

# Infections Due to *Acinetobacter baumannii* in the ICU: Treatment Options

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## Abstract

Bacteria within the genus *Acinetobacter* (principally *A. baumannii-calcoaceticus* complex [ABC]) are gram-negative coccobacilli that may cause nosocomial infections in critically ill or debilitated patients (particularly ventilator-associated pneumonia and infections of the bloodstream, urinary tract, and wounds). Treatment of *Acinetobacter* infections is difficult, as *Acinetobacter* spp. are *intrinsically* resistant to multiple antimicrobial agents, and have a remarkable ability to *acquire new resistance determinants* via mechanisms that include plasmids, transposons, integrons, and resistance islands. Since the 1990s, global resistance to antimicrobials has escalated dramatically among ABC. Global spread of multidrug-resistant (MDR)-*A. baumannii* strains reflects dissemination of a few clones between hospitals, geographic regions, and continents; excessive use of antibiotics amplifies this spread. Many isolates are resistant to all antimicrobials except colistin (polymyxin E) and tigecycline, and some infections are untreatable with existing antimicrobial agents. Antimicrobial resistance poses a serious threat to treat or prevent infections due to ABC. Strategies to curtail environmental colonization with MDR-ABC will require aggressive infection control efforts and cohorting of infected patients. Thoughtful antibiotic strategies are essential to limit the spread of MDR-ABC. Optimal therapy will likely require combination antimicrobial therapy of existing antibiotics as well as development of novel antibiotic classes.

## Keywords

- ▶ multidrug resistance
- ▶ antimicrobial resistance
- ▶ *Acinetobacter* spp.
- ▶ *Acinetobacter baumannii*
- ▶ plasmids
- ▶ clonal spread
- ▶ carbapenemases

## Microbiology

Bacteria within the genus *Acinetobacter* are encapsulated, non-lactose fermenting, oxidase-negative gram-negative coccobacilli that may cause infections in health care or community settings, particularly in patients with comorbidities or skin/soft-tissue injuries.<sup>1–3</sup> More than 20 *Acinetobacter* species have been identified,<sup>1</sup> but the vast majority of clinical infections are caused by organisms within the *A. calcoaceticus*-*A. baumannii* complex (ABC).<sup>1,4–6</sup> This complex comprises four species; *A. baumannii*, *A. nosocomialis*, and *A. pittii* cause clinical infections in humans, whereas *A. calcoaceticus* is an environmental organism of negligible clinical

significance.<sup>1</sup> *A. baumannii* is the most common species in most regions; the prevalence of *A. pittii* and *A. nosocomialis* is higher in Southeast Asia and *A. pittii* may be more common in Scandinavian countries.<sup>6–8</sup> *A. baumannii* has been associated with heightened mortality and a higher degree of antimicrobial resistance compared with other *Acinetobacter* spp.<sup>1,6,9</sup>

## Clinical Features

*Acinetobacter* species (spp.) most frequently cause nosocomial infections in critically ill or debilitated patients,<sup>10,11</sup> including ventilator-associated pneumonia (VAP),<sup>10,12–14</sup> bloodstream infections (BSI),<sup>6,11,15</sup> device-associated

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infections (DAI),<sup>16</sup> wound or skin and soft-tissue infections (SSTI),<sup>1,17</sup> burns,<sup>18,19</sup> urinary tract infections (UTI),<sup>1</sup> intra-abdominal infections (IAI),<sup>17</sup> and meningitis.<sup>1</sup> Additionally, *Acinetobacter* spp. have been implicated in SSTI sustained during disasters, including earthquakes,<sup>20</sup> tsunamis,<sup>21</sup> terrorist attacks,<sup>22</sup> and combat injuries in Vietnam,<sup>23</sup> Iraq and Afghanistan,<sup>24,25</sup> Ukraine,<sup>26</sup> Lebanon, and Syria.<sup>1,27</sup> Infections due to *Acinetobacter* spp. occur more frequently in subtropical or tropical regions; in temperate climates, infections are more common in the summer.<sup>1,24,28</sup> Community-acquired pneumonia (CAP) due to ABC rarely occurs in temperate climates, but fulminant CAP, sometimes with septic shock, has been described in Asian-Pacific regions.<sup>2,3,29–31</sup> Factors predisposing to ABC-associated CAP include alcoholism,<sup>32,33</sup> diabetes mellitus, male gender, renal or pulmonary disease, cirrhosis, advanced age, smoking.<sup>3,31</sup>

### Prognosis of Infections Due to *A. Baumannii*

Mortality rates with VAP or BSI due to *Acinetobacter* spp. are 30 to 75%; these high mortality rates in part reflect comorbidities and severity of illness.<sup>1,15,34–37</sup> In the EPIC II study, a multinational study of 14,414 ICU patients, infection with ABC was independently associated with a greater risk for hospital death (odds ratio [OR]: 1.53,  $p < 0.001$ ).<sup>38</sup> Within the past three decades, resistance rates among ABC have escalated globally.<sup>1</sup> Emergence of multidrug-resistant (MDR) strains has undoubtedly contributed to mortality. Not surprisingly, inappropriate initial empiric antibiotic therapy (IET) for pneumonia or sepsis due to ABC has been associated with heightened mortality.<sup>39–41</sup> In a recent retrospective review of 1,423 patients hospitalized with sepsis or pneumonia due to ABC, 82.3% of isolates were MDR.<sup>40</sup> MDR-ABC strongly predicted receipt of IET (OR: 5.5,  $p < 0.001$ ) and IET was associated with higher hospital mortality (OR: 1.8,  $p < 0.001$ ).<sup>40</sup> In light of the rising incidence of MDR-ABC,<sup>42</sup> a multinational consensus statement was recently published regarding the management and prevention of *A. baumannii* infections in the ICU.<sup>43</sup>

### Infections Due to ABC in the Hospital Setting

#### ICU Infections

Most ABC infections occur in hospitalized patients in the ICU, often with multiple comorbidities. Device-related infections (DRI) are typical (i.e., VAP, central venous catheter [CVC]-associated BSI, surgical site infections (SSI), catheter-associated UTIs). The EPIC II point prevalence study in 2007 comprising 75 countries implicated *Acinetobacter* spp. in 8.8% of all ICU infections, with rates of 19% in Asia and 17% in Eastern Europe.<sup>38</sup> In the SENTRY study from January 2009 to December 2011, ABCs were implicated in 7% of ICU infections in the United States and Europe.<sup>44</sup> Even higher rates of ABC infections have been reported in Latin America<sup>45,46</sup> and Asia.<sup>17,47,48</sup> In a review of Vietnamese pediatric ICUs, ABC was implicated in 18.4% of hospital-acquired infections (HAI); 65% of isolates were carbapenem

resistant (CPR).<sup>49</sup> In a prospective study from six hospitals in Iran (2011–2012), ABC was implicated in 35% of DRI among hospitalized adults.<sup>16</sup> Importantly, 70.5% were CPR.

#### Hospital-Acquired Pneumonia

ABC is a common cause of ICU-acquired pneumonia, accounting for 8 to 14% of VAP in the United States<sup>50</sup> and Europe,<sup>51</sup> but much higher rates (19% to >50%) in Asia,<sup>48,52</sup> Latin America,<sup>53</sup> and some Middle Eastern<sup>54</sup> countries. In the United States, rates of VAP due to ABC increased from 4% in 1986 to 7.0% in 2003; no increase was observed for any other gram-negative bacilli.<sup>55</sup> Data from 463 hospitals in the United States from January 2006 to October 2007 implicated *A. baumannii* in 8.4% of VAP.<sup>50</sup> In a study of 411 cases of VAP from nine European countries, *A. baumannii* was implicated in 13.9% of cases.<sup>51</sup> In a cohort of 827 cases of VAP in 27 ICUs in Europe, *A. baumannii* was implicated in 11% of early-onset and 26.5% of late-onset VAP.<sup>56</sup> In Greece and Turkey, ABC was the most common cause of VAP.<sup>56</sup> One prospective study in Turkey implicated ABC in 54% of VAP.<sup>54</sup> Rates of VAP due to ABC are high in tropical or subtropical regions, particularly in Asia. In a series of 621 cases of VAP in Japan from 2005 to 2011, *Acinetobacter* accounted for 54.3% of cases.<sup>52</sup> A prospective study in 10 Asian countries from 2008 to 2009 of HAP in adults ( $n = 2,554$ ) implicated *Acinetobacter* spp. in 36.5% of cases.<sup>47</sup> Importantly, 67.3% of *Acinetobacter* spp. isolates were resistant to imipenem.<sup>47</sup>

#### Risk Factors for Colonization or Infection with *Acinetobacter* spp.

In critically ill patients, *Acinetobacter* spp. may colonize the gastrointestinal (GI) tract, skin, and respiratory tract, and may cause serious infections.<sup>1,24</sup> Risk factors for acquisition of *Acinetobacter* spp. include invasive procedures or devices, prolonged ICU stay, mechanical ventilation (MV), enteral feedings, burns, and recent use of broad-spectrum antibiotics, particularly cephalosporins (CEPHS) or fluoroquinolones (FQs)<sup>1,24,34,57,58</sup> (–Table 1). A prospective study identified the following independent risk factors for ICU-acquired *A. baumannii*: (1) prior occupant in that room with *A. baumannii* (OR: 4.2,  $p < 0.001$ ) and (2) MV (OR: 9.3,  $p < 0.05$ ).<sup>59</sup> Diabetes mellitus may increase the risk of recurrent or persistent colonization with ABC.<sup>60</sup> Risk factors for ABC bacteremia among ICU patients include colonization with ABC; high APACHE II scores; MV; presence of an endotracheal tube; recent invasive procedures; CVCs; and prior antimicrobials.<sup>1</sup> In one study, colonization of CVCs with MDR-ABC was associated with a 28% risk of subsequent bacteremia.<sup>61</sup> Studies in patients with malignancies cited the following risk factors for *A. baumannii* infection: CVC and nasogastric tubes,<sup>62</sup> admission to the ICU,<sup>63</sup> dialysis, and prolonged ICU stay<sup>64</sup>; hematological malignancies; use of cefepime; and use of total parenteral nutrition (TPN).<sup>57</sup> In neonatal ICUs, low birth weight, TPN, and presence of CVCs were risk factors for bacteremias due to ABC compared with uninfected infants.<sup>65</sup>

**Table 1** Risk factors for *Acinetobacter* acquisition or infection

Risk factor	Reference
Invasive procedures, devices	62,65
ICU admission and/or prolonged stay	1,64,67
Mechanical ventilation and duration of mechanical ventilation	59,64,67
Nasogastric tube	62
Receipt of broad-spectrum antibiotics	57,62,64,67
Receipt of fluconazole	67
Prior hospital room occupant with <i>A. baumannii</i>	59
Colonization with <i>Acinetobacter</i>	1
Severity of illness score	67
Dialysis	64
Total parenteral nutrition	57,65
Hematologic malignancy	57
Exposure to contaminated fomites	43,66,67
Chronic pulmonary disease	67

*Acinetobacter* spp. are ubiquitous and may survive for prolonged periods on wet or dry surfaces.<sup>24,34</sup> Contaminated environmental sources and transmission via medical personnel may cause outbreaks of nosocomial infections.<sup>43,66,67</sup> Acquisition and spread of ABC has been noted in hospitals,<sup>66</sup> rehabilitation centers, and long-term care facilities (LTCFs), among pilgrims returning from the Hajj (Makkah)<sup>68</sup> and in the community (particularly among the elderly).<sup>1,2</sup> Colonized or infected patients, selection pressure from antimicrobial use, and incomplete compliance with infection control procedures may facilitate persistence or spread of MDR-ABC within hospital or institutional settings.<sup>1,66</sup> Removal or disinfection and sterilization of contaminated equipment (e.g., ventilator or nebulizer tubing) or fomites may eliminate the problem.<sup>24,66</sup> An outbreak of MDR-ABC in a surgical ICU was linked to aerosolization of ABC during pulsatile lavage of wounds.<sup>67</sup> Multifaceted infection control measures led to control of the outbreak. Interestingly, additional risk factors for acquisition of MDR-ABC included receipt of fluconazole (OR: 73.3), receipt of levofloxacin (OR: 11.5), and chronic pulmonary disease (OR: 11.5).<sup>67</sup>

### ABC Virulence Factors and Pathogenesis

The virulence mechanisms and pathogenesis of *A. baumannii* infections have been reviewed elsewhere.<sup>69,70</sup> *A. baumannii* has simple growth requirements and may survive in dry and desiccated conditions for prolonged periods<sup>1,69</sup>; further, *A. baumannii* is able to adhere to living or inert surfaces and form biofilms.<sup>1,2</sup> Additional bacterial factors that may heighten survival and virulence include outer membrane porins, capsule, lipopolysaccharide, regulatory proteins, and iron acquisition systems.<sup>1,2,71</sup>

### Mechanisms of Antimicrobial Resistance

*Acinetobacter* spp. have innate (chromosomal) resistance mechanisms against multiple antimicrobials but also can acquire new resistance determinants via mobile genetic elements such as plasmids, transposons, integrons, insertion sequences, and resistance islands.<sup>1–3,69,72–74</sup> Mechanisms of antimicrobial resistance are numerous and include (1) enzymatic inactivation or modification of antimicrobials; (2) alteration in the bacterial target site(s); (3) permeability barriers to uptake of antimicrobials; (4) active efflux pumps (that extrude antibiotics from bacterial cells); (5) combinations of mechanisms, which may occur as the result of large genomic islands containing multiple resistance genes.<sup>1–3,70,72</sup>

### Global Escalation of Antimicrobial Resistance

Within the past three decades, antimicrobial resistance rates among ABC have escalated dramatically worldwide.<sup>17,72,75</sup> In some countries, more than 90% of ABCs are MDR.<sup>17</sup> Molecular-based strain typing by pulse field gel electrophoresis (PFGE) or multilocus sequence typing (MLS) methods has documented global spread of MDR “epidemic clones” between hospitals, regions, and continents.<sup>72</sup> International spread has been extensively documented: for example, between Brazil and Argentina<sup>76</sup>; from Iraq to Germany and the United States among military personnel<sup>77,78</sup>; from northwestern Europe to the Czech Republic and globally<sup>79</sup>; from Turkey to Europe, the Middle East, and the rest of Asia<sup>80</sup>; from southern to northern Europe, the Middle East, rest of Asia, and Latin America<sup>81</sup>; from Europe to multiple continents.<sup>34</sup> The rate of increase may be amplified by selection pressure from antimicrobial use, crowding, lack of hygiene, and increased worldwide travel.<sup>24,34</sup>

### Impact of Antimicrobial Use on Antimicrobial Resistance

Not surprisingly, the use of broad-spectrum antimicrobials has been linked to emergence of antimicrobial resistance. In the early 1990s, the use of imipenem against cephalosporin-resistant *Klebsiella pneumoniae* was associated with emergence of imipenem-resistant ABC in one New York hospital.<sup>82</sup> Further, in multiple hospitals in Brooklyn, New York, there was an association between the use of third-generation CEPHS and aztreonam and CP-resistant ABC.<sup>83</sup> In one case-control study in a surgical ICU, risk factors for acquisition of imipenem-resistant (IR) and imipenem-susceptible (IS) strains of *A. baumannii* were assessed.<sup>84</sup> Risk factors for IR-ABC were ICU stay (OR: 21.5), prior exposure to imipenem (OR: 9.2), and prior exposure to third-generation CEPHS (OR: 2.1). Risk factors for IS-ABC include ICU stay (OR: 8.1) and prior exposure to third-generation CEPHS (OR: 2.1). Regionally and globally, selection pressure is the key determinant of emergence of CPR or MDR-ABC.

## Resistance to $\beta$ -Lactams

### $\beta$ -Lactamases

All *A. baumannii* strains possess a chromosomal AmpC cephalosporinase that confers resistance to penicillins and early-generation cephalosporins (CEPHS); however, under normal circumstances, resistance to third- and fourth-generation CEPHS due to AmpC is *clinically insignificant*.<sup>24,85</sup> *Clinically significant* resistance may develop via hyperproduction of the AmpC cephalosporinase,<sup>85</sup> the presence of insertion sequences that promote  $\beta$ -lactamase activity,<sup>46</sup> or incorporation of mobile resistance genes.<sup>86</sup>

$\beta$ -Lactamases are categorized based on molecular structure into groups A through D and functionally into three groups (1–3) based on the target enzyme they degrade.<sup>87,88</sup> Group 1 (class C) cephalosporinases are relatively narrow spectrum. Group 2 (classes A and D) include serine  $\beta$ -lactamases and extended-spectrum  $\beta$ -lactamases (ESBLs) and have a broader spectrum of activity.<sup>88</sup> Group 3 enzymes include metallo  $\beta$ -lactamases (class B), which are potent hydrolyzers of CP and are not inhibited by  $\beta$ -lactamase inhibitors.<sup>88</sup>  $\beta$ -Lactamases of the IMP, VIM, SIM, and NDM-1 families fall within Group 3.<sup>74</sup>

### Extended-Spectrum $\beta$ -Lactamases

Numerous extended-spectrum  $\beta$ -lactamases (ESBLs) including SHV, TEM, PER, VEB, GES, and CTX-M confer high-grade resistance to all CEPHS.<sup>1,34</sup> ESBL clones (TEM or SHV) were initially described in *Enterobacteriaceae* in France and Belgium in the late 1980s and mid-1990s,<sup>89,90</sup> and rapidly spread globally.<sup>91</sup> By the late 1990s, other plasmid-encoded ESBLs (e.g., PER-1, VEB, CTX-M, and GES) were described among *Enterobacteriaceae*<sup>91</sup> and less commonly among *P. aeruginosa* and *Acinetobacter* spp.<sup>34</sup> ESBL-containing plasmids (PER-1 type) among *A. baumannii* (as well as *P. aeruginosa*, and *Klebsiella* spp.) were first recognized in the late 1990s in Turkey<sup>80</sup> and France<sup>92</sup> and spread globally.<sup>34</sup> Clusters of ABC infections due to VEB-1 type ESBL were noted among French hospitals in 2003.<sup>93</sup> Rapid clonal spread to Belgium,<sup>94</sup> Argentina,<sup>95</sup> Lebanon,<sup>34</sup> and globally<sup>34</sup> ensued. Other ESBLs identified in ABC include TEM-92 and -116 from Italy and the Netherlands, respectively; SHV-12 from China and the Netherlands, CTX-M-2 and CTX-M-43 from Japan and Bolivia, respectively.<sup>4</sup> Later, CTX-M ESBLs were detected in India,<sup>96</sup> Haiti,<sup>97</sup> Brazil,<sup>98</sup> and globally.

### Carbapenemases

Many  $\beta$ -lactamases (including ESBLs) may also have hydrolytic activity against CPs via production of carbapenemases (CPE). The emergence of carbapenemases has created a major “hole” in antibiotic coverage against ABC. Carbapenemases include group 2 class D oxacillinases (e.g., OXA enzymes) and class B metallo- $\beta$ -lactamases (MBLs) (e.g., IMP, VIM, and SIM-1 groups)<sup>34,85</sup> and the newer CPE (i.e., KPC-like; GES-like,<sup>99–102</sup> New Delhi metallo- $\beta$ -lactamase-1 [NDM-1]).<sup>1,69,103,104</sup>

### Class D Serine Carbapenemases

Globally, the most common CPE in *A. baumannii* are the class D serine oxacillinases (OXA), represented by the OXA-23-,

OXA-24-, OXA-58-, and OXA-143-like types that can be encoded on *chromosomes* or *plasmids*.<sup>1,46,105–107</sup> The first CPE (an OXA-type enzyme) in ABC was discovered in Scotland 1985.<sup>108</sup> By the mid-1990s, CPR-ABC clones (principally OXA-type CPE) were noted in Latin America,<sup>46,109</sup> the United Kingdom (UK),<sup>110,111</sup> Europe,<sup>1,34,105</sup> North America,<sup>1,34</sup> Australia,<sup>1</sup> Africa, the Middle East, and Asia.<sup>112</sup> In 2003, the OXA-58 oxacillinase (*bla*<sub>OXA-58</sub> gene) was isolated from a CPR-*Acinetobacter* strain in Toulouse, France.<sup>105</sup> Subsequently, OXA-58-producing CPR-ABC strains were reported in other Mediterranean countries (e.g., Lebanon, Turkey)<sup>34</sup> and China.<sup>113</sup> After 2009, ABC-producing OXA-23 (*bla*<sub>OXA-23</sub> gene) became the dominant OXA in Europe,<sup>114</sup> United States,<sup>115</sup> Latin America,<sup>106</sup> and globally.<sup>69,116</sup> Three clonal lineages (known as Worldwide Clones 1, 2, and 3) dominate among clinical isolates of MDR-ABC globally.<sup>1,34</sup>

KPC, a CPE, first reported in 1996 in *K. pneumoniae* in North Carolina,<sup>117</sup> spreads rapidly within the northeastern United States<sup>118</sup> and to France,<sup>119</sup> Israel, Greece, Italy,<sup>120</sup> and globally.<sup>91</sup> KPC is encoded on plasmids in *Enterobacteriaceae* and *P. aeruginosa*,<sup>119,121</sup> but has not widely disseminated among ABC. KPC-producing ABCs were detected in 10 isolates of *A. baumannii* in Puerto Rico in 2010.<sup>122</sup> To our knowledge, KPC-producing ABCs have *not* been reported in other countries.<sup>121</sup>

A newer group of CPEs termed GES (Guiana extended-spectrum  $\beta$  – lactamases) was first identified in *K. pneumoniae* in 2000, and later reported in *Acinetobacter* spp. in France in 2009<sup>123</sup> followed by rapid spread to Belgium,<sup>100</sup> the Middle East, and Northern Africa.<sup>99,101,102,124–126</sup>

A novel CPE, termed NDM-1, was first detected in a *K. pneumoniae* isolate in a Swedish patient transferred from India.<sup>103</sup> Retrospective studies showed that NDM-1 had been endemic among *K. pneumoniae* and *Escherichia coli* in Indian hospitals since 2006.<sup>127</sup> By 2010, NDM-1-producing *Enterobacteriaceae* had been found on five continents and linked to travel in India or Pakistan.<sup>128</sup> In the United States, three cases of infections due to NDM-1-producing *Enterobacteriaceae* were reported in 2010; all three had recently received medical care in India.<sup>129</sup> From 2010 on, numerous publications cited NDM-1-producing ABC in Europe,<sup>72,126,130–134</sup> the Middle East,<sup>135–138</sup> Africa,<sup>132,139–144</sup> Asia.<sup>145–149</sup> Epidemiological reviews suggest that the majority of infections due to NDM-1-producing ABC occur in India, Asia, the Middle East, and the Balkans.<sup>104</sup> Berrazeg et al reviewed all publications of infections due to NDM-1-producing bacteria from 2009 to December 31, 2012, and identified 950 cases.<sup>104</sup> Only 36 cases (3.8%) were due to ABC. Although infections due to NDM-1-producing ABC have been cited in Brazil,<sup>150</sup> Paraguay,<sup>151</sup> Argentina,<sup>152</sup> and Honduras,<sup>153</sup> NDM-1-producing ABC appears to be rare in the Americas.

## Epidemiology and History of Antimicrobial Resistance among *Acinetobacter* spp.

In the 1970s, *Acinetobacter* spp. were usually susceptible to ampicillin, cephalosporins, carbapenems (CPs), and several antibiotic classes.<sup>1</sup> By the 1980s, resistance to various classes of antibiotics appeared, but nearly all isolates remained

susceptible to CPs. In the early 1990s, carbapenem-resistant (CPR) strains emerged.<sup>1</sup> Importantly, CPR-ABCs are often resistant to all classes of antimicrobials except colistin and tigecycline.<sup>1,34</sup> Ominously, strains of *Acinetobacter* resistant to colistin and tigecycline have been reported.<sup>154,155</sup> Drug resistance has an adverse impact on clinical outcomes. Compared with patients with CP-susceptible strains, patients with CPR-ABC infections have increased mortality and increased hospital and ICU length of stay.<sup>1</sup>

In the United States (and globally), CPR-ABCs have escalated dramatically over the past two decades. In the National Nosocomial Infections Surveillance (NNIS) System, CPR-ABC (ICU isolates) in the United States increased from 0% in 1986 to 20% in 2002.<sup>55</sup> In a survey of more than 300 hospitals in the United States, CPR-*A. baumannii* increased from 9% in 1995 to 40% in 2004.<sup>24</sup> The MYSTIC Study surveyed changes in antimicrobial resistance from clinical isolates from 15 U.S. hospitals over a decade; resistance to imipenem increased from 10% in 1999 to 48% in 2008.<sup>156</sup> The Surveillance Network (TSN) database examined more than 55,000 isolates of *Acinetobacter* spp. in the United States from 2002 to 2008; CPR increased from 20.6% in 2002 to 49.2% in 2008.<sup>157</sup> A survey of nine regions in the United States from 2005 to 2011 found that 30% of 2,900 isolates of ABC were MDR.<sup>158</sup> Another study in the United States in 2010 noted that 50% of 514 clinical isolates of ABC were CPR.<sup>159</sup> In the SENTRY study from 2009 to 2011, susceptibility rates to imipenem in the United States were 43% (ICU) and 63% (non-ICU) and in Europe 45% (ICU) and 56% (non-ICU).<sup>44</sup>

Worldwide, rates of CPR-ABC have been highest in Greece, Taiwan, and Latin America,<sup>46,106,160–162</sup> but remarkable differences between countries have been noted.<sup>17,163</sup> A survey of 48 European hospitals (MYSTIC) in 2006 cited CPR in 42.5% of ABC clinical isolates.<sup>164</sup> In the COMPACT study from 2008 to 2009 in Europe, the Middle East, and Africa, 49% of ABC isolates were resistant to imipenem.<sup>163</sup> Resistance rates were higher in Turkey, Greece, Italy, Spain, and England (45–85%) compared with France, Germany, and Sweden (4–20%).<sup>163</sup> In one tertiary care hospital in the United Kingdom, CPR among ABC bloodstream isolates (BSI) rose from 0% in 1998 to 55% in 2006.<sup>111</sup> A survey of 11 countries in Latin America in 2011 found that more than 50% of ABC clinical isolates were CPR.<sup>160</sup> In the SENTRY study of ABC isolates from 2006 to 2009, *global* CPR rates rose from 34.6% in 2006 to 59.8% in 2009.<sup>165</sup> The SMART surveillance study of urinary tract and IAI ABC isolates from 48 countries from 2011 to 2014 cited MDR ranging from 47% in North America to more than 93% in Europe and the Middle East.<sup>17</sup> In China, 58% of blood stream isolates of ABC in 2013 were CPR.<sup>112</sup> The SMART surveillance study, comprising 48 countries from 2001 to 2014, evaluated CPR resistance among ABC isolates from intra-abdominal and UTI.<sup>17</sup> The incidence of MDR-ABC was lowest in North America (47%) and ranged from 77 to 87% in Africa, Asia, and Latin America, and exceeded 93% in Europe and the Middle East.<sup>17</sup> This extraordinary rate of CPR-ABC reflects selection pressure from antibiotic usage. The use of CPs has been associated with increased incidence of CPR-ABC.<sup>162,166</sup> In one study, the

prevalence of infections due to MDR-ABC fell 2.24-fold after implementing a policy of restricting CP use in the ICU.<sup>167</sup>

## Treatment of Infections Due to *Acinetobacter* spp.

Nosocomial infections due to ABC have been associated with high mortality rates (particularly with BSI or VAP).<sup>24,34,35</sup> Early appropriate antimicrobial therapy is critical.<sup>3,11,35</sup> Optimal therapy for serious ABC infections has not been established,<sup>1</sup> as prospective randomized trials have not been done. For BSI, removal of invasive devices within 48 hours may reduce mortality.<sup>11</sup> For SSTI or SSI, debridement is an essential part of therapy.<sup>24</sup> Carbapenems, alone or combined with a second agent, has been considered the best therapy for ABC infections.<sup>1,34</sup> However, the emergence of CPR strains limits the use of these agents as monotherapy for *empirical* treatment *when CPR is a consideration*. We believe a combination of a carbapenem plus colistin is appropriate as *initial empirical* therapy for serious *A. baumannii* infections when CPR is suspected.<sup>43</sup> Other agents (e.g.,  $\beta$ -lactam/ $\beta$ -lactamase inhibitors, ceftazidime, or FQs) may be used, provided isolates are susceptible.

## Advanced Generation Cephalosporins

Third- and fourth-generation cephalosporins (e.g., ceftazidime, cefepime) are not reliable for empirical treatment of infections due to ABC. Globally, only 20 to 40% of ABCs are susceptible to expanded spectrum CEPHS.<sup>17</sup> CEPHS should not be used as empirical treatment for ABC infections, but may be considered for susceptible strains.

## Sulbactam

Among  $\beta$ -lactamase inhibitors, sulbactam has the greatest bactericidal activity against ABC.<sup>1</sup> Ampicillin-sulbactam (A/S) (due to the sulbactam component) may be effective therapy for some strains of ABC.<sup>168</sup> High-dose A/S and extended time of infusion may enhance bactericidal activity.<sup>169</sup> Clinical data supporting the use of sulbactam are limited to small series.<sup>168,170</sup> Sulbactam may display synergy against ABC when combined with other antibiotics (e.g., CP, colistin).<sup>171</sup>

## Fluoroquinolones

Fluoroquinolones may be active against some strains of ABC, but globally, fewer than 30% of ABCs are susceptible to FQs.<sup>17</sup> FQ resistance can emerge via mutations in the quinolone resistance determining regions (QRDR) of *gyrA* and *parC* genes and/or by overexpression of efflux pumps.<sup>69</sup>

## Aminoglycosides

Aminoglycoside resistance among ABCs may emerge via the production of aminoglycoside-modifying enzymes, 16S ribosomal RNA methyltransferase (ArmA), or efflux pumps.<sup>1</sup> In one French study, increased use of amikacin was associated with emergence of amikacin-resistant ABC; decreased amikacin use led to a decrease in case incidence.<sup>172</sup> The

activity of aminoglycosides against ABC is variable, but resistance rates exceed 60% in most countries.<sup>173</sup> See ► **Table 2** for summary of antimicrobial resistance mechanisms among *Acinetobacter* spp.

### Treatment of Infections Due to *Acinetobacter* spp.

In view of the high incidence of MDR-ABC, initial empirical therapy with combination therapy (typically CP plus colistin) is often employed while awaiting antimicrobial susceptibility results. Optimal therapy is not clear, as randomized, controlled studies are lacking. In the next sections, we will discuss antibiotics that are often used either as monotherapy or part of combination therapy for MDR-ABC.

#### Polymyxins (Colistin)

Polymyxins (e.g., polymyxin B and polymyxin E [colistin]) are cationic lipopeptides that disrupt the outer membrane of gram-negative bacteria and are rapidly bactericidal.<sup>155</sup> Polymyxins are usually highly active against MDR-ABC, including isolates resistant to tigecycline.<sup>1</sup> Colistin is administered intravenously as an inactive prodrug (colistimethate sodium [CMS]), whereas polymyxin B is an active drug. CMS is widely available, whereas polymyxin B is infrequently used. Resistance rates to colistin are generally low (< 1%),<sup>174</sup> but colistin resistance among ABCs has been increasing.<sup>155,175</sup> In a survey of 514 ABC isolates from 65 sites in the United States and Puerto Rico in 2010, 5% of isolates were resistant to colistin.<sup>159</sup>

Colistin can be administered by intravenous (IV) or inhaled routes.<sup>1</sup> IV colistin has potential renal toxicity<sup>1</sup> and neurotoxicity (principally paresthesias).<sup>1</sup> Risk factors for nephrotoxicity include colistin dose > 5 mg/kg/day ideal body weight<sup>176</sup> and concomitant use of rifampicin or nephrotoxins.<sup>176</sup> Optimal dosing regimens for IV colistin have not been established.<sup>1,177</sup> Colistin exhibits a concentration-dependent bactericidal activity; therapeutic effect depends on the ratio of peak serum concentration to minimum inhibitory concentration (MIC) or the ratio of the area under the curve (AUC) to MIC.<sup>1</sup> Strategies involving higher doses, longer dosing intervals, loading doses, extended infusions, and pharmacokinetic/pharmacodynamic (PK/PD) principles have been proposed to optimize efficacy and prevent the development of resistance.<sup>178–180</sup> However, colistin has relatively poor PK/PD properties, and it may be difficult to achieve high enough serum concentrations quickly.<sup>155</sup> CMS (a prodrug) has to be converted to the active form (colistin) in the plasma, and concentrations may be suboptimal for 2 to 3 days until a steady state is achieved; thus, a loading dose is recommended.<sup>1</sup> One in vitro study suggested that achievement of serum levels more than 1 mg/L within 1 hour had significant bactericidal activity.<sup>181</sup>

Studies reporting efficacy of colistin *monotherapy* for ABC infections are limited. In a prospective study of 35 episodes of VAP due to MDR-ABC, patients were treated with imipenem ( $n = 14$ ) versus colistin ( $n = 21$ ) based on susceptibility testing.<sup>182</sup> Cure rates were 57% in both groups; in-hospital mortality rates were similar (64 and 62%, respectively). The

**Table 2** Common mechanisms of antimicrobial resistance in *Acinetobacter* spp.

Resistance mechanism	Target antimicrobial	References
Enzymatic inactivation or modification of antimicrobials		
AmpC $\beta$ -lactamase with upstream insertion of IS <i>Aba1</i>	Cephalosporins	1,46,70
Non-carbapenemase oxacillinases (OXA)	Penicillins, cephalosporins	1,18,45,68,70
Metallo- $\beta$ -lactamases (IMP, VIM, SIM, NDM-1)	Penicillins, cephalosporins, carbapenems	1,103,124,130,135,145,150,153
Non-metallo- $\beta$ -lactamase carbapenemases (OXA, KPC)	Penicillins, cephalosporins, carbapenems, monobactams	1,70,122
Extended-spectrum $\beta$ – lactamases (SHV, TEM, PER, VEB, GES, CTX-M)	Penicillins, cephalosporins, monobactams	1,70,99,101,102,123–125
Aminoglycoside-modifying enzymes (AAC, APH, AAD)	Aminoglycosides	1,70
Modification of drug target site		
<i>gyrA</i> and <i>parC</i> mutations	Fluoroquinolones	1,69,70
Alteration of ribosomal-binding site (RmtB, ArmA)	Aminoglycosides	1,70
Altered lipid A of bacterial lipopolysaccharide (PmrAB two-component system mutation)	Colistin	1,70
Loss of lipopolysaccharide (mutated <i>lpxA</i> , <i>lpxC</i> , <i>lpxD</i> )	Colistin	1,70
Altered cell permeability		
Porin/outer membrane protein loss	Carbapenems, aminoglycosides	70
Efflux pumps		
RND efflux pump (AdeABC, AdeFGH, Ade IJK, AbeM)	Fluoroquinolones, $\beta$ -lactams, aminoglycosides, tetracyclines	1,70

impact of combination therapy has not been elucidated. Turkish investigators retrospectively assessed clinical outcomes in 250 patients with BSI due to extremely resistant ABC.<sup>183</sup> Thirty-six patients received colistin monotherapy; 214 received colistin plus a second agent. All isolates were susceptible to colistin. In-hospital mortality was lower in the combination group compared with monotherapy group (52.3 vs. 72.2%,  $p = 0.03$ ) and rate of microbiological eradication was higher in the combination therapy compared with monotherapy (79.9 vs. 55.6%,  $p = 0.001$ ). By multivariate analysis, Pitt bacteremia score, age, and duration of ICU stay were independent predictors of 14-day mortality. An observational study of 28 Spanish hospitals assessed 30-day mortality rates among 101 patients with serious infections due to MDR-ABC.<sup>184</sup> Pneumonia was present in 50.5%. Sixty-eight patients received monotherapy (MT) (usually a CP or colistin); 33 received combination therapy (CT). Thirty-day mortality rates were similar (23.5% for MT; 24.2% for CT;  $p = 0.94$ ). Another observational study reviewed 69 organ transplant recipients either colonized ( $n = 28$ ) or infected ( $n = 41$ ) with XDR *A. baumannii*.<sup>185</sup> Among 41 patients with infections, 37 received antimicrobial therapy. Clinical success at 28 days was achieved in 18/37 (49%), but clinical recurrence developed within 3 months in 8 of 18 (44%) within 3 months. Further, colistin resistance developed in 5 of 14 patients. The use of combination therapy with colistin and a carbapenem was an independent predictor of survival.<sup>185</sup> These various retrospective studies are inadequate to assess the role or benefit (if any) of combination therapy or the optimal agents to use for serious infections due to ABC.

Aerosolized (inhaled) colistin has been used in patients with cystic fibrosis and as adjunctive therapy for nosocomial pneumonia due to ABC, but data are limited to nonrandomized, retrospective studies.<sup>1,186</sup> One randomized open-label trial compared the efficacy of nebulized CMS (plus IV colistin) for 100 patients with gram-negative VAP, 60% of which were due to ABC. Microbiological outcome was better with nebulized plus IV therapy (60.9%) compared with 38.2% among IV CMS only group ( $p = -0.03$ ). Importantly, clinical outcomes were similar (51.0 vs. 53.1%,  $p = 0.94$ ). Further, there were more episodes of bronchospasm in the nebulized plus IV therapy group (7.8 vs. 2.0%, respectively,  $p = 0.36$ ). The clinical benefit of nebulized CMS to treat VAP has not been established.

Resistance to colistin may develop.<sup>185</sup> Plasmid-mediated resistance via *mcr-1* gene among *Enterobacteriaceae* was first reported China,<sup>187</sup> and human cases of *E. coli* or *Enterobacteriaceae* expressing *mcr-1* were described shortly thereafter in Switzerland,<sup>188,189</sup> Canada,<sup>190</sup> and Singapore.<sup>191</sup> The *mcr-1* gene has not yet been identified in *Acinetobacter* spp., but it is feasible that in time, MDR *Acinetobacter* could acquire this resistance mechanism. Colistin heteroresistance may also occur.<sup>155</sup> Colistin-resistant ABCs appear to have reduced fitness and less virulence,<sup>192</sup> including a decreased ability to form biofilms.<sup>193</sup>

### Tigecycline

Tigecycline, a semisynthetic derivative of minocycline, has excellent in vitro activity against MDR-ABC (including CPR

strains).<sup>194,195</sup> However, clinical studies assessing efficacy of tigecycline for serious ABC infections are limited. Favorable clinical responses have been cited with tigecycline (alone or in combination with colistin) in some patients with MDR-ABC infections,<sup>1,196</sup> but large, randomized trials are lacking. In one retrospective study, 266 patients with XDR-ABC infections treated with tigecycline alone or combined with other agents (i.e., CP, extended-spectrum CEPH, or piperacillin-tazobactam) were compared with 120 patients who received imipenem plus sulbactam to treat XDR-ABC.<sup>197</sup> All isolates were resistant to all antibiotics tested except tigecycline and colistin. Thirty-day mortality rates were similar (44.7 and 46.7%) between the groups. A prospective multicenter phase III trial cited lower cure rates in patients with ABC-VAP treated with tigecycline (68% cure) compared with imipenem (78% cure).<sup>198</sup> Overall mortality rates were similar with tigecycline (14.2%) and imipenem (12.2%). A retrospective study of adults with pneumonia in the ICU due to MDR-ABC matched 84 patients receiving tigecycline to 84 patients receiving colistin.<sup>199</sup> Mortality was higher (60.7%) among patients receiving tigecycline compared with colistin (44% mortality,  $p = 0.04$ ). This excess mortality was significant only for those with MIC greater than 2 µg/mL.<sup>199</sup> Ye et al retrospectively analyzed 168 hospitalized ICU patients with pneumonia due to ABC treated with either sulbactam or ampicillin/sulbactam ( $n = 84$ ) to patients treated with tigecycline ( $n = 84$ ).<sup>200</sup> Clinical responses (66.7% for each group) and mortality rates were similar (17.9% with sulbactam, 25.0% with tigecycline;  $p = 0.26$ ). Microbiological eradication was achieved more often with sulbactam (63.5 vs. 33.3%).

Tigecycline achieves low peak serum concentrations (< 0.8 mg/L) after a standard 100 mg loading dose,<sup>1</sup> a concentration below the MIC of many ABC isolates. Resistance to tigecycline may develop even while on therapy,<sup>194</sup> and persistence of infection (with or without resistance) may occur.<sup>1</sup> Efficacy of tigecycline for BSI due to ABC therefore cannot be assured. Importantly, tigecycline has been associated with an increased risk of death when studied against comparator antibiotics, especially among patients with hospital-acquired pneumonia (HAP).<sup>201</sup> Higher doses of tigecycline (75–100 mg twice daily) have been recommended by some investigators,<sup>43</sup> but randomized trials have not been done. Given the aforementioned limitations, we do not recommend tigecycline monotherapy to treat serious ABC infections.

### Eravacycline

Eravacycline is a novel fluorocycline of the tetracycline class with broad-spectrum activity against gram-negative and gram-positive aerobic and anaerobic pathogens.<sup>202</sup> Like tigecycline, eravacycline is not affected by many of the tetracycline-specific resistance mechanisms found in gram-negative bacteria, including acquired efflux systems and ribosomal protection.<sup>202</sup> Eravacycline is two- to fourfold more active (reduced MIC<sub>90</sub>) than tigecycline versus *A. baumannii*.<sup>203</sup> Whether this increased in vitro activity translates into greater clinical efficacy is not known.

## Other Antimicrobial Agents

### Rifampin

Rifampin exhibits activity against MDR-ABC in vitro and in animal models.<sup>1</sup> In animal models, the combination of rifampin plus colistin may confer additive or synergic bactericidal activity.<sup>1</sup> However, in two randomized trials of serious MDR-ABC infections, the combination of rifampin plus colistin was no better than colistin alone.<sup>204,205</sup> The role of rifampin as part of combination therapy has not been established.

### Other Combination Therapy Using Colistin

Combination therapy has been studied to treat MDR-ABC, particularly with colistin as part of the combination.<sup>171,183–185,206</sup> In vitro studies have shown that synergy may be achieved with combinations of colistin, carbapenems, and rifampicin, in both colistin-S and colistin-R strains of *Acinetobacter* spp.<sup>207,208</sup> In a retrospective multicenter study, Batirel et al evaluated 250 BSIs due to extremely drug resistant (XDR)-ABC (all isolates were susceptible to colistin).<sup>183</sup> Groups included colistin monotherapy ( $n = 36$ ); colistin + CP ( $n = 102$ ); colistin + sulbactam ( $n = 69$ ); and colistin + other agents ( $n = 43$ ). Complete response rates, 14-day and in-hospital survival, and microbiologic eradication were significantly higher in the combination group, but no differences could be seen between the various combinations.<sup>183</sup> A multicenter prospective observational study in Spain of 101 patients with MDR-ABC infections demonstrated no significant difference in 30-day mortality between combination therapy with colistin versus monotherapy with various agents, predominantly a CP.<sup>184</sup> Cheng et al prospectively studied 176 episodes of bacteremia due to XDR-*A. baumannii* in three hospitals in Taiwan.<sup>206</sup> Among infections with tigecycline MIC > 2 mg/L, combination therapy with colistin plus tigecycline was associated with significantly higher 14-day mortality and more breakthrough bacteremias compared with colistin plus CP.<sup>206</sup>

The addition of glycopeptides (agents with gram-positive activity) to colistin has displayed synergy against ABC in vitro.<sup>155</sup> However, clinical studies are limited, and data are conflicting.<sup>209,210</sup>

### Novel Agents

It is obvious that new agents are needed to treat ABC infections. Anti-GNB compounds that belong to old classes of agents such as  $\beta$ -lactams, CPs, FQs, and  $\beta$ -lactamase inhibitors are in development, as are novel classes.<sup>211–214</sup> Ceftazidime/avibactam contains an older third-generation CEPH (i.e., ceftazidime), with avibactam, a synthetic non- $\beta$ -lactam,  $\beta$ -lactamase inhibitor that inhibits the activities of Ambler class A and C  $\beta$ -lactamases and some Ambler class D enzymes.<sup>215–217</sup> Limited data suggest that the addition of avibactam does not improve the activity of ceftazidime against *Acinetobacter* spp.<sup>215</sup> Ceftolozane is a novel cephalosporin with a chemical structure similar to that of ceftazi-

dime, with the exception of a modified side chain at the three-position of the cephem nucleus, which confers potent antipseudomonal activity.<sup>217,218</sup> The addition of tazobactam extends the activity of ceftolozane to include most ESBL producers as well as some anaerobic species.<sup>218</sup> Limited data suggest that ceftolozane/tazobactam is 8- to 16-fold more active than ceftazidime versus *A. baumannii*.<sup>218</sup> Whether this increased in vitro activity translates into greater clinical efficacy is not known.

Plazomicin is a next-generation aminoglycoside that was synthetically derived from sisomicin.<sup>219</sup> Plazomicin demonstrates activity against both gram-negative and gram-positive bacterial pathogens, including isolates harboring all clinically relevant aminoglycoside-modifying enzymes.<sup>212,216,219</sup> Limited data suggest that plazomicin demonstrates approximately eightfold more active than gentamicin versus *A. baumannii*.<sup>220</sup> Whether this increased in vitro activity translates into greater clinical efficacy is not known.

Among the new classes of antimicrobials, bis-indole compounds inhibit DNA and RNA synthesis and some have had very good in vitro activity against MDR ABC.<sup>221</sup> Applying structure-based drug design, pyrrolopyrimidine agents were developed that inhibit both of the bacterial topoisomerases (DNA gyrase and topoisomerase IV) of GNB including ABC, *Pseudomonas aeruginosa*, and *E. coli*.<sup>222</sup> Antimicrobial peptides, naturally occurring molecules of the innate immune systems of all types of living organisms, are potential new treatments for MDR organisms.<sup>223</sup> Some of these, including melittin, indolicidin, and mastoparan, exhibit activity against colistin-susceptible and colistin-resistant ABC isolates in vitro.<sup>224</sup>

### Prevention

Hospital outbreaks of *Acinetobacter* infections may reflect environmental contamination<sup>24,66,225–227</sup> or carriage of *A. baumannii* on the hands of health care workers.<sup>66</sup> Aggressive infection-control measures including identifying sources of transmission,<sup>67,225</sup> environmental cleaning, contact precautions, and hand hygiene and isolating or cohorting infected and colonized patients<sup>66,228</sup> may be critical to stop or prevent outbreaks. In one study, daily chlorhexidine baths in ICU patients reduced the development VAP due to *Acinetobacter*.<sup>229</sup>

### Conclusion

The dramatic global rise of antimicrobial resistance among ABCs reflects acquisition of novel resistance elements and spread via a few international clones. Many isolates are resistant to all antimicrobials except colistin, and some infections are untreatable with existing agents. Novel approaches including combinations of agents and extended infusion times may be required to optimize therapy. Appropriate use of antimicrobials and infection-control measures are critical to minimize antimicrobial resistance.<sup>43,66</sup>

## References

- 1 Doi Y, Murray GL, Peleg AY. *Acinetobacter baumannii*: evolution of antimicrobial resistance-treatment options. *Semin Respir Crit Care Med* 2015;36(1):85–98
- 2 Jones CL, Clancy M, Honnold C, et al. Fatal outbreak of an emerging clone of extensively drug-resistant *Acinetobacter baumannii* with enhanced virulence. *Clin Infect Dis* 2015;61(2):145–154
- 3 Davis JS, McMillan M, Swaminathan A, et al. A 16-year prospective study of community-onset bacteremic *Acinetobacter pneumoniae*: low mortality with appropriate initial empirical antibiotic protocols. *Chest* 2014;146(4):1038–1045
- 4 Peleg AY, Seifert H, Paterson DL. *Acinetobacter baumannii*: emergence of a successful pathogen. *Clin Microbiol Rev* 2008;21(3):538–582
- 5 Abbott I, Cerqueira GM, Bhuiyan S, Peleg AY. Carbapenem resistance in *Acinetobacter baumannii*: laboratory challenges, mechanistic insights and therapeutic strategies. *Expert Rev Anti Infect Ther* 2013;11(4):395–409
- 6 Wisplinghoff H, Paulus T, Lugenheim M, et al. Nosocomial bloodstream infections due to *Acinetobacter baumannii*, *Acinetobacter pittii* and *Acinetobacter nosocomialis* in the United States. *J Infect* 2012;64(3):282–290
- 7 Wang X, Chen T, Yu R, Lü X, Zong Z. *Acinetobacter pittii* and *Acinetobacter nosocomialis* among clinical isolates of the *Acinetobacter calcoaceticus-baumannii* complex in Sichuan, China. *Diagn Microbiol Infect Dis* 2013;76(3):392–395
- 8 Karah N, Haldorsen B, Hegstad K, Simonsen GS, Sundsfjord A, Samuelsen Ø; Norwegian Study Group of *Acinetobacter*. Species identification and molecular characterization of *Acinetobacter* spp. blood culture isolates from Norway. *J Antimicrob Chemother* 2011;66(4):738–744
- 9 Chuang YC, Sheng WH, Li SY, et al. Influence of genospecies of *Acinetobacter baumannii* complex on clinical outcomes of patients with *Acinetobacter* bacteremia. *Clin Infect Dis* 2011;52(3):352–360
- 10 Lee YT, Kuo SC, Yang SP, et al. Bacteremic nosocomial pneumonia caused by *Acinetobacter baumannii* and *Acinetobacter nosocomialis*: a single or two distinct clinical entities? *Clin Microbiol Infect* 2013;19(7):640–645
- 11 Freire MP, de Oliveira Garcia D, Garcia CP, et al. Bloodstream infection caused by extensively drug-resistant *Acinetobacter baumannii* in cancer patients: high mortality associated with delayed treatment rather than with the degree of neutropenia. *Clin Microbiol Infect* 2016;22(4):352–358
- 12 Özgür ES, Horasan ES, Karaca K, Ersöz G, Naycı Atış S, Kaya A. Ventilator-associated pneumonia due to extensive drug-resistant *Acinetobacter baumannii*: risk factors, clinical features, and outcomes. *Am J Infect Control* 2014;42(2):206–208
- 13 Galal YS, Youssef MR, Ibrahim SK. Ventilator-associated pneumonia: incidence, risk factors and outcome in paediatric intensive care units at Cairo University Hospital. *J Clin Diagn Res* 2016;10(6):SC06–SC11
- 14 Sievert DM, Ricks P, Edwards JR, et al; National Healthcare Safety Network (NHSN) Team and Participating NHSN Facilities. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. *Infect Control Hosp Epidemiol* 2013;34(1):1–14
- 15 Tsitsopoulos PP, Iosifidis E, Antachopoulos C, et al. Nosocomial bloodstream infections in neurosurgery: a 10-year analysis in a center with high antimicrobial drug-resistance prevalence. *Acta Neurochir (Wien)* 2016;158(9):1647–1654
- 16 Jahani-Sherafat S, Razaghi M, Rosenthal VD, et al. Device-associated infection rates and bacterial resistance in six academic teaching hospitals of Iran: Findings from the International Nosocomial Infection Control Consortium (INICC). *J Infect Public Health* 2015;8(6):553–561
- 17 Lob SH, Hoban DJ, Sahn DF, Badal RE. Regional differences and trends in antimicrobial susceptibility of *Acinetobacter baumannii*. *Int J Antimicrob Agents* 2016;47(4):317–323
- 18 Gao J, Zhao X, Bao Y, et al. Antibiotic resistance and OXA-type carbapenemases-encoding genes in airborne *Acinetobacter baumannii* isolated from burn wards. *Burns* 2014;40(2):295–299
- 19 Öncül O, Öksüz S, Acar A, et al. Nosocomial infection characteristics in a burn intensive care unit: analysis of an eleven-year active surveillance. *Burns* 2014;40(5):835–841
- 20 Öncül O, Keskin O, Acar HV, et al. Hospital-acquired infections following the 1999 Marmara earthquake. *J Hosp Infect* 2002;51(1):47–51
- 21 Maegele M, Gregor S, Steinhausen E, et al. The long-distance tertiary air transfer and care of tsunami victims: injury pattern and microbiological and psychological aspects. *Crit Care Med* 2005;33(5):1136–1140
- 22 Zanetti G, Blanc DS, Federli I, et al. Importation of *Acinetobacter baumannii* into a burn unit: a recurrent outbreak of infection associated with widespread environmental contamination. *Infect Control Hosp Epidemiol* 2007;28(6):723–725
- 23 Murray CK, Yun HC, Griffith ME, Hospenthal DR, Tong M J. *Acinetobacter* infection: what was the true impact during the Vietnam conflict? *Clin Infect Dis* 2006;43(3):383–384
- 24 Munoz-Price LS, Weinstein RA. *Acinetobacter* infection. *N Engl J Med* 2008;358(12):1271–1281
- 25 Petersen K, Cannegieter SC, van der Reijden TJ, et al. Diversity and clinical impact of *Acinetobacter baumannii* colonization and infection at a military medical center. *J Clin Microbiol* 2011;49(1):159–166
- 26 Granzer H, Hagen RM, Warnke P, et al. Molecular epidemiology of Carbapenem-resistant *Acinetobacter Baumannii* complex isolates from patients that were injured during the eastern Ukrainian conflict. *Eur J Microbiol Immunol (Bp)* 2016;6(2):109–117
- 27 Tokajian S, Eisen JA, Jospin G, et al. Draft genome sequences of *Acinetobacter baumannii* strains harboring the bla<sub>NDM-1</sub> gene isolated in Lebanon from civilians wounded during the Syrian Civil War. *Genome Announc* 2016;4(1):1678–1715
- 28 Christie C, Mazon D, Hierholzer W Jr, Patterson JE. Molecular heterogeneity of *Acinetobacter baumannii* isolates during seasonal increase in prevalence. *Infect Control Hosp Epidemiol* 1995;16(10):590–594
- 29 Dexter C, Murray GL, Paulsen IT, Peleg AY. Community-acquired *Acinetobacter baumannii*: clinical characteristics, epidemiology and pathogenesis. *Expert Rev Anti Infect Ther* 2015;13(5):567–573
- 30 Leung WS, Chu CM, Tsang KY, Lo FH, Lo KF, Ho PL. Fulminant community-acquired *Acinetobacter baumannii* pneumonia as a distinct clinical syndrome. *Chest* 2006;129(1):102–109
- 31 Chen MZ, Hsueh PR, Lee LN, Yu CJ, Yang PC, Luh KT. Severe community-acquired pneumonia due to *Acinetobacter baumannii*. *Chest* 2001;120(4):1072–1077
- 32 Anstey NM, Currie BJ, Hassell M, Palmer D, Dwyer B, Seifert H. Community-acquired bacteremic *Acinetobacter pneumoniae* in tropical Australia is caused by diverse strains of *Acinetobacter baumannii*, with carriage in the throat in at-risk groups. *J Clin Microbiol* 2002;40(2):685–686
- 33 Falagas ME, Karveli EA, Kelesidis I, Kelesidis T. Community-acquired *Acinetobacter* infections. *Eur J Clin Microbiol Infect Dis* 2007;26(12):857–868
- 34 Kempf M, Rolain JM. Emergence of resistance to carbapenems in *Acinetobacter baumannii* in Europe: clinical impact and therapeutic options. *Int J Antimicrob Agents* 2012;39(2):105–114
- 35 Garnacho-Montero J, Gutiérrez-Pizarraya A, Díaz-Martín A, et al. *Acinetobacter baumannii* in critically ill patients: molecular

- epidemiology, clinical features and predictors of mortality. *Enferm Infecc Microbiol Clin* 2016;34(9):551–558
- 36 Brotfain E, Borer A, Koyfman L, et al. Multidrug resistance *Acinetobacter* bacteremia secondary to ventilator-associated pneumonia: risk factors and outcome. *J Intensive Care Med* 2016;0885066616632193
  - 37 Henig O, Weber G, Hoshen MB, et al. Risk factors for and impact of carbapenem-resistant *Acinetobacter baumannii* colonization and infection: matched case-control study. *Eur J Clin Microbiol Infect Dis* 2015;34(10):2063–2068
  - 38 Vincent JL, Rello J, Marshall J, et al; EPIC II Group of Investigators. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009;302(21):2323–2329
  - 39 Esterly JS, Griffith M, Qi C, Malczynski M, Postelnick MJ, Scheetz MH. Impact of carbapenem resistance and receipt of active antimicrobial therapy on clinical outcomes of *Acinetobacter baumannii* bloodstream infections. *Antimicrob Agents Chemother* 2011;55(10):4844–4849
  - 40 Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. Multidrug resistance, inappropriate empiric therapy, and hospital mortality in *Acinetobacter baumannii* pneumonia and sepsis. *Crit Care* 2016;20(1):221
  - 41 Tal-Jasper R, Katz DE, Amrami N, et al. Clinical and epidemiological significance of Carbapenem resistance in *Acinetobacter baumannii* infections. *Antimicrob Agents Chemother* 2016;60(5):3127–3131
  - 42 Teo J, Lim TP, Hsu LY, et al. Extensively drug-resistant *Acinetobacter baumannii* in a Thai hospital: a molecular epidemiologic analysis and identification of bactericidal Polymyxin B-based combinations. *Antimicrob Resist Infect Control* 2015;4(1):2
  - 43 Garnacho-Montero J, Dimopoulos G, Poulakou G, et al; European Society of Intensive Care Medicine. Task force on management and prevention of *Acinetobacter baumannii* infections in the ICU. *Intensive Care Med* 2015;41(12):2057–2075
  - 44 Sader HS, Farrell DJ, Flamm RK, Jones RN. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalized in intensive care units in United States and European hospitals (2009–2011). *Diagn Microbiol Infect Dis* 2014;78(4):443–448
  - 45 Martins AF, Kuchenbecker R, Sukiennik T, et al. Carbapenem-resistant *Acinetobacter baumannii* producing the OXA-23 enzyme: dissemination in Southern Brazil. *Infection* 2009;37(5):474–476
  - 46 Viana GF, Zago MC, Moreira RR, et al. ISAbal/blaOXA-23: a serious obstacle to controlling the spread and treatment of *Acinetobacter baumannii* strains. *Am J Infect Control* 2016;44(5):593–595
  - 47 Chung DR, Song JH, Kim SH, et al; Asian Network for Surveillance of Resistant Pathogens Study Group. High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. *Am J Respir Crit Care Med* 2011;184(12):1409–1417
  - 48 Kim T, Chong YP, Park SY, et al. Risk factors for hospital-acquired pneumonia caused by carbapenem-resistant Gram-negative bacteria in critically ill patients: a multicenter study in Korea. *Diagn Microbiol Infect Dis* 2014;78(4):457–461
  - 49 Le NK, Hf W, Vu PD, et al. High prevalence of hospital-acquired infections caused by gram-negative carbapenem resistant strains in Vietnamese pediatric ICUs: A multi-centre point prevalence survey. *Medicine (Baltimore)* 2016;95(27):e4099
  - 50 Hidron AI, Edwards JR, Patel J, et al; National Healthcare Safety Network Team; Participating National Healthcare Safety Network Facilities. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. *Infect Control Hosp Epidemiol* 2008;29(11):996–1011
  - 51 Koulenti D, Blot S, Dulhunty JM, et al; EU-VAP/CAP Study Group. COPD patients with ventilator-associated pneumonia: implications for management. *Eur J Clin Microbiol Infect Dis* 2015;34(12):2403–2411
  - 52 Inchai J, Pothirat C, Liwsrisakun C, Deesomchok A, Kositsakulchai W, Chalermpanchai N. Ventilator-associated pneumonia: epidemiology and prognostic indicators of 30-day mortality. *Jpn J Infect Dis* 2015;68(3):181–186
  - 53 Resende MM, Monteiro SG, Callegari B, Figueiredo PM, Monteiro CR, Monteiro-Neto V. Epidemiology and outcomes of ventilator-associated pneumonia in northern Brazil: an analytical descriptive prospective cohort study. *BMC Infect Dis* 2013;13:119
  - 54 Leblebicioglu H, Rosenthal VD, Arikian OA, et al; Turkish Branch of INICC; Findings of the International Nosocomial Infection Control Consortium (INICC). Device-associated hospital-acquired infection rates in Turkish intensive care units. *J Hosp Infect* 2007;65(3):251–257
  - 55 Gaynes R, Edwards JR; National Nosocomial Infections Surveillance System. Overview of nosocomial infections caused by gram-negative bacilli. *Clin Infect Dis* 2005;41(6):848–854
  - 56 Koulenti D, Tsigou E, Rello J. Nosocomial pneumonia in 27 ICUs in Europe: perspectives from the EU-VAP/CAP study. *Eur J Clin Microbiol Infect Dis* 2016
  - 57 Huang ST, Chiang MC, Kuo SC, et al. Risk factors and clinical outcomes of patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia. *J Microbiol Immunol Infect* 2012;45(5):356–362
  - 58 Trouillet JL, Chastre J, Vuagnat A, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. *Am J Respir Crit Care Med* 1998;157(2):531–539
  - 59 Nseir S, Blazejewski C, Lubret R, Wallet F, Courcol R, Durocher A. Risk of acquiring multidrug-resistant Gram-negative bacilli from prior room occupants in the intensive care unit. *Clin Microbiol Infect* 2011;17(8):1201–1208
  - 60 Lin CY, Chen YM, Lin MC, et al. Risk factors of multidrug-resistant *Acinetobacter baumannii* recurrence after successful eradication in ventilated patients. *Biomed J* 2016;39(2):130–138
  - 61 Apisarnthanarak A, Apisarnthanarak P, Warren DK, Fraser VJ. Is central venous catheter tips' colonization with multi-drug resistant *Acinetobacter baumannii* a predictor for bacteremia? *Clin Infect Dis* 2011;52(8):1080–1082
  - 62 Turkoglu M, Mirza E, Tunçan OG, et al. *Acinetobacter baumannii* infection in patients with hematologic malignancies in intensive care unit: risk factors and impact on mortality. *J Crit Care* 2011;26(5):460–467
  - 63 Chiang MC, Kuo SC, Chen SJ, et al. Clinical characteristics and outcomes of bacteremia due to different genomic species of *Acinetobacter baumannii* complex in patients with solid tumors. *Infection* 2012;40(1):19–26
  - 64 Fukuta Y, Muder RR, Agha ME, et al. Risk factors for acquisition of multidrug-resistant *Acinetobacter baumannii* among cancer patients. *Am J Infect Control* 2013;41(12):1249–1252
  - 65 Hsu JF, Chu SM, Lien R, et al. Case-control analysis of endemic *Acinetobacter baumannii* bacteremia in the neonatal intensive care unit. *Am J Infect Control* 2014;42(1):23–27
  - 66 Gavalda L, Soriano AM, Cámara J, et al. Control of endemic extensively drug-resistant *Acinetobacter baumannii* with a cohorting policy and cleaning procedures based on the 1 room, 1 wipe approach. *Am J Infect Control* 2016;44(5):520–524
  - 67 Young LS, Sabel AL, Price CS. Epidemiologic, clinical, and economic evaluation of an outbreak of clonal multidrug-resistant *Acinetobacter baumannii* infection in a surgical intensive care unit. *Infect Control Hosp Epidemiol* 2007;28(11):1247–1254
  - 68 Leangapichart T, Gautret P, Griffiths K, et al. Acquisition of a high diversity of bacteria during the Hajj pilgrimage, including *Acinetobacter baumannii* with blaOXA-72 and *Escherichia coli* with blaNDM-5 Carbapenemase genes. *Antimicrob Agents Chemother* 2016;60(10):5942–5948

- 69 Peleg AY, de Breijl A, Adams MD, et al. The success of *Acinetobacter* species; genetic, metabolic and virulence attributes. *PLoS One* 2012;7(10):e46984
- 70 Potron A, Poirel L, Nordmann P. Emerging broad-spectrum resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: mechanisms and epidemiology. *Int J Antimicrob Agents* 2015;45(6):568–585
- 71 Liou ML, Soo PC, Ling SR, Kuo HY, Tang CY, Chang KC. The sensor kinase BfmS mediates virulence in *Acinetobacter baumannii*. *J Microbiol Immunol Infect* 2014;47(4):275–281
- 72 Dortet L, Poirel L, Nordmann P. Worldwide dissemination of the NDM-type carbapenemases in Gram-negative bacteria. *BioMed Res Int* 2014;2014:249856
- 73 Antunes LC, Visca P, Towner KJ. *Acinetobacter baumannii*: evolution of a global pathogen. *Pathog Dis* 2014;71(3):292–301
- 74 Pagano M, Martins AF, Barth AL. Mobile genetic elements related to carbapenem resistance in *Acinetobacter baumannii*. *Braz J Microbiol* 2016;47(4):785–792
- 75 Nordmann P, Poirel L, Walsh TR, Livermore DM. The emerging NDM carbapenemases. *Trends Microbiol* 2011;19(12):588–595
- 76 Gales AC, Pfaller MA, Sader HS, Hollis RJ, Jones RN. Genotypic characterization of carbapenem-nonsusceptible *Acinetobacter* spp. isolated in Latin America. *Microb Drug Resist* 2004;10(4):286–291
- 77 Perez F, Endimiani A, Ray AJ, et al. Carbapenem-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae* across a hospital system: impact of post-acute care facilities on dissemination. *J Antimicrob Chemother* 2010;65(8):1807–1818
- 78 Perez F, Hujer AM, Hulten EA, et al. Antibiotic resistance determinants in *Acinetobacter* spp and clinical outcomes in patients from a major military treatment facility. *Am J Infect Control* 2010;38(1):63–65
- 79 Nemeč A, Dijkshoorn L, van der Reijden TJ. Long-term predominance of two pan-European clones among multi-resistant *Acinetobacter baumannii* strains in the Czech Republic. *J Med Microbiol* 2004;53(Pt 2):147–153
- 80 Vahaboglu H, Oztürk R, Aygün G, et al. Widespread detection of PER-1-type extended-spectrum beta-lactamases among nosocomial *Acinetobacter* and *Pseudomonas aeruginosa* isolates in Turkey: a nationwide multicenter study. *Antimicrob Agents Chemother* 1997;41(10):2265–2269
- 81 Woodford N, Turton JF, Livermore DM. Multiresistant Gram-negative bacteria: the role of high-risk clones in the dissemination of antibiotic resistance. *FEMS Microbiol Rev* 2011;35(5):736–755
- 82 Go ES, Urban C, Burns J, et al. Clinical and molecular epidemiology of *Acinetobacter* infections sensitive only to polymyxin B and sulbactam. *Lancet* 1994;344(8933):1329–1332
- 83 Manikal VM, Landman D, Saurina G, Oydna E, Lal H, Quale J. Endemic carbapenem-resistant *Acinetobacter* species in Brooklyn, New York: citywide prevalence, interinstitutional spread, and relation to antibiotic usage. *Clin Infect Dis* 2000;31(1):101–106
- 84 Lee SO, Kim NJ, Choi SH, et al. Risk factors for acquisition of imipenem-resistant *Acinetobacter baumannii*: a case-control study. *Antimicrob Agents Chemother* 2004;48(1):224–228
- 85 Poirel L, Nordmann P. Carbapenem resistance in *Acinetobacter baumannii*: mechanisms and epidemiology. *Clin Microbiol Infect* 2006;12(9):826–836
- 86 Mathlouthi N, Al-Bayssari C, Bakour S, Rolain JM, Chouchani C. Prevalence and emergence of carbapenemases-producing Gram-negative bacteria in Mediterranean basin. *Crit Rev Microbiol* 2017;43(1):43–61
- 87 Bush K, Jacoby GA. Updated functional classification of beta-lactamases. *Antimicrob Agents Chemother* 2010;54(3):969–976
- 88 Mehrad B, Clark NM, Zhanell GG, Lynch JP III. Antimicrobial resistance in hospital-acquired gram-negative bacterial infections. *Chest* 2015;147(5):1413–1421
- 89 Chong Y, Ito Y, Kamimura T. Genetic evolution and clinical impact in extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*. *Infect Genet Evol* 2011;11(7):1499–1504
- 90 Livermore DM, Canton R, Gniadkowski M, et al. CTX-M: changing the face of ESBLs in Europe. *J Antimicrob Chemother* 2007;59(2):165–174
- 91 Lynch JP III, Clark NM, Zhanell GG. Evolution of antimicrobial resistance among Enterobacteriaceae (focus on extended spectrum beta-lactamases and carbapenemases). *Expert Opin Pharmacother* 2013;14(2):199–210
- 92 Poirel L, Karim A, Mercat A, et al. Extended-spectrum beta-lactamase-producing strain of *Acinetobacter baumannii* isolated from a patient in France. *J Antimicrob Chemother* 1999;43(1):157–158
- 93 Naas T, Coignard B, Carbonne A, et al; French Nosocomial Infection Early Warning Investigation and Surveillance Network. VEB-1 Extended-spectrum beta-lactamase-producing *Acinetobacter baumannii*, France. *Emerg Infect Dis* 2006;12(8):1214–1222
- 94 Naas T, Bogaerts P, Bauraing C, Degheldre Y, Glupczynski Y, Nordmann P. Emergence of PER and VEB extended-spectrum beta-lactamases in *Acinetobacter baumannii* in Belgium. *J Antimicrob Chemother* 2006;58(1):178–182
- 95 Pasterán F, Rapoport M, Petroni A, et al. Emergence of PER-2 and VEB-1a in *Acinetobacter baumannii* Strains in the Americas. *Antimicrob Agents Chemother* 2006;50(9):3222–3224
- 96 Shakil S, Khan AU. Detection of CTX-M-15-producing and carbapenem-resistant *Acinetobacter baumannii* strains from urine from an Indian hospital. *J Chemother* 2010;22(5):324–327
- 97 Potron A, Muñoz-Price LS, Nordmann P, Cleary T, Poirel L. Genetic features of CTX-M-15-producing *Acinetobacter baumannii* from Haiti. *Antimicrob Agents Chemother* 2011;55(12):5946–5948
- 98 Zago MC, Viana GF, Ecker AB, et al. First report of CTX-M-15-producing *Acinetobacter baumannii* in Brazil. *J Hosp Infect* 2016;92(3):298–299
- 99 Bonnin RA, Nordmann P, Potron A, Lecuyer H, Zahar JR, Poirel L. Carbapenem-hydrolyzing GES-type extended-spectrum beta-lactamase in *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2011;55(1):349–354
- 100 Bogaerts P, Naas T, El Garch F, et al. GES extended-spectrum beta-lactamases in *Acinetobacter baumannii* isolates in Belgium. *Antimicrob Agents Chemother* 2010;54(11):4872–4878
- 101 Chihi H, Bonnin RA, Bourouis A, et al. GES-11-producing *Acinetobacter baumannii* clinical isolates from Tunisian hospitals: long-term dissemination of GES-type carbapenemases in North Africa. *J Glob Antimicrob Resist* 2016;5:47–50
- 102 Charfi-Kessiss K, Mansour W, Ben Haj Khalifa A, et al. Multidrug-resistant *Acinetobacter baumannii* strains carrying the bla(OxA-23) and the bla(GES-11) genes in a neonatology center in Tunisia. *Microb Pathog* 2014;74:20–24
- 103 Yong D, Toleman MA, Giske CG, et al. Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India. *Antimicrob Agents Chemother* 2009;53(12):5046–5054
- 104 Berrazeg M, Diene S, Medjahed L, et al. New Delhi Metallo-beta-lactamase around the world: an eReview using Google Maps. *Euro Surveill* 2014;19(20):20809
- 105 Poirel L, Marqué S, Héritier C, Segonds C, Chabanon G, Nordmann P. OXA-58, a novel class D beta-lactamase involved in resistance to carbapenems in *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2005;49(1):202–208
- 106 Rodríguez CH, Balderrama Yrhuí N, Nastro M, et al. Molecular epidemiology of carbapenem-resistant *Acinetobacter baumannii* in South America. *J Med Microbiol* 2016;65(10):1088–1091
- 107 Pagano M, Barin J, Martins AF, Zavascki AP. High endemic rates of OXA-23-producing carbapenem-resistant *Acinetobacter*

- baumannii* isolates caused by the persistence of major clones in hospitals in a Brazilian city 5 years after an outbreak. Infect Control Hosp Epidemiol 2015;36(7):860–862
- 108 Paton R, Miles RS, Hood J, Amyes SG, Miles RS, Amyes SG. ARI 1: beta-lactamase-mediated imipenem resistance in *Acinetobacter baumannii*. Int J Antimicrob Agents 1993;2(2):81–87
  - 109 Dias VC, Diniz CG, Peter AC, et al. Epidemiological characteristics and antimicrobial susceptibility among carbapenem-resistant non-fermenting bacteria in Brazil. J Infect Dev Ctries 2016;10(6):544–553
  - 110 Coelho JM, Turton JF, Kaufmann ME, et al. Occurrence of carbapenem-resistant *Acinetobacter baumannii* clones at multiple hospitals in London and Southeast England. J Clin Microbiol 2006;44(10):3623–3627
  - 111 Wareham DW, Bean DC, Khanna P, et al. Bloodstream infection due to *Acinetobacter* spp: epidemiology, risk factors and impact of multi-drug resistance. Eur J Clin Microbiol Infect Dis 2008;27(7):607–612
  - 112 Xu A, Zheng B, Xu YC, Huang ZG, Zhong NS, Zhuo C. National epidemiology of carbapenem-resistant and extensively drug-resistant Gram-negative bacteria isolated from blood samples in China in 2013. Clin Microbiol Infect 2016;22(Suppl 1):S1–S8
  - 113 Fu Y, Jiang J, Zhou H, et al. Characterization of a novel plasmid type and various genetic contexts of bla OXA-58 in *Acinetobacter* spp. from multiple cities in China. PLoS One 2014;9(1):e84680
  - 114 Merino M, Poza M, Roca I, et al. Nosocomial outbreak of a multiresistant *Acinetobacter baumannii* expressing OXA-23 carbapenemase in Spain. Microb Drug Resist 2014;20(4):259–263
  - 115 Adams-Haduch JM, Onuoha EO, Bogdanovich T, et al. Molecular epidemiology of carbapenem-nonsusceptible *Acinetobacter baumannii* in the United States. J Clin Microbiol 2011;49(11):3849–3854
  - 116 Mezzatesta ML, Caio C, Gona F, et al. Carbapenem and multidrug resistance in Gram-negative bacteria in a single centre in Italy: considerations on in vitro assay of active drugs. Int J Antimicrob Agents 2014;44(2):112–116
  - 117 Yigit H, Queenan AM, Anderson GJ, et al. Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of *Klebsiella pneumoniae*. Antimicrob Agents Chemother 2001;45(4):1151–1161
  - 118 Bradford PA, Bratu S, Urban C, et al. Emergence of carbapenem-resistant *Klebsiella* species possessing the class A carbapenem-hydrolyzing KPC-2 and inhibitor-resistant TEM-30 beta-lactamases in New York City. Clin Infect Dis 2004;39(1):55–60
  - 119 Naas T, Nordmann P, Vedel G, Poyart C. Plasmid-mediated carbapenem-hydrolyzing beta-lactamase KPC in a *Klebsiella pneumoniae* isolate from France. Antimicrob Agents Chemother 2005;49(10):4423–4424
  - 120 Baraniak A, Izdebski R, Fiett J, et al; MOSAR WP2, WP3, and WP5 Study Groups. KPC-like carbapenemase-producing Enterobacteriaceae colonizing patients in Europe and Israel. Antimicrob Agents Chemother 2015;60(3):1912–1917
  - 121 Martinez T, Martinez I, Vazquez GJ, Aquino EE, Robledo IE. Genetic environment of the KPC gene in *Acinetobacter baumannii* ST2 clone from Puerto Rico and genomic insights into its drug resistance. J Med Microbiol 2016;65(8):784–792
  - 122 Robledo IE, Aquino EE, Santé MI, et al. Detection of KPC in *Acinetobacter* spp. in Puerto Rico. Antimicrob Agents Chemother 2010;54(3):1354–1357
  - 123 Moubareck C, Brémont S, Conroy MC, Courvalin P, Lambert T. GES-11, a novel integron-associated GES variant in *Acinetobacter baumannii*. Antimicrob Agents Chemother 2009;53(8):3579–3581
  - 124 Bonnin RA, Rotimi VO, Al Hubail M, et al. Wide dissemination of GES-type carbapenemases in *Acinetobacter baumannii* isolates in Kuwait. Antimicrob Agents Chemother 2013;57(1):183–188
  - 125 Cicek AC, Saral A, Iraz M, et al. OXA- and GES-type beta-lactamases predominate in extensively drug-resistant *Acinetobacter baumannii* isolates from a Turkish University Hospital. Clin Microbiol Infect 2014;20(5):410–415
  - 126 Bonnin RA, Poirel L, Naas T, et al. Dissemination of New Delhi metallo-beta-lactamase-1-producing *Acinetobacter baumannii* in Europe. Clin Microbiol Infect 2012;18(9):E362–E365
  - 127 Castanheira M, Deshpande LM, Mathai D, Bell JM, Jones RN, Mendes RE. Early dissemination of NDM-1- and OXA-181-producing Enterobacteriaceae in Indian hospitals: report from the SENTRY Antimicrobial Surveillance Program, 2006–2007. Antimicrob Agents Chemother 2011;55(3):1274–1278
  - 128 Moellering RC Jr. NDM-1—a cause for worldwide concern. N Engl J Med 2010;363(25):2377–2379
  - 129 Centers for Disease Control and Prevention (CDC). Detection of Enterobacteriaceae isolates carrying metallo-beta-lactamase - United States, 2010. MMWR Morb Mortal Wkly Rep 2010;59(24):750
  - 130 Poirel L, Hombrouck-Alet C, Freneaux C, Bernabeu S, Nordmann P. Global spread of New Delhi metallo-beta-lactamase 1. Lancet Infect Dis 2010;10(12):832
  - 131 Poirel L, Bonnin RA, Boulanger A, Schrenzel J, Kaase M, Nordmann P. Tn125-related acquisition of blaNDM-like genes in *Acinetobacter baumannii*. Antimicrob Agents Chemother 2012;56(2):1087–1089
  - 132 Hammerum AM, Larsen AR, Hansen F, et al. Patients transferred from Libya to Denmark carried OXA-48-producing *Klebsiella pneumoniae*, NDM-1-producing *Acinetobacter baumannii* and methicillin-resistant *Staphylococcus aureus*. Int J Antimicrob Agents 2012;40(2):191–192
  - 133 El-Sayed-Ahmed MA, Amin MA, Tawakol WM, Loucif L, Bakour S, Rolain JM. High prevalence of bla(NDM-1) carbapenemase-encoding gene and 16S rRNA armA methyltransferase gene among *Acinetobacter baumannii* clinical Isolates in Egypt. Antimicrob Agents Chemother 2015;59(6):3602–3605
  - 134 Pfeifer Y, Wilharm G, Zander E, et al. Molecular characterization of blaNDM-1 in an *Acinetobacter baumannii* strain isolated in Germany in 2007. J Antimicrob Chemother 2011;66(9):1998–2001
  - 135 Ghazawi A, Sonnevend A, Bonnin RA, et al. NDM-2 carbapenemase-producing *Acinetobacter baumannii* in the United Arab Emirates. Clin Microbiol Infect 2012;18(2):E34–E36
  - 136 Espinal P, Fugazza G, López Y, et al. Dissemination of an NDM-2-producing *Acinetobacter baumannii* clone in an Israeli rehabilitation center. Antimicrob Agents Chemother 2011;55(11):5396–5398
  - 137 El-Herte RI, Kanj SS, Matar GM, Araj GF. The threat of carbapenem-resistant Enterobacteriaceae in Lebanon: an update on the regional and local epidemiology. J Infect Public Health 2012;5(3):233–243
  - 138 Kaase M, Nordmann P, Wichelhaus TA, Gatermann SG, Bonnin RA, Poirel L. NDM-2 carbapenemase in *Acinetobacter baumannii* from Egypt. J Antimicrob Chemother 2011;66(6):1260–1262
  - 139 Bonnin RA, Poirel L, Nordmann P. New Delhi metallo-beta-lactamase-producing *Acinetobacter baumannii*: a novel paradigm for spreading antibiotic resistance genes. Future Microbiol 2014;9(1):33–41
  - 140 Khorsi K, Messai Y, Hamidi M, Ammari H, Bakour R. High prevalence of multidrug-resistance in *Acinetobacter baumannii* and dissemination of carbapenemase-encoding genes blaOXA-23-like, blaOXA-24-like and blaNDM-1 in Algiers hospitals. Asian Pac J Trop Med 2015;8(6):438–446
  - 141 Mathlouthi N, El Salabi AA, Ben Jomâa-Jemili M, et al. Early detection of metallo-beta-lactamase NDM-1- and OXA-23 carbapenemase-producing *Acinetobacter baumannii* in Libyan hospitals. Int J Antimicrob Agents 2016;48(1):46–50
  - 142 Decousser JW, Jansen C, Nordmann P, et al. Outbreak of NDM-1-producing *Acinetobacter baumannii* in France, January to May 2013. Euro Surveill 2013;18(31):20547

- 143 Boulanger A, Naas T, Fortineau N, Figueiredo S, Nordmann P. NDM-1-producing *Acinetobacter baumannii* from Algeria. *Antimicrob Agents Chemother* 2012;56(4):2214–2215
- 144 Poirel L, Revathi G, Bernabeu S, Nordmann P. Detection of NDM-1-producing *Klebsiella pneumoniae* in Kenya. *Antimicrob Agents Chemother* 2011;55(2):934–936
- 145 Zhang R, Hu YY, Yang XF, et al. Emergence of NDM-producing non-*baumannii* *Acinetobacter* spp. isolated from China. *Eur J Clin Microbiol Infect Dis* 2014;33(5):853–860
- 146 Huang YM, Zhong LL, Zhang XF, et al. NDM-1-Producing *Citrobacter freundii*, *Escherichia coli*, and *Acinetobacter baumannii* Identified from a Single Patient in China. *Antimicrob Agents Chemother* 2015;59(8):5073–5077
- 147 Nakazawa Y, Ii R, Tamura T, et al. A case of NDM-1-producing *Acinetobacter baumannii* transferred from India to Japan. *J Infect Chemother* 2013;19(2):330–332
- 148 Chen Y, Zhou Z, Jiang Y, Yu Y. Emergence of NDM-1-producing *Acinetobacter baumannii* in China. *J Antimicrob Chemother* 2011;66(6):1255–1259
- 149 Yang J, Chen Y, Jia X, et al. Dissemination and characterization of NDM-1-producing *Acinetobacter pittii* in an intensive care unit in China. *Clin Microbiol Infect* 2012;18(12):E506–E513
- 150 Pagano M, Poirel L, Martins AF, et al. Emergence of NDM-1-producing *Acinetobacter pittii* in Brazil. *Int J Antimicrob Agents* 2015;45(4):444–445
- 151 Pasteran F, Mora MM, Albornoz E, et al. Emergence of genetically unrelated NDM-1-producing *Acinetobacter pittii* strains in Paraguay. *J Antimicrob Chemother* 2014;69(9):2575–2578
- 152 Montaña S, Cittadini R, Del Castillo M, et al. Presence of New Delhi metallo- $\beta$ -lactamase gene (NDM-1) in a clinical isolate of *Acinetobacter junii* in Argentina. *New Microbes New Infect* 2016;11:43–44
- 153 Waterman PE, McGann P, Snesrud E, et al. Bacterial peritonitis due to *Acinetobacter baumannii* sequence type 25 with plasmid-borne New Delhi metallo- $\beta$ -lactamase in Honduras. *Antimicrob Agents Chemother* 2013;57(9):4584–4586
- 154 Kim Y, Bae IK, Lee H, Jeong SH, Yong D, Lee K. In vivo emergence of colistin resistance in *Acinetobacter baumannii* clinical isolates of sequence type 357 during colistin treatment. *Diagn Microbiol Infect Dis* 2014;79(3):362–366
- 155 Cai Y, Chai D, Wang R, Liang B, Bai N. Colistin resistance of *Acinetobacter baumannii*: clinical reports, mechanisms and antimicrobial strategies. *J Antimicrob Chemother* 2012;67(7):1607–1615
- 156 Rhomberg PR, Jones RN. Summary trends for the Meropenem Yearly Susceptibility Test Information Collection Program: a 10-year experience in the United States (1999–2008). *Diagn Microbiol Infect Dis* 2009;65(4):414–426
- 157 Mera RM, Miller LA, Amrine-Madsen H, Sahm DF. *Acinetobacter baumannii* 2002–2008: increase of carbapenem-associated multiclass resistance in the United States. *Microb Drug Resist* 2010;16(3):209–215
- 158 Denys GA, Callister SM, Dowzicky MJ. Antimicrobial susceptibility among gram-negative isolates collected in the USA between 2005 and 2011 as part of the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.). *Ann Clin Microbiol Antimicrob* 2013;12:24
- 159 Queenan AM, Pillar CM, Deane J, et al. Multidrug resistance among *Acinetobacter* spp. in the USA and activity profile of key agents: results from CAPITAL Surveillance 2010. *Diagn Microbiol Infect Dis* 2012;73(3):267–270
- 160 Jones RN, Guzman-Blanco M, Gales AC, et al. Susceptibility rates in Latin American nations: report from a regional resistance surveillance program (2011). *Braz J Infect Dis* 2013;17(6):672–681
- 161 Lee MH, Chen TL, Lee YT, et al. Dissemination of multidrug-resistant *Acinetobacter baumannii* carrying BlaOxA-23 from hospitals in central Taiwan. *J Microbiol Immunol Infect* 2013;46(6):419–424
- 162 Lee HS, Loh YX, Lee JJ, Liu CS, Chu C. Antimicrobial consumption and resistance in five Gram-negative bacterial species in a hospital from 2003 to 2011. *J Microbiol Immunol Infect* 2015;48(6):647–654
- 163 Nordmann P, Picazo JJ, Mutters R, et al; COMPACT study group. Comparative activity of carbapenem testing: the COMPACT study. *J Antimicrob Chemother* 2011;66(5):1070–1078
- 164 Turner PJ. Meropenem activity against European isolates: report on the MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) 2006 results. *Diagn Microbiol Infect Dis* 2008;60(2):185–192
- 165 Gales AC, Jones RN, Sader HS. Contemporary activity of colistin and polymyxin B against a worldwide collection of Gram-negative pathogens: results from the SENTRY Antimicrobial Surveillance Program (2006–09). *J Antimicrob Chemother* 2011;66(9):2070–2074
- 166 Kuo SC, Lee YT, Yang SP, et al. Evaluation of the effect of appropriate antimicrobial therapy on mortality associated with *Acinetobacter nosocomialis* bacteraemia. *Clin Microbiol Infect* 2013;19(7):634–639
- 167 Ogutlu A, Guclu E, Karabay O, Utku AC, Tuna N, Yahyaoglu M. Effects of Carbapenem consumption on the prevalence of *Acinetobacter* infection in intensive care unit patients. *Ann Clin Microbiol Antimicrob* 2014;13:7
- 168 Oliveira MS, Prado GV, Costa SF, Grinbaum RS, Levin AS. Ampicillin/sulbactam compared with polymyxins for the treatment of infections caused by carbapenem-resistant *Acinetobacter* spp. *J Antimicrob Chemother* 2008;61(6):1369–1375
- 169 Jaruratanasirikul S, Wongpoowarak W, Aeinlang N, Jullangkoon M. Pharmacodynamics modeling to optimize dosage regimens of sulbactam. *Antimicrob Agents Chemother* 2013;57(7):3441–3444
- 170 Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *J Infect* 2008;56(6):432–436
- 171 Laishram S, Anandan S, Devi BY, et al. Determination of synergy between sulbactam, meropenem and colistin in carbapenem-resistant *Klebsiella pneumoniae* and *Acinetobacter baumannii* isolates and correlation with the molecular mechanism of resistance. *J Chemother* 2016;28(4):297–303
- 172 Buisson Y, Tran Van Nhieu G, Ginot L, et al. Nosocomial outbreaks due to amikacin-resistant tobramycin-sensitive *Acinetobacter* species: correlation with amikacin usage. *J Hosp Infect* 1990;15(1):83–93
- 173 Lesho E, Chukwuma U, Sparks M, et al. Anatomic, geographic, and taxon-specific relative risks of carbapenem resistance in the health care system of the U.S. Department of Defense. *J Clin Microbiol* 2016;54(6):1546–1551
- 174 Lesho EP, Waterman PE, Chukwuma U, et al. The antimicrobial resistance monitoring and research (ARMoR) program: the US Department of Defense response to escalating antimicrobial resistance. *Clin Infect Dis* 2014;59(3):390–397
- 175 Göttig S, Gruber TM, Higgins PG, Wachsmuth M, Seifert H, Kempf VA. Detection of pan drug-resistant *Acinetobacter baumannii* in Germany. *J Antimicrob Chemother* 2014;69(9):2578–2579
- 176 Pogue JM, Lee J, Marchaim D, et al. Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system. *Clin Infect Dis* 2011;53(9):879–884
- 177 Leporati M, Bua RO, Mariano F, et al. Determination by LC-MS/MS of colistins A and B in plasma and ultrafiltrate from critically ill patients undergoing continuous venovenous hemodiafiltration. *Ther Drug Monit* 2014;36(2):182–191
- 178 De Pascale G, Montini L, Pennisi M, et al. High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria. *Crit Care* 2014;18(3):R90

- 179 Rao GG, Ly NS, Bulitta JB, et al. Polymyxin B in combination with doripenem against heteroresistant *Acinetobacter baumannii*: pharmacodynamics of new dosing strategies. *J Antimicrob Chemother* 2016;71(11):3148–3156
- 180 Cheah SE, Li J, Tsuji BT, Forrest A, Bulitta JB, Nation RL. Colistin and polymyxin B dosage regimens against *Acinetobacter baumannii*: differences in activity and the emergence of resistance. *Antimicrob Agents Chemother* 2016;60(7):3921–3933
- 181 Cheah SE, Johnson MD, Zhu Y, et al. Polymyxin resistance in *Acinetobacter baumannii*: genetic mutations and transcriptomic changes in response to clinically relevant dosage regimens. *Sci Rep* 2016;6:26233
- 182 Garnacho J, Sole-Violan J, Sa-Borges M, Diaz E, Rello J. Clinical impact of pneumonia caused by *Acinetobacter baumannii* in intubated patients: a matched cohort study. *Crit Care Med* 2003;31(10):2478–2482
- 183 Batirel A, Balkan II, Karabay O, et al. Comparison of colistin-carbapenem, colistin-sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant *Acinetobacter baumannii* bloodstream infections. *Eur J Clin Microbiol Infect Dis* 2014;33(8):1311–1322
- 184 López-Cortés LE, Cisneros JM, Fernández-Cuenca F, et al; GEIH/REIPI-Ab2010 Group. Monotherapy versus combination therapy for sepsis due to multidrug-resistant *Acinetobacter baumannii*: analysis of a multicentre prospective cohort. *J Antimicrob Chemother* 2014;69(11):3119–3126
- 185 Shields RK, Clancy CJ, Gillis LM, et al. Epidemiology, clinical characteristics and outcomes of extensively drug-resistant *Acinetobacter baumannii* infections among solid organ transplant recipients. *PLoS One* 2012;7(12):e52349
- 186 Chen YM, Fang WF, Kao HC, et al. Influencing factors of successful eradication of multidrug-resistant *Acinetobacter baumannii* in the respiratory tract with aerosolized colistin. *Biomed J* 2014;37(5):314–320
- 187 Liu YY, Wang Y, Walsh TR, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *Lancet Infect Dis* 2016;16(2):161–168
- 188 Poirel L, Kieffer N, Liassine N, Thanh D, Nordmann P. Plasmid-mediated carbapenem and colistin resistance in a clinical isolate of *Escherichia coli*. *Lancet Infect Dis* 2016;16(3):281
- 189 Nordmann P, Lienhard R, Kieffer N, Clerc O, Poirel L. Plasmid-mediated colistin-resistant *Escherichia coli* in bacteremia in Switzerland. *Clin Infect Dis* 2016;62(10):1322–1323
- 190 Payne M, Croxen MA, Lee TD, et al. mcr-1-positive colistin-resistant *Escherichia coli* in traveler returning to Canada from China. *Emerg Infect Dis* 2016;22(9):1673–1675
- 191 Teo JW, Chew KL, Lin RT. Transmissible colistin resistance encoded by mcr-1 detected in clinical Enterobacteriaceae isolates in Singapore. *Emerg Microbes Infect* 2016;5(8):e87
- 192 Rolain JM, Roch A, Castanier M, Papazian L, Raoult D. *Acinetobacter baumannii* resistant to colistin with impaired virulence: a case report from France. *J Infect Dis* 2011;204(7):1146–1147
- 193 López-Rojas R, Domínguez-Herrera J, McConnell MJ, et al. Impaired virulence and in vivo fitness of colistin-resistant *Acinetobacter baumannii*. *J Infect Dis* 2011;203(4):545–548
- 194 Hua X, Chen Q, Li X, Yu Y. Global transcriptional response of *Acinetobacter baumannii* to a subinhibitory concentration of tigecycline. *Int J Antimicrob Agents* 2014;44(4):337–344
- 195 Hoban DJ, Reinert RR, Bouchillon SK, Dowzicky MJ. Global in vitro activity of tigecycline and comparator agents: Tigecycline Evaluation and Surveillance Trial 2004–2013. *Ann Clin Microbiol Antimicrob* 2015;14:27
- 196 Ku K, Pogue JM, Moshos J, et al. Retrospective evaluation of colistin versus tigecycline for the treatment of *Acinetobacter baumannii* and/or carbapenem-resistant Enterobacteriaceae infections. *Am J Infect Control* 2012;40(10):983–987
- 197 Lee YT, Tsao SM, Hsueh PR. Clinical outcomes of tigecycline alone or in combination with other antimicrobial agents for the treatment of patients with healthcare-associated multidrug-resistant *Acinetobacter baumannii* infections. *Eur J Clin Microbiol Infect Dis* 2013;32(9):1211–1220
- 198 Freire AT, Melnyk V, Kim MJ, et al; 311 Study Group. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. *Diagn Microbiol Infect Dis* 2010;68(2):140–151
- 199 Chuang YC, Cheng CY, Sheng WH, et al. Effectiveness of tigecycline-based versus colistin-based therapy for treatment of pneumonia caused by multidrug-resistant *Acinetobacter baumannii* in a critical setting: a matched cohort analysis. *BMC Infect Dis* 2014;14:102
- 200 Ye JJ, Lin HS, Yeh CF, et al. Tigecycline-based versus sulbactam-based treatment for pneumonia involving multidrug-resistant *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex. *BMC Infect Dis* 2016;16:374
- 201 Prasad P, Sun J, Danner RL, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. *Clin Infect Dis* 2012;54(12):1699–1709
- 202 Abdallah M, Olafisoye O, Cortes C, Urban C, Landman D, Quale J. Activity of eravacycline against Enterobacteriaceae and *Acinetobacter baumannii*, including multidrug-resistant isolates, from New York City. *Antimicrob Agents Chemother* 2015;59(3):1802–1805
- 203 Livermore DM, Mushtaq S, Warner M, Woodford N. In vitro activity of eravacycline against carbapenem-resistant Enterobacteriaceae and *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2016;60(6):3840–3844
- 204 Aydemir H, Akduman D, Piskin N, et al. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *Epidemiol Infect* 2013;141(6):1214–1222
- 205 Durante-Mangoni E, Signoriello G, Andini R, et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant *Acinetobacter baumannii*: a multicenter, randomized clinical trial. *Clin Infect Dis* 2013;57(3):349–358
- 206 Cheng A, Chuang YC, Sun HY, et al. Excess mortality associated with colistin-tigecycline compared with colistin-carbapenem combination therapy for extensively drug-resistant *Acinetobacter baumannii* bacteremia: a multicenter prospective observational study. *Crit Care Med* 2015;43(6):1194–1204
- 207 Hong DJ, Kim JO, Lee H, et al. In vitro antimicrobial synergy of colistin with rifampicin and carbapenems against colistin-resistant *Acinetobacter baumannii* clinical isolates. *Diagn Microbiol Infect Dis* 2016;86(2):184–189
- 208 Park GC, Choi JA, Jang SJ, et al. In vitro interactions of antibiotic combinations of colistin, tigecycline, and doripenem against extensively drug-resistant and multidrug-resistant *Acinetobacter baumannii*. *Ann Lab Med* 2016;36(2):124–130
- 209 Garnacho-Montero J, Amaya-Villar R, Gutiérrez-Pizarraya A, et al. Clinical efficacy and safety of the combination of colistin plus vancomycin for the treatment of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*. *Chemotherapy* 2013;59(3):225–231
- 210 Petrosillo N, Giannella M, Antonelli M, et al. Clinical experience of colistin-glycopeptide combination in critically ill patients infected with Gram-negative bacteria. *Antimicrob Agents Chemother* 2014;58(2):851–858
- 211 Bassetti M, Ginocchio F, Mikulska M, Taramasso L, Giacobbè DR. Will new antimicrobials overcome resistance among Gram-negatives? *Expert Rev Anti Infect Ther* 2011;9(10):909–922
- 212 Syue LS, Chen YH, Ko WC, Hsueh PR. New drugs for the treatment of complicated intra-abdominal infections in the era of increasing antimicrobial resistance. *Int J Antimicrob Agents* 2016;47(4):250–258

- 213 Higgins PG, Stefanik D, Page MG, Hackel M, Seifert H. In vitro activity of the siderophore monosulfactam BAL30072 against meropenem-non-susceptible *Acinetobacter baumannii*. *J Antimicrob Chemother* 2012;67(5):1167–1169
- 214 López-Rojas R, Sánchez-Céspedes J, Docobo-Pérez F, Domínguez-Herrera J, Vila J, Pachón J. Pre-clinical studies of a new quinolone (UB-8902) against *Acinetobacter baumannii* resistant to ciprofloxacin. *Int J Antimicrob Agents* 2011;38(4):355–359
- 215 Zhanel GG, Lawson CD, Adam H, et al. Ceftazidime-avibactam: a novel cephalosporin/ $\beta$ -lactamase inhibitor combination. *Drugs* 2013;73(2):159–177
- 216 Bassetti M, Righi E. New antibiotics and antimicrobial combination therapy for the treatment of gram-negative bacterial infections. *Curr Opin Crit Care* 2015;21(5):402–411
- 217 van Duin D, Bonomo RA. Ceftazidime/Avibactam and Ceftolozane/Tazobactam: second-generation  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations. *Clin Infect Dis* 2016;63(2):234–241
- 218 Zhanel GG, Chung P, Adam H, et al. Ceftolozane/tazobactam: a novel cephalosporin/ $\beta$ -lactamase inhibitor combination with activity against multidrug-resistant gram-negative bacilli. *Drugs* 2014;74(1):31–51
- 219 García-Salguero C, Rodríguez-Avial I, Picazo JJ, Culebras E. Can plazomicin alone or in combination be a therapeutic option against carbapenem-resistant *Acinetobacter baumannii*? *Antimicrob Agents Chemother* 2015;59(10):5959–5966
- 220 Zhanel GG, Lawson CD, Zelenitsky S, et al. Comparison of the next-generation aminoglycoside plazomicin to gentamicin, tobramycin and amikacin. *Expert Rev Anti Infect Ther* 2012;10(4):459–473
- 221 Jacobs MR, Bajaksouzian S, Good CE, et al. Novel bis-indole agents active against multidrug-resistant *Acinetobacter baumannii*. *Diagn Microbiol Infect Dis* 2011;69(1):114–116
- 222 Trzoss M, Bensen DC, Li X, et al. Pyrrolopyrimidine inhibitors of DNA gyrase B (GyrB) and topoisomerase IV (ParE), Part II: development of inhibitors with broad spectrum, Gram-negative antibacterial activity. *Bioorg Med Chem Lett* 2013;23(5):1537–1543
- 223 Yount NY, Yeaman MR. Peptide antimicrobials: cell wall as a bacterial target. *Ann N Y Acad Sci* 2013;1277:127–138
- 224 Vila-Farres X, Garcia de la Maria C, López-Rojas R, Pachón J, Giralt E, Vila J. In vitro activity of several antimicrobial peptides against colistin-susceptible and colistin-resistant *Acinetobacter baumannii*. *Clin Microbiol Infect* 2012;18(4):383–387
- 225 La Forgia C, Franke J, Hacek DM, Thomson RB Jr, Robicsek A, Peterson LR. Management of a multidrug-resistant *Acinetobacter baumannii* outbreak in an intensive care unit using novel environmental disinfection: a 38-month report. *Am J Infect Control* 2010;38(4):259–263
- 226 Mirhoseini SH, Nikaeen M, Shamsizadeh Z, Khanahmad H. Hospital air: A potential route for transmission of infections caused by  $\beta$ -lactam-resistant bacteria. *Am J Infect Control* 2016;44(8):898–904
- 227 Munoz-Price LS, Namias N, Cleary T, et al. *Acinetobacter baumannii*: association between environmental contamination of patient rooms and occupant status. *Infect Control Hosp Epidemiol* 2013;34(5):517–520
- 228 Łysakowska ME, Ciebiada-Adamiec A, Klimek L, Sienkiewicz M. The activity of silver nanoparticles (Axonnite) on clinical and environmental strains of *Acinetobacter* spp. *Burns* 2015;41(2):364–371
- 229 Martínez-Reséndez MF, Garza-González E, Mendoza-Olazarán S, et al. Impact of daily chlorhexidine baths and hand hygiene compliance on nosocomial infection rates in critically ill patients. *Am J Infect Control* 2014;42(7):713–717