 2007). MDR Acinetobacter has been classified as multi-drug resistant, extensively drug resistant (XDR) and pan-drug resistant (PDR). For more details about this classification, a review has recently been published (Magiorakos et al., 2012).

**Monotherapy for Acinetobacter**

Therapeutic options against carbapenem-resistant Acinetobacter (CRAB) are restricted. In Brazil, CRAB is generally associated with carbapenemase production (OXA-23), which is reported in other countries (Dalla-Costa et al., 2003; Corrêa et al., 2012). Ampicillin/sulbactam may be a safe option, even for severe Acinetobacter infections (Levin et al., 2003; Oliveira et al., 2008; Chu et al., 2013). Amoxicillin/sulbactam may be another option because sulbactam is the main active molecule with antimicrobial properties against Acinetobacter (Kitzis et al., 1983).

Carbapenem resistance may also be intrinsic, due to weak production of carbapenemase, which is not usually a problem because Acinetobacter is quickly saturated with carbapenems. However, such an intrinsic resistance mechanism may be a problem in severe patients, considering that imipenem or meropenem would not achieve therapeutic concentrations with the usual dosage (Villegas et al., 2011). Furthermore, surveillance studies have shown a high prevalence of reduced susceptibility for carbapenems, with resistance percentages between 40 and 60% (Cereda et al., 2011; Gales et al., 2011). These epidemiological studies motivated some medical centres to institute polymyxins as one of the empirical drugs of choice in the treatment of HAI (Mukhopadhyay et al., 2008). Tigecycline emerged as an alternative drug for CRAB infections. This broad-spectrum antibiotic has a pharmacokinetic profile that is not favourable for severe bloodstream infections (Curcio et al., 2008). Serum levels of tigecycline are low because of the large distribution volume. This property allows the prescription of tigecycline for surgical site infections but not for bloodstream infection. Other drugs have been used as off-label single drug alternatives, including doxycycline, aminoglycosides and rarely piperacillin/tazobactam or cefepime.

Current studies support monotherapy with sulbactam, carbapenems (meropenem or imipenem) or polymyxins in the treatment of severe infections caused by A. baumannii (Levin et al., 1999, 2003; Oliveira et al., 2008). However, there are many doubts about monotherapy in other severe infections, such as meningitis and even recurrent pneumonia (Tuon et al., 2010a, b).

**Combined therapy for Acinetobacter**

Combined therapy with two or more drugs for Acinetobacter infection has always been a controversial topic. Most recently, such controversy re-emerged after the epidemic spread of carbapenem-resistant Enterobacteriaceae (CRE). There are several studies evaluating combined therapy against Acinetobacter, including in vitro and in vivo models, as well as case series.

**In vitro**

In vitro studies are used to evaluate drug combinations, which classify the combination as synergism, additive effect or even antagonism among the antibiotics evaluated. Time–kill curve is the most commonly used in vitro study method. In summary, for each antibiotic and its combinations, time–kill studies are performed using 4 × MIC, 2 × MIC, 1 × MIC, 0.5 × MIC and 0.25 × MIC concentrations. Tenfold dilutions are inoculated onto Mueller–Hinton agar and colony counts are determined at 0, 4, 8 and 24 h. Bactericidal activity is defined as a ≥ 3 log10 decrease compared with the initial inoculum. Synergy is defined as ≥ 2 log10 decrease by the combination compared with the most active single agent.

Several publications using this method are listed in Table 1. Santimaleeworagun et al. (2011) evaluated combination of fosfomycin, colistin, sulbactam and meropenem. In this study, no important synergism was found against XDR Acinetobacter isolates.

Even in PDR Acinetobacter, synergism may be hard to demonstrate in a few clinical samples (< 10%) (Arroyo et al., 2009; Principe et al., 2009). It is important to remember that antagonism may also occur with tigecycline and piperacillin/tazobactam in combination (Principe et al., 2009).

Polymyxins are considered bactericidal drugs due to their activity in cell membrane. However, these drugs seem to be only bacteriostatic when used alone against XDR Acinetobacter samples. Polymyxins combined with tigecycline, rifampicin or meropenem may be bactericidal in XDR Acinetobacter strains (Wareham & Bean, 2006; Lim et al., 2011). The combination of rifampicin with colistin has been advocated by some authors after consistent in vitro demonstrations (Timurkaynak et al., 2006; Pantopoulou et al., 2007). The synergism of rifampicin with colistin seems to be evident, although it may only occur late (> 36 h) in animal models (Hogg et al., 1998; Song et al., 2009). Such synergism occurs not only with polymyxins but also with sulbactam (Tascini et al., 1998; Wolff et al., 1999), which may be an alternative treatment for Acinetobacter infections (Levin et al., 2003; Curcio et al., 2008).

Other synergisms with divergent results were colistin with azithromycin, cefepime, aztreonam or imipenem...
<table>
<thead>
<tr>
<th>Reference</th>
<th>Model</th>
<th>Strain</th>
<th>Drugs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hornsey &amp; Warham (2011), Hornsey</td>
<td>TKC</td>
<td>XDR</td>
<td>Colistin and vancomycin/teicoplanin/teflavancin</td>
<td></td>
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<tr>
<td>et al. (2011)</td>
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<tr>
<td>Yilmaz (2012)</td>
<td>TKC</td>
<td>XDR</td>
<td>Colistin and tigecycline</td>
<td></td>
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<tr>
<td>Santimaleeworagun et al. (2011)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin B, tigecycline, fosfomycin and sulbactam</td>
<td></td>
</tr>
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<td>Hornsey et al. (2012, 2013)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin, meropenem, rifampin, tigecycline</td>
<td>Synergism</td>
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<td>Yilmaz (2012)</td>
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<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin</td>
<td></td>
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<td>Santimaleeworagun et al. (2011)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and sulbactam and aztreonam</td>
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<td>Lim et al. (2011)</td>
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<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
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<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
<td></td>
</tr>
<tr>
<td>Alp et al. (2006); Arroyo et al.</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
<td></td>
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<tr>
<td>(2009)</td>
<td></td>
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<tr>
<td>Pumplou et al. (2006)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
<td></td>
</tr>
<tr>
<td>Kiler et al. (2005)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
<td></td>
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<tr>
<td>Song et al. (2009)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
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<tr>
<td>Pantopoulou et al. (2007)</td>
<td>TKC</td>
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<td>Timmerman et al. (2007)</td>
<td>TKC</td>
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<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
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<tr>
<td>Sabl &amp; Jones (2005)</td>
<td>TKC</td>
<td>XDR</td>
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<td>Brubaker-Wilhelm et al. (2005)</td>
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<td>Erigo et al. (2005)</td>
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<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
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<td>Savov (2002)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
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<td>Joly-Guillou et al. (2000)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
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<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
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<td>Wolff et al. (1999)</td>
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<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
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<tr>
<td>Tascini et al. (1998)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
<td></td>
</tr>
<tr>
<td>Martinez-Martinez et al. (1996)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
<td></td>
</tr>
<tr>
<td>Chang et al. (1995)</td>
<td>TKC</td>
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<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
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<tr>
<td>Dinn et al. (1995)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
<td></td>
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<tr>
<td>Tor (2015)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
<td></td>
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<tr>
<td>Yadav et al. (2015)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
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<td>Tascini et al. (1998)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
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<tr>
<td>Martinez-Martinez et al. (1996)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
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<td>Chang et al. (1995)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
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<td>Dinn et al. (1995)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
<td></td>
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<tr>
<td>Tor (2015)</td>
<td>TKC</td>
<td>XDR</td>
<td>Polymyxin and azithromycin, imipenem, rifampin, meropenem</td>
<td></td>
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</tbody>
</table>

TKC, time-kill curve; MCBT, multiple-combination bactericidal antibiotic testing.
Table 2. Outcomes in previous studies involving combined therapy in the treatment of MDR *A. baumannii* in different topographies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Bacteria</th>
<th>Site</th>
<th>Study design</th>
<th>Study drugs</th>
<th>N</th>
<th>Overall mortality</th>
<th>%</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levin et al. (1999)</td>
<td><em>Acinetobacter/ Pseudomonas</em></td>
<td>Mixed</td>
<td>R</td>
<td>Colistin</td>
<td>60</td>
<td>25</td>
<td>42</td>
<td></td>
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<tr>
<td>Levin et al. (1999)</td>
<td><em>Acinetobacter</em></td>
<td>VAP/HAP</td>
<td>R</td>
<td>Combined polymixin/other antibiotics</td>
<td>20</td>
<td>15</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Levin et al. (1999)</td>
<td><em>Acinetobacter</em></td>
<td>VAP/HAP</td>
<td>R</td>
<td>Combined polymixin/other antibiotics</td>
<td>29</td>
<td>6</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Motaouakkil et al. (2006b)</td>
<td>MDR <em>Acinetobacter</em></td>
<td>VAP</td>
<td>R</td>
<td>Colistin + rifampicin</td>
<td>14</td>
<td>7</td>
<td>50</td>
<td>Clinical/microbiological cure in 7 patients</td>
</tr>
<tr>
<td>Bassetti (2008)</td>
<td>MDR <em>Acinetobacter</em></td>
<td>BSI (10), VAP 17, mixed (2)</td>
<td>R</td>
<td>Colistin + rifampicin</td>
<td>29</td>
<td>9</td>
<td>31</td>
<td>Clinical/microbiological cure in 27 patients</td>
</tr>
<tr>
<td>Song et al. (2009)</td>
<td>MDR <em>Acinetobacter</em></td>
<td>VAP</td>
<td>R</td>
<td>Colistin + rifampicin</td>
<td>10</td>
<td>3</td>
<td>30</td>
<td>Clinical/microbiological cure in 7 patients</td>
</tr>
<tr>
<td>Guber (2011)</td>
<td>MDR <em>Acinetobacter</em></td>
<td>Mixed in ICU</td>
<td>R</td>
<td>Tigecycline + aminoglycoside or cefoperazone</td>
<td>33</td>
<td>10</td>
<td>30</td>
<td>Clinical/microbiological cure in 21 patients</td>
</tr>
<tr>
<td>Simsek (2012)</td>
<td>MDR <em>Acinetobacter</em></td>
<td>Mixed in ICU</td>
<td>R</td>
<td>Colistin vs combined therapy</td>
<td>51</td>
<td>20</td>
<td>39</td>
<td>Clinical cure in 22 patients, and microbiological in 34</td>
</tr>
<tr>
<td>Lee et al. (2013)</td>
<td>MDR <em>Acinetobacter</em></td>
<td>Mixed</td>
<td>R</td>
<td>Tigecycline vs other than colistin</td>
<td>386</td>
<td>211</td>
<td>55</td>
<td>Combined therapy was not superior to tigecycline alone</td>
</tr>
<tr>
<td>Lee et al. (2013)</td>
<td>MDR <em>Acinetobacter</em></td>
<td>Mixed</td>
<td>R</td>
<td>Tigecycline alone</td>
<td>108</td>
<td>147</td>
<td>55</td>
<td>Tigecycline was superior to drugs other than colistin</td>
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<tr>
<td>Lee et al. (2013)</td>
<td>MDR <em>Acinetobacter</em></td>
<td>Mixed</td>
<td>R</td>
<td>Tigecycline associated with ceftazidime,</td>
<td>158</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ceftiraxone, piperacillin/tazobac tam,</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>carbapenem</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Other than tigecycline</td>
<td>120</td>
<td>64</td>
<td>53</td>
<td></td>
</tr>
</tbody>
</table>

VAP, ventilator-associated pneumonia; HAP, hospital-associated pneumonia; BSI, bloodstream infection; ICU, intensive care unit; P, prospective study; R, retrospective study.
Combined therapy may even prevent antibiotic resistance emergence during the treatment. Fluoroquinolones are classic antibiotics associated with induction of resistance, but when used in combination, they may prevent resistance (Drago et al., 2005), for example, the synergic combination of fluoroquinolones with beta-lactams. Colistin and polymyxin are nephrotoxic drugs, and interruption is common due to this complication (Tuon et al., 1999). A recent publication tested an in vitro model with combination of high doses of imipenem in continuous infusion and aminoglycosides, showing microbiological eradication, suggesting that this option should be considered in adverse situations (Yadav et al., 2015). A meta-analysis published in 2015 summarized all these findings above, but we know the limitations of in vitro studies (Ni et al., 2015). In vivo models should be the first step before well-designed clinical studies.

In vivo models

There are several in vivo models to study combined therapy against Acinetobacter. One of the most reported models uses Galleria mellonella larvae to evaluate combined therapy (Peleg et al., 2009). The model consists of infection with Acinetobacter ATCC-19606 or other strains from patients and incubation from 3 to 5 days. The melanization of the larvae suggests sepsis and survival curves are used to evaluate the response to different therapeutic combinations. Hornsey et al. (2013) evaluated combined therapy with colistin and glycopeptide using this model in two studies. First, the combination of colistin and telavancin was evaluated in comparison with monotherapy (colistin or tigecycline). In such an experiment, A. baumannii lineage OXA-23 clone 1 was susceptible only when colistin (MIC $\leq 0.5 \mu g/ml^{-1}$) and tigecycline (MIC 0.5 $\mu g/ml^{-1}$) were used (Hornsey et al., 2013). The results showed a significant superiority of the combined therapy. This synergism was verified in other studies (Hornsey & Wareham, 2011; Hornsey et al., 2012). Although glycopeptides as monotherapy are ineffective against Acinetobacter, colistin destabilizes the external membrane, allowing the entrance of telavancin, vancomycin or teicoplanin.

Nevertheless, not all in vitro studies succeeded when in vivo models were analysed. For instance, tigecycline combined with colistin was not superior to either drug as monotherapy in a model of pneumonia in rats by Mutlu Yilmaz et al. (2012), although the drugs were synergic in the time–kill curve analysis performed before the animal study. Despite such findings, there was a most significant decrease in lung bacterial load at 48 h with the combination regimen. One may conclude that tigecycline and colistin combination may be used until there is an improvement of clinical signs, then treatment can be continued with monotherapy, considering the cost and side effects.

In another model of pneumonia, imipenem and amikacin showed antagonism, not only by pharmacodynamics, but also by pharmacokinetic pattern (Bernabeu-Wittel et al., 2005). Older studies have confirmed this antagonism (Joly-Guillou et al., 2000; Rodriguez-Hernández et al., 2000).

Clinical studies and series

Before implementation of polymyxins in routine prescription for hospital infections, several reports and series of cases were published, trying to propose a therapeutic option for CRAB, listed in Table 2. The increasing incidence of CRAB infections necessitated the introduction of novel polymyxins in the therapeutic armamentarium. Levin et al. (1999) reported 60 infections treated with colistin with a mortality rate of 75% for hospital-acquired pneumonia. Unfortunately, they included some infections caused by Pseudomonas aeruginosa (Levin et al., 1999). Considering the high mortality rate observed in the initial series, other studies evaluated polymyxins in combined therapy (Sobieszczyn et al., 2004). Colistin or polymyxin B were the most studied drugs, but some studies included other multi-resistant Gram-negative bacteria in the analysis (mainly Pseudomonas aeruginosa) (Markou et al., 2003; Ouderkirk et al., 2003; Michalopoulos et al., 2005; Heyland et al., 2008).

After the in vitro results showing the synergism of colistin with rifampicin, Petrosillo et al. evaluated 14 patients taking such a combination, but there were no possible conclusions drawn at that time because 50% of the patients died and there was no control group (Petrosillo et al., 2005). A similar study with 21 patients evaluated the same combination for ventilator associated pneumonia and bloodstream infection, with 100% microbiological and clinical cure, but overall mortality was not evaluated (Motaouakkil et al., 2006a,b).

Tigecycline is an antibiotic commonly prescribed for A. baumannii infections. However, this drug has not been recommended in the treatment of severe infections, mainly in the intensive care unit, including ventilator-associated pneumonia (Kuo et al., 2007). A large study with 386 patients showed that CRAB infections may not be treated with other drugs, but only tigecycline or polymyxins. Lee et al. (2013) found a significant benefit of tigecycline use in comparison with other drugs, as colistin. The most interesting finding of this study was the similarity of the outcome in patients treated either with combined therapy or with tigecycline alone.

Conclusion

Several in vitro studies report synergic effects between diverse drugs for the treatment of Acinetobacter. However,
these results should not be extrapolated to real life. Clinical studies are unfortunately retrospective and without control groups, which may be considered a low grade of evidence. Considering the current panorama, there is a lack of evidence favouring combined therapy for CRAB. Some authors have used combined therapy as a salvage option in severe or refractory cases. In such salvage therapy, rifampicin and/or glycopeptide are options to be combined with polymyxins.

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