Novel therapies for treatment of multidrug-resistant Acinetobacter baumannii skin infections

Mircea Radu Mihu and Luis R. Martinez

1Department of Medicine; Sound Shore Medical Center of Westchester; New Rochelle, NY USA; 2Department of Biomedical Sciences; Long Island University–C.W. Post Campus; Brookville, NY USA; 3Departments of Medicine (Division of Infectious Diseases) and Microbiology and Immunology; Albert Einstein College of Medicine; Bronx, NY USA

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The Gram-negative coccobacillus Acinetobacter baumannii (Ab) has become an increasingly prevalent cause of hospital-acquired infections during the last two decades, primarily resulting in pneumonia and complicated infections, including wound infections in troops injured in Afghanistan and Iraq. Moreover, the majority of clinical Ab isolates display high-level resistance to commonly utilized antimicrobial drugs, which severely compromises our capacity to care for patients with Ab disease. Thus, radically new approaches are urgently needed. This review focuses on novel therapies that can challenge the evolving ability of Ab to develop resistance and cause disease.

Clinical Importance of Acinetobacter baumannii

Acinetobacter baumannii (Ab) is a Gram-negative coccobacillus that has emerged as one of the most troublesome causative agents of hospital-related infections in the world. The current clinical spectrum of Ab infections primarily encompasses diverse nosocomial illnesses, including intensive care unit (ICU)-acquired pneumonia, bloodstream infections, urinary tract infections, meningitis and in rare cases, endocarditis. Additionally, the microbe is responsible for the majority of community-acquired pneumonia in certain tropical climates. More recently, it has been associated with infected traumatic wounds acquired in battlefield and natural disaster conditions.

Moreover, there is significant morbidity and mortality associated with this opportunistic microbe. In the United States (US), Ab ICU-acquired pneumonia is usually encountered in 5–10% of patients receiving mechanical ventilation. More than 35% of ICU patients with bloodstream infections die. Both ICU-related conditions typically have late onsets after prolonged hospitalization and prior antibiotic exposure. Mortality from post-neurosurgical Ab meningitis in patients with external ventricular shunts may be as high as 70%. Community-acquired pneumonia affects alcoholics in tropical regions primarily during rainy season and frequently leads to systemic infection and has a mortality rate of ~50%. The organism causes 2.1% of ICU-acquired skin/soft tissue infections and has been isolated from >30% of combat victims with open tibial fractures in Iraq or Afghanistan.

To exacerbate the problem, during the last decade the number and incidence of multidrug-resistant Ab strains has increased considerably. Ab is generally intrinsically resistant to a number of commonly used antibiotics, including aminopenicillins, first- and second-generation cephalosporins and chloramphenicol. It also has a remarkable capacity to acquire resistance to broad-spectrum β-lactams, aminoglycosides, fluoroquinolones and tetracyclines. Of particular concern is resistance to carbapenems—broad-spectrum β-lactams that were introduced in 1985 and that, for years, have been the most important agents for the treatment of infections caused by multidrug-resistant (MDR) Ab. Although clinical Ab isolates were shown to be invariably susceptible to carbapenems in early studies, hospital outbreaks caused by carbapenem-resistant strains were reported by the early 1990s and currently, the frequency of these strains in some areas can exceed 25%. Recently, bacteria resistant to all available antibiotics, including polymyxins and tigecycline, have been described, indicating that Ab can cause infections that are fully refractory to the currently available antimicrobial armory.

At present, MDR Ab has emerged as a common problem in many hospitals in the US and Europe. As a result of its resistance to most antibiotics available, Ab infections are difficult and costly to treat; therefore, radically new approaches are urgently needed for its eradication. This review describes recent advances in developing novel therapies for treatment of MDR Ab with special emphasis on skin infections.

Persistence of Acinetobacter baumannii in Hospitals

The most striking manifestation of Ab is the current endemic and epidemic occurrence of MDR strains in hospitals. An epidemic strain is most commonly introduced by a patient who is colonized. Once on a ward, the strain can then spread to other patients and their environment. Ab can survive in dry conditions and during outbreaks has been recovered from various sites in the patients’ environment, including bed curtains, furniture and hospital equipment. These observations and the subsequent successes that cleaning and disinfecting patients' rooms has had in halting outbreaks emphasizes the role of the hospital environment as a reservoir for Ab during outbreaks. Ab can disperse through the air over short distances in water droplets and in scales of skin from colonized patients, but the most common
mode of transmission is from the hands of hospital staff.\textsuperscript{21-23} Patients who are colonized or infected by a particular \textit{Ab} strain can carry this strain at different body sites for periods of days to weeks, and colonization can go unnoticed if the epidemic strain is not detected in clinical specimens.\textsuperscript{24,25}

**Acinetobacter baumannii Mechanisms of Antimicrobial Resistance**

The resistance of \textit{Ab} to antimicrobial agents is mediated by all of the major resistance mechanisms known to occur in bacteria, including modification of target sites, enzymatic inactivation, active efflux and decreased influx of drugs (reviewed in ref. 11). Additionally, NaCl, a monovalent cation largely found in our skin, has recently been associated with enhanced \textit{Ab} multidrug resistance.\textsuperscript{26} Carbapenem resistance is the best example that demonstrates the variety of mechanisms that provide resistance of \textit{Ab} to a particular group of antibiotics.\textsuperscript{12} This microbe produces metallo-\textit{β}-lactamases (VIM-, IMP- and SIM-types), which have been reported worldwide and confer resistance to most \textit{β}-lactams.\textsuperscript{27,28} Nevertheless, the most widespread carbapenemases in \textit{Ab} are class D \textit{β}-lactamases.\textsuperscript{11} In addition to the intrinsic OXA-51-like enzymes, three unrelated groups of these carbapenem-hydrolysing oxacillinases have been distinguished, which are represented by OXA-23, -24 and -58, respectively. Reduced susceptibility to carbapenems has also been associated with the modification of penicillin-binding proteins and porins or with upregulation of the AdeABC efflux system, and it has been suggested that the interplay of different mechanisms might result in high-level carbapenem resistance in \textit{Ab}.\textsuperscript{29} Interestingly, most genes that encode inactivating enzymes and specific efflux pumps are present only in some strains and are associated with genetic elements such as transposons, integrons or plasmids, which suggest they were acquired by horizontal transfer.\textsuperscript{30} A few of these resistance genes are specific for the genus Acinetobacter whereas others are shared with other genera, specifically Gram-negative bacteria.

**Host-Acinetobacter baumannii Interactions**

There is little information about the mechanisms of \textit{Ab} interaction with human hosts. Environmental survival and growth require attributes such as resistance to desiccation, versatility in growth requirements, biofilm-forming capacity and, probably, quorum-sensing activity.\textsuperscript{15,31-35} Also, adequate stress-response mechanisms are presumably required for adaptation to different conditions. Outgrowth on mucosal surfaces and medical devices, such as intravascular catheters and endotracheal tubes, can result in biofilm formation, which enhances the risk of infection of the bloodstream and airways.\textsuperscript{32} Survival and growth on host skin and mucosal surfaces require that the organisms can resist antibiotics and inhibitory agents and the conditions that are exerted by these surfaces. After invasion, the presence of a polysaccharide capsule might protect \textit{Ab} against phagocytic cells.\textsuperscript{36} Iron-acquisition mechanisms and resistance to the bactericidal activity of human serum are considered to be important for survival in the blood during bloodstream infections.\textsuperscript{37-39} In vitro studies using bronchial epithelial cells have shown that the microbe uses fimbriae, phospholipase D, and the outer membrane protein A (Omp A) to adhere and colonize host cells.\textsuperscript{33,40,41} One other virulence factor studied is the outer membrane protein 38 (Omp 38) which can induce apoptosis of epithelial cells in early stages of infection.\textsuperscript{42} Additionally, TLR2 and TLR 4 receptor stimulation by lipopolysaccharide endotoxin promotes inflammatory signaling in human monocyctic cells.\textsuperscript{43}

**New Generation of Antibiotics against Acinetobacter baumannii**

Combination therapy has been studied as a possible solution of the resistant \textit{Ab} challenge with few studies reporting promising results such as with the use of colistin-rifampin and carbapenem-sulbactam combinations.\textsuperscript{44,45} However, new antibiotics to be used alone or in combination are being developed in an effort to combat increasingly resistant microorganisms and some have demonstrated good in vitro efficacy against resistant strains of \textit{Ab}. For example, fimafloxacin is a novel flooroquinolone that has shown superior activity as compared to ciprofloxacin against ciprofloxacin-sensitive and ciprofloxacin-resistant \textit{Ab} strains in acidic conditions and comparable efficacy at normal pH, with possible application in the treatment of infections at acidic body compartments.\textsuperscript{46} The most recent member of the carbapenem family, doripenem, has been found to have significant bactericidal activity in combination with polymyxin B and rifampin against strains of \textit{Ab} resistant to carbapenems and rifampin alone, with the triple therapy showing potential for inhibiting other resistant Gram negative bacteria as well.\textsuperscript{47} Since combination therapy of \textit{Ab} has recently been extensively reviewed in references 48 and 49, we will focus on other novel approaches for treatment.

**Novel Therapies for Treatment of Acinetobacter baumannii**

Bactericidal gene transfer therapy. Gene transfer therapy consists of designing plasmids containing bactericidal genes that can be introduced into recipient pathogenic organisms by conjugation using attenuated donor cells.\textsuperscript{50} The expression of the bactericidal genes on the conjugative plasmid is repressed while in the host cells, but becomes de-repressed once transferred to the bacterial cell and induces lethal effects by disruption of essential activities such as protein synthesis. The efficacy of this method has been demonstrated using a murine burn infection model where the animals were infected with a MDR strain of \textit{Ab}. Mice treated with a single dose of 10\textsuperscript{6} CFU of donor cells containing bactericidal genes had fewer \textit{Ab} in burn wounds compared to untreated mice.\textsuperscript{50} The likelihood of developing resistance to this therapy is considered to be low because the bactericidal genes disrupt the entire bacterial genome within one or two cell cycles. However, the therapeutic use is limited to infected wound surfaces, since the donor cells need to come in contact with the pathogen to conjugate and transfer genetic material.
Bioengineered human skin tissue. An innovative approach to combat *Ab* wound infections utilizes bioengineered human skin tissue able to produce host defense peptides with antimicrobial activity. For instance, Thomas-Virnig et al. constructed genetically engineered non-tumorigenic, pathogen-free human keratinocyte progenitor cells (NIKS) capable of synthesizing elevated levels of human cathelicidin hCAP-18.\(^5\) When the skin is damaged, keratinocytes produce host defense peptides such as cathelicidins and defensins, important in skin homeostasis and wound healing.\(^2\) The hCAP-18 is the only cathelicdin described in humans to date.\(^5\) hCAP-18 is produced as a precursor in epithelial cells, and further cleaved by skin and leukocyte derived enzymes to a peptide that has broad range antimicrobial activity.\(^5\) Using an *Ab*-infected murine burn wound model, application of NIKS:hCAP-18 cells significantly reduced the bacterial burden compared to controls. However, the major advantage of using NIKS:hCAP-18 cells was that enhanced production of cathelicidin supported wound healing by increasing angiogenesis and stimulation of growth and migration of keratinocyte.\(^5\)

**Nitric oxide-releasing nanoparticles.** An inexpensive and stable nitric oxide (NO)-releasing nanoparticle (NO-np) platform using nanotechnology based on a silane hydrogel has been recently developed.\(^5\) This technology has the potential to serve as a novel easily applied topical class of antimicrobials, such as NO, for the treatment of complex cutaneous infections and wounds. In the healthy state and under pathologic conditions, it is well established that NO maintains skin homeostasis by regulating circulation, ultraviolet-mediated melanogenesis, sunburn erythema and the maintenance of the protective barrier against microorganisms.\(^5\) Notably, NO modulates immune responses and is a significant regulator of wound healing.\(^5,6\) In this regard, Mihu et al. studied the biological effect of the NO-np against *Ab* using a murine wound and soft tissue models.\(^5\) Compared to control animals, NO-np-treated mice had significant reductions in bacterial CFUs, enhanced wound healing rates and histologic sections revealed NO-np-treated wounds had decreased suppurative inflammation, minimal bacterial burden and less collagen degradation by bacterial collagenases, providing potential mechanisms for biological activity. Furthermore, NO-np treatment alters the local cytokine milieu to the benefit of the host. In fact, the simplicity and the stability of NO-np make them a very attractive treatment modality in many conditions, including combat or disaster situations, especially since they have proven high efficacy against other MDR bacteria that are challenging the success of antibiotic use.\(^5,6,9\)

Studies involving nanotechnology safety and toxicity have been extensively published in references 61 and 62. Nanomaterials can penetrate through intact skin in animal and human ex vivo models.\(^6,3\) Notably, cutaneous penetration can be enhanced depending on the delivery vehicle or barrier disruption which is especially advantageous in cases of open wounds. However, toxicity is a major concern since systemic penetration and ultimate circulation of certain nanomaterials through various orifices have been reported in references 66 and 67. In this regard, Friedman et al. showed that NO-np show minimal toxicity toward human fibroblasts in vitro.\(^9\) Furthermore, safety is being currently evaluated in vivo. For instance, systemically (intravenously) NO-np injected hamsters have shown minimal cytotoxicity and no clinical adverse events.\(^8\)

**Phage therapy.** Bacteriophages are viruses that specifically infect bacteria and are considered be the most widely distributed and diverse entities in the biosphere. They have been used for over 60 years as an alternative to antibiotics in the former Soviet Union and Eastern Europe. They are seen as a possible therapy against multidrug-resistant strains of many bacteria, including *Ab*. Recently, Lin et al. investigated the lytic effect of a pool of phages isolated from wastewater on 127 clinical isolates of *Ab* and isolates of other bacteria: *E. coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.\(^6\) They found that *Ab* phages were specifically lytic against 89% of the *Ab* isolates, out of which 97.3% were multidrug-resistant strains, but not against any of the other bacterial genera tested. In fact, one of the phages, named *AB2*, was further characterized due to its high infectivity and ability to lyse the standard *Ab* 17978 strain, whose genome has been fully sequenced. *AB2* had a rapid and effective attachment and penetration of *Ab* (75% within 2 min, 95% in 4 min and almost 100% in 10 min), followed by complete destruction of bacterial cells, with a short latent period (less than 10 min) and a large burst size (~200 PFU/cell). The study is the starting point for developing new efficient therapies against MDR *Ab* and possibly other bacteria based on environmental isolation of phages that can be used as therapeutic, prophylactic or disinfectant agents.

**Photodynamic therapy.** Photodynamic therapy (PDT) is a rapidly expanding approach to the treatment of diseases, because it can eliminate unwanted cells, such as malignant cancer cells and infectious microbial cells. PDT involves the combination of nontoxic photosensitizers (PSs) and harmless visible light that, in the presence of oxygen, produce reactive oxygen species by energy or electron transfer from the PS excited state that are able to oxidize biomolecules and thereby kill cells.\(^9\) The use of PDT to treat localized infections generally involves the topical application of a PS into the infected tissue, followed by illumination with red or near-infrared light that is able to penetrate the tissue.\(^7\) This technique has been effectively demonstrated against *Ab* using a murine burn wound model. PDT efficiently killed bacteria enhancing mice survival without interfering with wound healing.\(^7\) In this regard, selectivity for bacteria over host tissue can be obtained by the appropriate chemical design of the PS to ensure that the molecule will preferentially bind to bacterial cells rather than mammalian cells. It has been determined by many researchers that the most important features of this molecular design are a combination of an overall cationic charge and water solubility.\(^7,3\) Cationic charge is even more important in the case of Gram-negative bacteria that possess a double membrane structure, because this structure excludes many anionic and uncharged lipophilic molecules that can effectively penetrate Gram-positive bacterial and fungal cells.\(^7\)

**Radioimmunotherapy.** Radioimmunotherapy (RIT) has been utilized for cancer treatment and this approach takes advantage of the specificity of antigen-antibody interactions to deliver radionuclides that emanate lethal doses of cytotoxic radiation close to the target cell.\(^7\) Likewise, RIT can kill
microorganisms quickly and efficiently, but this treatment has not been exploited clinically as a therapeutic antimicrobial strategy. However, the development of RIT for infectious diseases is potentially easier than its application to tumor therapy given antigenic and tissue perfusion differences between the sites of microbial infection and normal organs.77 Recently, RIT has been successfully adapted for the treatment of experimental fungal (Cryptococcus neoformans and Histoplasma capsulatum), bacterial (Streptococcus pneumoniae and Bacillus anthracis), and viral (HIV-1 and HPV) infections.78-83 RIT produced none or only transient hematological toxicity in experimental animals. Investigation of radiobiological mechanisms of RIT of infections have revealed that microbial cells are killed by both “direct-hit” and “cross-fire” radiation. Monoclonal antibodies (mAbs) radiolabeled with either alpha- or beta-emitters can stimulate apoptosis-like cell death, whereas only mAbs radiolabeled with alpha-emitter (213) Bismuth also decreased the metabolic activity of microbial cells.84 Since generating specific mAbs against Ab antigenic determinants is not difficult, one can imagine situations where it may be possible to directly treat diverse Ab infections with RIT. In this regard, active and passive immunization using outer membrane proteins of Ab virulent strains resulted in the production of a variety of antibody isotypes and protection in challenged rodents.85,86 Interestingly, mAbs against the iron regulated outer membrane proteins of Ab have been previously generated.87 Novel therapeutic strategies against Ab infections may also be designed by combining RIT and conventional antimicrobial therapy.

Unconventional therapy. To combat the emergence of diverse MDR mechanisms that are limiting the utility of our current antimicrobials, several groups are assessing the modulatory and synergistic effects of plant compounds with or without traditional antimicrobials. For example, the effects of four known compounds extracted from ginger (the rhizome of Zingiber officinale) used alone or in combination with tetracycline on clinical strains of Ab isolated from patients with hospital acquired infections have recently been investigated.88 [6]-dehydrogingerdione was the most effective compound tested as demonstrated by in vitro growth inhibition, followed in order of their activity by [10]-gingerol, [6]-shogaol and [6]-gingerol. Notably, the antimicrobial activity correlated with the intensity of the antioxidant effect. Moreover, despite the fact that the examined Ab strains were resistant to tetracycline, the MIC values of ginger compounds decreased dramatically when combined to tetracycline. Therefore, the use of natural extracts to enhance the antimicrobial spectrum of commonly used antibiotics is a resource with high potential for development. Furthermore, promising results have been reported not only for ginger compounds, but also for propolis extract.89

Conclusion
In the face of the continued emergence of resistant pathogens there is a clear need for innovative therapeutic options. Although there have been important novel developments for combating Ab infection, the majority are in pre-clinical development. However, we are hopeful that these promising approaches will progress into reliable therapies. Furthermore, we strongly support interdisciplinary approaches involving epidemiologists, health-care personnel, and basic scientist in the investigation and development of novel strategies for either preventing or eradicating MDR Ab.

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