Chapter 1

Multi-Drug Resistant Acinetobacter baumannii

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First Published November 21, 2016


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Introduction

In recent years multidrug resistant Acinetobacter baumannii has emerged as one of the most important nosocomial infectious agents world-wide. A. baumannii is a gram negative coccobacillus and is non motile. The organism is non fastidious, catalase positive, oxidase negative, a strict aerobe, and is widely distributed in nature in soil, water, and food. Originally named Micrococcus calcoaceticus by a Dutch microbiologist in 1911 [1], the genus Acinetobacter was established in 1971 [2].

Currently, 32 species of Acinetobacter have been distinguished most of which are not associated with human disease [3]. A subset of the species, A. calcoaceticus, A. baumannii, Acinetobacter genomic species 3, and Acinetobacter genomic species 13TU are closely related phenotypically and comprise the A. calcoaceticus – A. baumannii complex [4,5]. This group is clinically important and accounts for 80% of clinical infections caused by Acinetobacter species [6,7].

The term multi-drug resistant Acinetobacter baumannii (MRAB) varies in the literature. Common terms include multidrug resistant (MDR), extensive drug resistant (XDR), and pan-drug resistant (PDR). Historically MDR refers to resistance to three or more different classes of antibiotics, XDR refers to those organisms that are MDR as well as resistant to carbapenems, and PDR Acinetobacter is resistant to all antibiotics including colistin [8-10]. Controversy has existed over the term MDR and the most recent consensus definitions are the following: MDR refers
to an organism that is resistant to at least one antibiotic in more than three classes. XDR refers to an organism that is resistant to at least one agent in all except two classes. PDR is an organism that is resistant to all antimicrobial agents [9]. MRAB has spread rapidly in a variety of clinical settings making the choice of an appropriate antibiotic difficult [11]. Infections caused by MRAB include pneumonia, urinary tract infections, bacteremia, meningitis, endocarditis, and soft tissue infections. In addition, A. baumannii has the ability to survive on hospital surfaces and medical devices for weeks rendering infection control problematic [12]. Over recent years there have been several outbreaks of A. baumannii in hospital intensive care units (ICUs) resulting in significant mortality [13]. The CDC has identified MRAB as a serious public health threat [14]. This chapter will review recent developments in the epidemiology, early diagnosis, clinical impact, and treatment of MRAB.

**Epidemiology**

Colonization or infection with multidrug-resistant Acinetobacter species is associated with the length of hospital stay, exposure to the intensive care unit, mechanical ventilation, exposure to antimicrobial agents, invasive procedures and severe illness [15,16]. Several case control studies have demonstrated that the most important risk factors for developing MRAB are prior antibiotic exposure and mechanical ventilation [17,18]. Outbreaks of infection with A. baumannii have been associated with environmental contamination such as curtains, laryngoscope blades, patient lifting equipment, door handles, mops, and keyboards [19]. Other fomites include shared medical equipment such as respiratory care devices, humidifiers and patient care items [20]. An outbreak of A. baumannii in several ICUs was traced to the use of contaminated pressure transducers [21]. The plasmid profiles for isolates cultured from the transducers and the patients were identical. Acinetobacter infections, especially bacteremia, increase during the summer months [22,23]. A time-series analysis demonstrated an increased 17% monthly A. baumannii infection rate for each 10°F in outdoor temperature [24]. Among injured military personnel arriving at the Naval Medical Center (USA) Acinetobacter baumannii represented 63% of all isolates recovered [25] and the organism was notably high in wounds of patients with infected open tibial fractures returning from Iraq and Afghanistan [26]. In the United States Acinetobacter is responsible for 12,000 healthcare-associated infections annually. Approximately 7,000 of these infections are multidrug-resistant and are associated with 500 deaths [27].

The rapid emergence of MRAB has been impressive in part due to its long evolutionary exposure to soil organisms that produce antibiotics. In addition, conjugation, plasmids, and transposons transfer resistance genes between different strains. As seen in Table 1 the rate of carbapenem resistance has been increasing worldwide over past two decades and varies by geographic region.
Table 1: Increasing Carbepenem Resistance by Geographic Region.

<table>
<thead>
<tr>
<th>Geographic Region</th>
<th>Study</th>
<th>Time period</th>
<th>Resistance Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>CHINET</td>
<td>2006-2013</td>
<td>30.1-62.8</td>
<td>28</td>
</tr>
<tr>
<td>Taiwan</td>
<td>TNIS</td>
<td>2000-2010</td>
<td>22.0-66.8</td>
<td>29</td>
</tr>
<tr>
<td>India</td>
<td>Tertiary ICU</td>
<td>2004-2012</td>
<td>25.0-35.0</td>
<td>30</td>
</tr>
<tr>
<td>Europe</td>
<td>MYSTIC</td>
<td>1996-2006</td>
<td>18.0-42.5</td>
<td>31</td>
</tr>
<tr>
<td>Greece</td>
<td>GSSAR</td>
<td>1996-2006</td>
<td>0-85</td>
<td>32</td>
</tr>
<tr>
<td>United States</td>
<td>CDC</td>
<td>1999-2006</td>
<td>5.9-27.6</td>
<td>33</td>
</tr>
<tr>
<td>United States</td>
<td>NHSN</td>
<td>2007-2010</td>
<td>33-60</td>
<td>34</td>
</tr>
<tr>
<td>Argentina</td>
<td>SENTRY</td>
<td>1997-2010</td>
<td>6.4-84.9</td>
<td>35</td>
</tr>
</tbody>
</table>

Current data from South Korea demonstrates the proportion of carbapenem resistance in A. baumannii between 32 and 56% [36]. The rapid rise of carbapenem resistant organisms over the past decade is a clear and present danger. Therapy is difficult and increasingly relies on salvage therapy with colistin and tigecycline. Resistance to these agents is also increasing leading to pan-resistant A. baumannii [37,38].

Molecular typing methods such as pulse-field gel electrophoresis (PFGE), amplified fragment length polymorphism (AFLP) analysis, multiple-locus variable-number tandem repeat analysis (MLVA), multilocus sequence typing (MLST), polymerase chain reaction (PCR) and whole-genome sequencing (WGS) have been used to study the molecular epidemiology of A. baumannii [39,40]. PFGE analysis is widely used to investigate clonal outbreaks, whereas AFLP and MLVA are higher resolution typing methods that analyze DNA polymorphisms. These later techniques are more expensive and technically demanding than PFGE [39]. PCR and whole genome sequencing methodologies are used to study strain phylogeny and large-scale epidemiology [39]. MLST is helpful in determining the population structure and global epidemiology of bacteria, and has organized the population structure of A. baumannii into nine distinct clonal lineages worldwide [39]. Three clonal organisms (WW1, WW2, WW3) have been identified globally and predominate in the US and Europe [41]. Universally, the gene most associated with carbapenem resistance is blaOXA-23 [42].

In recent years the epidemiology of A. baumannii has expanded with infections spreading to conventional wards [42] and long term care facilities [43,44]. In addition, the organism has become an important source of community-acquired pneumonia [45,46] and soft tissue infection [47]. Potential community reservoirs of A. baumannii include human skin [48,49], pets [50], farm animals [51], and body lice [52,53].

Mechanisms of Resistance to Antibiotics

The emergence and spread of MRAB is of great concern due to lack of an effective treatment regimen. These opportunistic nosocomial organisms are particularly worrisome in critical care units and in immunocompromised
patients. There are three clonal complexes (I, II, and III) that are responsible world wide for the majority of hospital outbreaks caused by A. baumannii [54-56]. Though considered an organism of low virulence A. baumannii has become a very important pathogen due to its ability to rapidly acquire resistance through lateral transfer (plasmids, transposons, integrons) and its ability to survive on surfaces in hostile environments for several weeks [56].

Several A. baumannii strains have been sequenced [56] and the multi-resistant isolate AYE was found to have an 86-kb resistance island (AbaR) containing several mobile genetic elements (45 gene cluster) for antibiotic and heavy metal resistance [56,57]. Other large genomic islands include R2, R3, and R5 that have been acquired from other gram negative species such as Pseudomonas, Salmonella, and Escherichia [3,57]. The ease at which A. baumannii acquires exogenous genes (expansion of dispensable genome) will lead to rapid expansion of the A. baumannii pan genome as novel sequences are made available. Thus A. baumannii is considered to have an open pan-genome, and it is expected that the organism will evolve toward enhanced pathogenicity [58].

A. baumannii strains use various mechanisms to counter antibiotic toxicity with inactivating enzymes serving a more important role than efflux pumps [59]. Several resistance mechanisms are specific to a single class of antimicrobial agents or may combine to resist a particular class of antibiotic. The major resistance modalities include target site modification, efflux pumps, β-lactamases, aminoglycoside-modifying enzymes and permeability defects (Table 2).

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Antibiotic</th>
<th>Gene</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target site modification</td>
<td>Methicillin</td>
<td>mecA</td>
<td>Penicillin-binding protein alteration</td>
</tr>
<tr>
<td></td>
<td>Quinolone</td>
<td>gyrA, parC [60]</td>
<td>DNA gyrase mutation</td>
</tr>
<tr>
<td></td>
<td>Tetracycline</td>
<td>tetM, armA [60]</td>
<td>Ribosomal protection</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim</td>
<td>folA, dfr, dbf [60]</td>
<td>Dihydrofolate reductase</td>
</tr>
<tr>
<td></td>
<td>Aminoglycoside</td>
<td>armA, RmtA [61]</td>
<td>16s rRNA methyltransferase</td>
</tr>
<tr>
<td>Efflux pumps</td>
<td>Tigecycline</td>
<td>AdeABC, AdeIJK, AdeF-GH [61]</td>
<td>Membrane transport of antibiotic out of cell</td>
</tr>
<tr>
<td></td>
<td>Quinolone</td>
<td>AdeABC, AdeIJK, AdeF-GH, Ahec, AbeM [61]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aminoglycosides</td>
<td>adeB [61]</td>
<td></td>
</tr>
<tr>
<td>β-lactamases</td>
<td>Cephalosporins</td>
<td>AmpC [62]</td>
<td>Cephalosporinase</td>
</tr>
<tr>
<td></td>
<td>Carbapenems</td>
<td>OXA-23, OXA-51 [61]</td>
<td>Carbapenemase</td>
</tr>
<tr>
<td></td>
<td>Aminoglycoside modifying</td>
<td>Aminoglycosides</td>
<td>aadC1, aadA1, aacA4 [60]</td>
</tr>
<tr>
<td>Permeability defects</td>
<td>β-lactams</td>
<td>OmpA [60,61]</td>
<td>Reduced membrane permeability to antibiotic</td>
</tr>
</tbody>
</table>

In the past A. baumannii has been viewed as a pathogen of low virulence however, the organism is one of the most successful human pathogens [62]. A. baumannii contains virulence factors which allow it to survive for long periods on surfaces, to attach to epithelial cells, insulate itself against immune response by biofilm formation, utilize host nutrients, and colonize and invade host cells [63-70].

The ability of A. baumannii to form a biofilm allows its attachment to abiotic surfaces such as medical devices as
well as host tissue [71,72]. Rodriguez-Bano et al. demonstrated in a multicenter study that all catheter related urinary tract infections and bacteremias due to A. baumannii were associated with biofilm-forming strains [73]. The biofilm-associated protein (Bap) is important in biofilm production and adhesion to human epithelial cells, and its inhibition can prevent A. baumannii infection [74]. Exopolysaccharide, a component of biofilm, interferes with the function of neutrophils [75]. The Omp A protein and phospholipases permit A. baumannii to invade eukaryotic cells leading to apoptosis [76,77]. Acinetobacter secretes the siderophore acinetobactin which is important in iron uptake [78,79]. Some patients exhibit an exaggerated response to Acinetobacter baumannii leading to systemic inflammatory response syndrome, septic shock, or disseminated intravascular coagulation. This severe pro-inflammatory response is caused by A. baumannii polysaccharide via Toll Like Receptor-4 (TLR-4) [80]. Other important virulence factors include quorum sensing, zinc uptake, surface motility, and stress resistance [81].

**Early Diagnosis of MRAB**

Due to increasingly limited antibiotic choice MDR-AB is difficult to treat and is associated with morbidity and mortality. Several studies have demonstrated that a delay in effective antibiotic administration leads to poor outcomes [82]. Historically definitive diagnosis and antibiotic sensitivities depended on culture results that take 48-72 hours. It is customary to start broad-spectrum antibiotic treatment on an empiric basis while awaiting a definitive microbial diagnosis. Once a definitive diagnosis is made the antibiotic regimen is then adjusted to provide the specific therapy. Empiric treatment leads to potential problems of possible ineffective antibiotic treatment, increased antibiotic resistance, and increased costs [83,84]. The most widely used test for identification and antibiotic sensitivity for microorganisms determine phenotypic resistance by growth in the presence of the antibiotic of interest. There are several commercial products available based on broth microdilution, antimicrobial gradient methods (e.g. Etest strips), and disc diffusion [85]. Rapid diagnosis of A. baumannii would not only lead to improved outcomes and decreased cost, but would also assist with antibiotic stewardship by reducing the use of ineffective therapy [86].

**Polymerase Chain Reaction (PCR) Based Techniques**

PCR-based techniques utilize genetic sequence amplification and analysis to identify microorganisms. Initially PCR was used as a rapid (several hours) test to identify and quantify A. baumannii, however with the discovery of genomic resistance islands and other determinants of resistance, PCR is now used to determine antibiotic resistance patterns [87,88]. PCR has been especially useful in identifying a number of cephalosporinase and carbe-
nepemase genes [89-91]. Gadsby et al. demonstrated an accurate PCR assay for several bacterial pathogens including A. baumannii in lower respiratory tract infections. In this study PCR was found to have 100% concordance with culture positive sputum specimens [92]. PCR can be performed on clinical samples without the need for purity cultures and significantly reduces the time required to identify a specific organism and its antibiotic sensitivity profile. Real-time PCR can also quantify the number of copies of a specific nucleic acid sequence and the information can be used to measure bacterial growth. One of the problems with PCR is discordance between resistance genes and its phenotypic expression [85]. Some carbapenemases (Oxa51) may be in the A. baumannii genome but the phenotype resistance depends on its level of expression. Another problem with PCR is that it will not detect new resistant variants unless the genetic determinant sequence is known [93,94].

Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight Mass Spectrometry (MALDI-TOF MS)

MALDI-TOF MS is laser irradiation of a sample matrix and identification of molecules according to their time of flight through a vacuum tube. Molecules are identified based on their mass/charge ratio (m/z) and a spectrum is created which is then compared to a reference database. This technology has been used to detect small molecules, lipids, peptides, and proteins [95-102]. MALDI-TOF can be used to rapidly identify Acinetobacter and to determine its antibiotic sensitivity. The hydrolysis products of antibiotics exposed to A. baumannii can be measured using MALDI-TOFMS and correlated to the activity of β lactamase [103]. Kemph et al. report a sensitivity and specificity of 100% using imipenem to identify carbapenem resistance in A. baumannii [104].

It is important to distinguish closely related members of A. baumannii strains such as A. baumannii, A. pittii, and A. nosocomialis because of differences in presentation and outcome [105]. Biochemical phenotypic tests are often inadequate to distinguish between these strains and genetic tests are labor intensive [106]. MALDI-TOFMS analysis is able to detect differences in their protein spectra to permit accurate identification in several minutes [106]. Mencacci et al. showed that MALDI-TOF is faster than DNA-based tests for identifying outbreaks of A. baumannii [107]. This technique has also been used for the rapid detection of carbapenemase activity directly from positive blood culture vials [108].

Microarrays

A microarray is a solid support upon which is fixed many known oligonucleotide sequences (probes) which hybridize to complementary oligonucleotides (targets) belonging to specific nucleic acid sequences. Thousands of probes can be assembled closely together and hybridization with the complimentary target oligonucleotide can be monitored using different fluorescent tags. Using this
technique, thousands of sequences can be determined in a single assay by noting the colors of the corresponding tags.

Microarrays can be created to detect large numbers of resistant genes present in bacterial isolates whereas PCR can only detect a few genes [109]. Dally et. al developed a DNA microarray for the simultaneous detection of 91 resistance determinants in A. baumannii. The assay is accurate and reliable in predicting the resistance phenotype of clinical A. baumannii isolates [109]. Microarrays have been used for rapid high-throughput identification of carbapenemase genes [110], and efflux pumps [111,112]. This technique has also been used to study transcriptional changes associated with virulence such as iron acquisition mechanisms [113].

Digital Microscopy

Digital microscopy is a technique that detects immobilized live bacteria on a transparent surface and monitors the growth rate and mass of each growing clone over several hours. When combined with fluorescence in situ hybridization (FISH) multiple organisms can be identified in the same sample. Automated microscopy can be used to acquire time-lapse images of the organism and an algorithm then converts the growth rate into an MIC for each antibiotic [114]. Multiplexed automatic digital microscopy (MADM) has been shown to be rapid (4 hours) and sensitive compared to conventional microbiology techniques. MADM demonstrated its potential in analyzing highly resistant A. baumannii isolates directly from specimens. Not only can the antibiotic sensitivity be determined, but the quantity of bacteria in the specimen can be calculated as well [115].

Price et al. used MADM to rapidly identify (2 hours) multidrug resistant organisms that infect wounded soldiers. She has demonstrated a 97% sensitivity and specificity in blood cultures, and has performed antibiotic susceptibility testing within 5 hours for several organisms including A. baumannii [116]. MADM has also been used for surveillance of broncho-alveolar lavage (BAL) samples in order to detect pneumonia in at-risk mechanically ventilated patients [117].

Microfluidics and Nanotechnology

Microfluidics and nanoscale techniques are evolving as diagnostic and antibiotic sensitivity test (AST) methods. Weibull et al. have studied the use of a nanowell slide and real-time processing of optical data to develop a multiplex AST device. The MIC of several antibiotics was determined for E. coli within 4 hours [118]. Choi et al. used microfluidic agarose channels and microscopy to monitor the growth of single organisms by time lapse imaging [119]. In addition to microscopy and electrochemical quantification, pH sensing [120] has been developed to detect microbial growth curves and perform rapid AST. These techniques allow sensitivities to be determined
within 2 hours and a greater than 90% percent agreement with standard antibiotic susceptibility testing methods. Another promising microfluidic technique for AST is the use of asynchronous magnetic bead rotation (AMBR) to measure the change in environmental viscosity due to bacterial growth. Using AMBR, Sinn et al. successfully determined the MIC of a uropathogenic E. coli isolate within 100 minutes [121]. If this technique can be adapted to analyze several isolates simultaneously from clinical samples it will provide point of care AST for many microbial infections including multi-resistant A. baumannii.

Clinical Implications and Cost

The rise of Gram-negative infections such as multi drug resistant A. baumannii (MRAB) presents a formidable challenge to global health. Several authors have suggested that the return to a pre antibiotic era is on the horizon if effective treatments are not instituted [122-124]. MRAB causes health-care associated infection and often complicates the care of critically ill, immune-compromised patients, and in patients receiving invasive procedures treated with broad spectrum antibiotics [63]. A. baumannii is an increasing cause of ventilator associated pneumonia, urinary tract infections, and bacteremia. A survey of European intensive care units demonstrated that Acinetobacter spp. account for 21.8% of pneumonias, 17.1% of bacteremias, and 11.9% of urinary tract infections [125]. Acinetobacter is also frequently isolated in skin and soft tissue infections as well as the intraperitoneum and central nervous system. The impact of MRAB has recently been highlighted in combat-associated wounds in Iraq and Afghanistan [126].

In recent years carbapenems have been the drugs of choice for treating Acinetobacter due to resistance to other beta-lactams, aminoglyocides, and quinolones [127]. In a systematic review and meta-analysis Lemos et al. reported that patients with carbenicillin resistant A. baumannii have higher mortality rates than patients having sensitive strains [128]. This analysis was confounded by severity of illness and inappropriate empirical antibiotic treatment as well as small sample size in many of the studies. The crude mortality rate of resistant A. baumannii has been reported to be 26-58% [129,130]. In a case control study of MRAB bacteremia Gulen et al. determined a crude mortality rate of 52.4% and an attributable mortality rate of 24.4% [131]. In this study there was an increase in mean hospitalization and antibiotic costs in cases vs. controls which did not reach statistical significance. In a well matched case control study Abbo et al. report increased in-hospital mortality, length of stay, need for mechanical ventilation, and reduced functional status at discharge from hospital [132]. This study adds to the evidence that MRAB is independently associated with poor outcomes. Another study by Gu et al. demonstrated that patients with malignancies (especially hematologic) have higher mortality due to MRAB [133].
Several studies have demonstrated increased cost associated with MRAB. Lee et al. found that MRAB (cases) and non-MRAB (controls) differed significantly with regard to length of hospital stay (54.2 vs. 34.1 days; P=.006), hospitalization cost ($9,349 vs. $4,865; P=.001), and antibiotic therapy cost ($2,257 vs. $1,610; P=.014). This study concludes that MRAB bacteremia is associated with an increase of 13.4 hospital days and $3,758 increase in costs [134]. Economic modeling has been used to estimate the financial burden of A. baumannii to hospitals [135]. Over a one year period (2006-2007) 28,502 healthcare-associated infections were reported by 463 hospitals to the National Healthcare Safety Network. Of these infections 902 (2.7%) were caused by A. baumannii at an estimated cost of $7.4 million to $26.1 million. This represents a significant economic burden for hospitals that must invest in infection control to prevent outbreaks of MRAB.

There is a sizable financial burden associated with the implementation of a strict policy to control the spread of multi drug resistant organisms. In a French study, the average cost per case ranged from $4887 for a single case to $14,129 per case in an outbreak. Interruption of normal admission activity was the most costly measure in an outbreak representing 81.7% of the overall cost. Additional staffing requirements (8.7%), laboratory costs (6.6%), and contact precautions (3%) accounted for the remaining costs [136].

Treatment Options

Due to limited options for effective therapy carbapenem-resistant A. baumannii is named as nosocomial pathogen of concern by the Infectious Diseases Society of America (IDSA) [137]. The majority of MRAB strains are resistant to penicillin derivatives, macrolides, cephalosporins, ciprofloxacin and chloramphenicol. There continues to be unreliable susceptibility to aminoglycosides, sulbactam, piperacillin/tazobactam and quinolones, and single-drug therapy often results in high rates of failure [138]. Previously, carbapenems have been the preferred antimicrobial drugs for the management of A. baumannii, however the emergence of resistance to carbapenem has lead to the consideration of other therapies. Resistance to carbapenem is often a proxy for resistance to all other commonly used antibiotics [139].

Colistin and polymyxin B are cationic polypeptides and their mechanism of action involves damage to the bacterial outer membrane through interference with lipopolysaccharide [140]. Colistin is a mainstay of therapy for MRAB however complications arise due to its unpredictable pharmacokinetics and emergence of colistin resistance resulting in treatment failures [141]. Colistin can be administered via the intravenous route or as an inhalant. For adults with normal creatinine clearance the dose is 2.5 to 5 mg/kg/day as an intravenous colistin base in two to four doses. Colistin does not cross the blood-brain barrier in sufficient concentration thus may be given by intrathecal or intra-ventricular routes [141]. Nephrotox-
Antimicrobial Resistance

Combination therapy with polymyxins (colistin or polymyxin B) and tigecycline, a carbapenem, or sulbac-tam has proved helpful in combating MRAB [143]. A retrospective study from Turkey demonstrated a lower mortality rate (52.3% vs.72.2%, p=.03) with combination therapy compared to colistin monotherapy [139]. An in vitro study by Park et al. has also noted synergistic therapy using colistin in combination with doripenem and tigecycline [143]. Combination therapy using colistin and rifampin was initially thought to be effective for MRAB however a multi-center, randomized study demonstrated no survival benefit [144].

Several novel combination therapies for MRAB under development include polymyxin and netropsin (an anti-tumor and antiviral drug) [145], carbapenem and plazomycin (a next generation aminoglycoside) [146], colistin and vancomycin [147], and sulperazone and tanreqing [149]. Sulperazone is a mixture of cefoperazone and sulbac-tam; tanreqing consists of radix scutellariae, bear bile powder, cornu gorais, honeysuckle and fructus forsythia. Tanreqing has been studied in China and shown to help resolve respiratory secretions, enhance the immune system, and is bacteriostatic to many pathogenic microbes [148]. The combination of colistin and vancomycin is unusual since vancomycin cannot normally penetrate the Gram negative cell membrane. Colistin increases the permeability of the outer membrane thus allowing vancomycin to access the periplasmic space in an adequate concentration to exert its bacteriocidal effect [147].

In addition to the search for more effective antimicrobial agents to treat MRAB, the development of non-antibiotic therapies is an active area of research. The A. baumannii antigen, Ompp1 is being investigated as a novel protective vaccine to prevent MRAB infection. Ompp1 was partially successful (60%) in preventing a murine model of pneumonia [149]. Other potential treatments include bactericidal gene transfer therapy [150], phage therapy with phi AB2 [151], and natural ginger extracts [152].

Summary

Acinetobacter baumannii infection has become a serious health problem worldwide. In the U.S. alone this organism is responsible for over 7000 hospital-acquired infections and more than 500 deaths [14]. In one U.S. city hospital researchers report 72% of A. baumannii isolates were multidrug resistant [10]. Multi-drug resistant Acinetobacter baumannii epitomizes the organisms responsible for the feared post antibiotic era. The emergence of MRAB represents a perfect storm of multiple antibiotic resistance mechanisms, protective biofilm formation and other virulence factors, as well as the ability to survive environmental adverse conditions for prolong periods. Significant progress has been achieved over the past two dec-
ades with respect to defining the epidemiology of MRAB and its genomic and phenotypic profiles. In addition, we now have several diagnostic tools for early detection and surveillance as well as sensitive assays to determine antibiotic sensitivities. The reduction in time to definitive diagnosis from 48 hours using traditional culture methods to 4 hours using molecular assays is a significant advance. We have not made significant progress, however, with respect to effective antibiotic therapy. Carbapenems, the mainstay of therapy over the past decade have become unreliable and drug combinations with colistin along with other agents are now in vogue. Research efforts are intensifying to find new effective antibiotics and non-antibiotic therapy such as vaccines, phage and gene therapies, and natural extracts. While we await the development of effective therapy we must intensify our infection control efforts such as contact precautions, hand washing, and alcohol hand decontamination in order to prevent MRAB outbreaks.

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