Recent Advances in the Immunopathogenesis of Acinetobacter baumannii Infection

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1. Introduction

Organisms belonging to the species Acinetobacter baumannii are capsulated coccobacillary, gram-negative bacteria. They can be found in the environment, will colonize various body tissues and food products and can persist on inanimate objects for a prolonged time period. Among the genus Acinetobacter, A. baumannii is the best described and most often associated with human disease and casualties. It is regarded as an opportunistic pathogen (1) and mostly targets susceptible hosts where it causes pneumonia, urinary tract infections, wound infections and meningitis. Over the last decade, we have witnessed a significant rise in the number and severity of cases of A. baumannii infections from hospital outbreaks as well as sporadic community-associated and wound-associated cases (2).

It is believed that the ability of A. baumannii to persist in the environment, notably by forming protective biofilms, as well as its remarkable spectrum of antibiotic resistance have allowed it to emerge as a particularly problematic human pathogen (3, 4). Although these attributes appear to explain the resilience of this microbe, one must remember that a large array of innocuous bacterial species, including non-pathogenic members of the Acinetobacter genus, can resist antibiotics and form biofilms. Hence, the question of why A. baumannii is such a successful and lethal pathogen becomes more pertinent. Does it display additional unique features in its interactions with the host that favour successful colonization or infection? This chapter will bring together recent research in an attempt to answer these questions. It will strive to be both informative and perhaps inspire new strategies to better control this pathogen.

2. Clinical manifestations of A. baumannii pneumonia

The major risk factor for infection with A. baumannii, also seen as the one that increases the overall susceptibility of the host, is the use of an invasive procedure such as mechanical
ventilation during intensive care (5). Patients first become infected following colonization from the environment. Sources of contamination include surgical equipment, endotracheal or nasogastric tubes, catheters and previously colonized health care staff. The length of stay at the ICU has repeatedly been associated with increased risk of colonization and infection (5-7). Colonization is usually asymptomatic but will increase the likelihood of subsequent infection, which may proceed when the host natural barriers are weakened by trauma, surgery or other invasive procedures.

Respiratory tract infections constitute a major portal of entry leading to *A. baumannii* bacteremia and are almost always hospital-acquired (8). Positive blood cultures are not commonly recognized in patients with nosocomial pneumonia (8). However, pneumonia caused by this organism are significantly more frequently associated with bacteremia and result in higher mortality rates (up to 50% of cases) (8). The clinical manifestations of *A. baumannii* lung infection, both in patients and in animal models, match those of the typical bacterial pneumonia, with alveolar congestion, edema and leukocytic infiltrations. Extracellular bacteria can be readily identified and cultured from lung biopsies and post-mortem samples (8). Hence, it is alleged that bacteremia and sepsis are in most cases the final causes of death, not asphyxia and hypoxemia caused by pneumonia *per se*, although co-morbidity significantly contributes to mortality (9).

### 3. Multidrug resistance and antibiotic treatment

*Acinetobacter baumannii* has acquired resistance to many antibiotics over the last two decades (10) and the incidence of infections caused by multi-drug resistant strains of *A. baumannii* have significantly increased worldwide. This has coincided with the appearance of carbapenem-resistant *A. baumannii* strains in North America, Asia, South America, South Africa and Australia. The global dissemination of carbapenem-resistant strains of *A. baumannii* demonstrates the success of this pathogen to cause epidemic outbreaks (11). *A. baumannii* appears able to acquire antibiotic resistance through multiple mechanisms such as over-expression of bacterial efflux pumps, changes in cell wall channels (porins), acquisition of extended-spectrum β-lactamases, gene mutations and expression of certain enzymes that modify the metabolism of the antibiotic (reviewed in (12-17)). In addition, it is reported that the *A. baumannii* genome contains a “resistance island” with 45 resistance genes (18). *A. baumannii* can also rapidly acquire genetic entities for resistance, including some genes derived from other bacterial species (19). To date, *A. baumannii* strains have demonstrated resistance not only to β-lactams, aminoglycosides, fluoroquinolones, chloramphenicol, tetracycline, and rifampicin, but also to some relatively new antibiotics such as tigecycline, a novel broad-spectrum glycylcycline (20).

The emergence of multi- and pan-drug resistant *A. baumannii* strains clearly presents significant challenges to the clinical management of the infection. The antibiotic selection for those *A. baumannii* strains is very limited. Despite its potential toxicity, polymyxin B and E (colistin) are probably the most commonly used and effective antibiotics for the treatment of resistant strains of *A. baumannii* at present (12, 14-16, 21-23). Other antibiotic candidates are tigecycline and imipenem (14, 21-24) but, as discussed above, resistance to tigecycline has developed in some *A. baumannii* strains (20). To combat the multidrug resistance of *A. baumannii*, it is also a common clinical practice to prescribe several antibiotics as a combination therapy although such practice remains controversial among the medical
profession (12, 24). Although antibiotic resistance and clinical treatment are the most important aspects of the management of A. baumannii infection, this topic is out of the main scope of this chapter. Readers are referred to some recent excellent review articles on the details of antibiotic resistance mechanisms and the advances and challenges in the development of new therapeutics for the treatment of A. baumannii infections (12-17, 21-23).

4. Experimental models of A. baumannii pneumonia

Many clinical cases of A. baumannii have been rigorously described and are very informative about the disease course, risk factors and the prevalence of antibiotic resistance and other genetic traits in the isolates. However, these studies are not experimental in nature and are based on retrospective analysis of hospital-based cases. Thus, they generally fail to establish a causal relationship between the attributes of a given isolate and disease transmissibility, severity and clinical course, which define virulence. Knowledge of virulence factors can help both identify potentially dangerous pathogens before they strike and help develop new methods of control or treatments. Unfortunately, to date, aside from antibiotic-resistance genes, few virulence factors have been identified in A. baumannii (Table 1), despite wide variation in the ability of different laboratory strains and clinical isolates to cause disease in experimental models (25, 26). In addition, although a number of host factors have been examined for their potential involvement in the control of A. baumannii, only a few have been shown to play a role in resistance to infection (Table 2).

<table>
<thead>
<tr>
<th>Contributing factors</th>
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<th>Reference</th>
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<tr>
<td>LPS</td>
<td>Serum sensitivity</td>
<td>in vitro</td>
<td>Resistance to normal human serum</td>
<td>(38)</td>
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<tr>
<td>LPS</td>
<td>Rat soft tissue Human serum</td>
<td>Subcutaneous in vitro</td>
<td>Bacterial growth/survival</td>
<td>(39)</td>
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<tr>
<td>Many genes and loci including urease</td>
<td>Caenorhabditis elegans Dictyostelium discoideum</td>
<td>in vitro</td>
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<td>OmpA</td>
<td>A549 epithelial cells</td>
<td>in vitro</td>
<td>Adherence, apoptosis</td>
<td>(42)</td>
</tr>
<tr>
<td>OmpA</td>
<td>A549 epithelial cells Mouse</td>
<td>in vitro Intratracheal</td>
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<td>(43)</td>
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<tr>
<td>PBP-7/8</td>
<td>Rat soft tissue Rat pneumonia Human serum</td>
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<td>Bacterial growth/survival</td>
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<tr>
<td>Phospholipase D</td>
<td>Human serum Epithelial cells Mouse</td>
<td>in vitro in vitro Intranasal</td>
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<td>pmrB</td>
<td>Mouse</td>
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<td>Survival, microbial growth in spleen</td>
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<td>ptk, epsA, capsule</td>
<td>Human ascites fluid Rat soft tissue</td>
<td>in vitro Subcutaneous</td>
<td>Bacterial growth/survival</td>
<td>(40)</td>
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<td>RecA</td>
<td>Macrophages Mouse</td>
<td>in vitro Intraperitoneal</td>
<td>Bacterial survival Mortality</td>
<td>(50)</td>
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Table 1. Identified virulence factors of A. baumannii
The most widely used model for the study of *A. baumannii* virulence and host responses is based on the mouse (26-28). It has been exploited to study pneumonia as well as septicaemia caused by *A. baumannii* and was successful in identifying or validating both microbial virulence and host resistance factors. Overall, conventional mice (such as C57BL/6 and BALB/c) show relatively high resistance to respiratory infection with *A. baumannii*. Mice inoculated intranasally with up to $10^8$ viable *A. baumannii* develop an acute, self-limiting bronchopneumonia and infected mice generally clear the infection by 96 hours after inoculation (28). Moreover, the infection is usually limited to the respiratory tract with minimal systemic dissemination. As expected, treatment of mice with immunosuppressive drugs (such as cyclophosphamide) greatly exacerbate the infection and can convert an otherwise self-limiting infection into a lethal one (27). In addition, a rat model has been established and used to study both pneumonia and soft tissue injury (29). Human studies are so far limited to bactericidal assays using serum or ascites fluid and the use of human peripheral blood mononuclear cells and various epithelial cell lines (29-33). More basic *in vivo* models involving inhibition of *Caenorhabditis elegans* and *Dictyostelium discoideum* were employed for screening the virulence of multiple *A. baumannii* transposon insertional mutants (34). In many studies, more than one aspect of virulence was explored to generate a more complete picture.

### 5. Virulence factors of *A. baumannii*

One of the defining attributes of *A. baumannii*, both biologically and clinically, is its ability to resist a number of antibiotic classes. It is often debated whether antibiotic resistance genes can be considered virulence factors. On the one hand, they do contribute to the capacity of the pathogen to cause disease by resisting treatment. On the other hand, they do not directly affect the natural course of the infection and only play a role when an exogenous chemotherapeutic compound is administered. However, this distinction is blurred when that resistance to antibiotics impacts on virulence in the absence of the antibiotic. For instance it was reported that colistin-resistant *A. baumannii* isolates show a general lower...
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Fitness as assessed by animal mortality and bacterial burdens in organs (35). The mutation conferring antibiotic resistance was mapped to the *pmrB* gene. The *pmrABC* operon mediates resistance to colistin and other polymyxins through modification of the lipid A portion of LPS (36). Polymyxins bind to LPS; resistance can occur by the complete loss of lipid A through disruption of the biosynthetic genes, yielding LPS-deficient, Gram-negative bacteria (37). LPS was identified in at least two independent studies as contributing to bacterial virulence. It was first found to be important for serum resistance whereas capsular polysaccharide was dispensable (38). This was recently reproduced and further investigated in a wound infection model where LPS was found to be important for bacterial growth and survival (39). Hence, it is not surprising that downregulation of LPS as a means to resist polymyxins will significantly impact the virulence of the organism and might explain the low prevalence of colistin resistance in clinical isolates (21).

While capsular polysaccharides may not be required for serum resistance, the capsule was shown to be a major contributor to virulence since the growth of capsule-deficient variants of *A. baumannii* was attenuated in human ascites fluid and in a wound infection model (40). Hence, it is evident that different virulence factors may be manifest at distinct stages and physiological locations of the infection. Another iteration of that concept is found with outer membrane protein A (AbOmpA), a porin-like protein of *A. baumannii* which appears to mediate multiple functions. This protein is homologous to OmpA proteins from *Enterobacteria* and outer membrane protein F (OprF) of *Pseudomonas sp.* (41). AbOmpA was reported to mediate cytotoxicity in human HEP-2 cells (32) and dendritic cells (33). It also mediates interaction and invasion of lung epithelial cells as well as biofilm formation on abiotic surfaces (42, 43). Whether these *in vitro* events (attachment, invasion and apoptosis) are important for *in vivo* virulence is still uncertain. Moreover, AbOmpA was recently shown to play a role in iron metabolism, another feature that may impact virulence (44). In this regard, blood dissemination of OmpA-deficient bacteria was less pronounced in the mouse pneumonia model (43), suggesting that this protein influences virulence at one or many of the steps leading to bacteremia. One of these steps could be resistance to complement-mediated lysis (45).

Random transposon mutagenesis has the potential to provide a large amount of unbiased information about microbial virulence. In the last few years, this approach has been adapted for the study of *A. baumannii* physiology and pathogenesis. The first study reported by Michael G. Smith and colleagues (2007) combined high-density pyrosequencing with transposon mutagenesis and identified a number of putative pathogenicity loci (34). Their screen was based on inhibition of *Dictyostelium* and *Caenorhabditis elegans* by *A. baumannii* mutants. They reported that a large proportion of the pathogen’s genome consisted of foreign DNA and found six islands associated with virulence. This underlined once more the ability of this pathogen to adapt and evolve by acquiring genetic material for antibiotic resistance and virulence. While informative, this screen was only a first step since the mutants were not complemented nor were they tested in a mammalian model. More recently, Russo *et al.* (2009) identified a putative low-molecular-mass penicillin-binding protein 7/8 (PBP-7/8) as a virulence gene based on serum sensitivity and validated it in the rat models of pneumonia and soft tissue infection (46). PBP-7/8 affects cell morphology and is suspected to play a role in peptidoglycan synthesis and cell wall structure. A similar mutagenesis study using serum sensitivity as the readout and pneumonia as the validation step identified phospholipase D (PLD) as a *bona fide* virulence factor (47). Interestingly, PLD...
is also associated with virulence in *Neisseria gonorrhoeae* (48) and *Corynebacterium pseudotuberculosis* (49). Hence this enzyme could be used as a drug target for the design of novel antimicrobials.

Another bacterial enzyme that was recently shown to play a role in virulence is recA (50). This protein was found not only to mediate DNA repair in *A. baumannii* but also played a role in desiccation resistance, prevented killing inside macrophages as well as contributed to mouse lethality. It may be argued that such a pleotropic protein may not qualify as an authentic virulence factor, for which the defining function is to ensure development inside a live host independently of *in vitro* or environmental fitness. Nevertheless, recA shows promise as a specific antimicrobial target and its implication in virulence underscores the importance of a microorganism’s DNA repair pathway in the battle between host and pathogen.

6. Biofilm formation

One of the hallmark features of the *Acinetobacter* genus is the ability to form biofilms on animate and inanimate surfaces. Biofilm formation is associated with bacterial persistence in chronic diseases and in the environment; however, it is not yet clear whether production of biofilms by *A. baumannii* is involved in virulence. A high level of heterogeneity has been observed between isolates with respect to biofilm formation, which could not be correlated with virulence or disease severity (51-53). Moreover, biofilm production and adherence to airway epithelial cells is also observed at similar frequencies in low virulence species of Acinetobacters (30). Nevertheless, biofilm formation may contribute to disease transmissibility by promoting survival of *A. baumannii* on surgical instruments, catheters and external body surfaces and enabling colonization. It is likely that a combination of features, including the various virulence factors, resistance to multiple antibiotics and general hospital infection management etc., make *A. baumannii* a successful clinical pathogen.

7. Iron acquisition

One last feature that is under scrutiny is the role of iron in *A. baumannii* pathogenesis. Iron is a redox metal essential to most life forms; it is a component of many enzymes and factors such as ribonucelotide reductase (54) and the cytochromes of the aerobic electron transport chain (55). Although abundant inside the body, iron is usually found in association with host macromolecules like heme and transferrin and, thus, is not readily available to bacteria. As a result, *A. baumannii* must develop strategies to capture and retain iron for its survival and growth. Using a proteomics-based approach, 58 proteins were found to be differentially expressed in *A. baumannii* in response to iron modulation, including AbOmpA (44). Although the importance of iron acquisition in pathogenesis has not been experimentally established, this suggests that *A. baumannii* has evolved sophisticated regulatory mechanisms to respond to iron deprivation which are meant to ensure survival in the host, where this metal is scarce.

The production of siderophores is one strategy used by the pathogen to grow under iron-limiting conditions (56, 57). Siderophores are small secreted molecules that bind iron with high affinity and can be taken up by bacteria as a way to scavenge trace iron from their surroundings. The siderophore produced by the *A. baumannii* type strain 19606 was termed “acinetobactin” (58). It is structurally related to the siderophore produced by *Vibrio anguillarum* and resembles catechol-type siderophores such as the enterobactins (59). Of note, *A. baumannii*
isolates often differ in the structure of the siderophores and other iron acquisition factors they express (60). Another way that A. baumannii can acquire iron in the circulation is by utilizing hemin, a salt of heme generated from the breakdown of hemoglobin (61). Conversely, A. baumannii cannot use hemoglobin itself (61) and does not bind the iron transporter transferrin (57), unlike other gram-negative bacteria such as Neisseria and Moraxella (62).

The importance of iron metabolism was also supported by the discovery that a novel monobactam-class antibiotic, BAL30072, is particularly active against A. baumannii when tested against a panel of pathogenic gram-negative species (63, 64). BAL30072 is a catecholic β-lactam that binds iron and acts as a siderophore (63). Under iron-restricted conditions such as those encountered in vivo, the molecule would be taken up efficiently by the bacteria’s siderophore capture machinery, acting as a Trojan horse to deliver the antibiotic inside the cell. Hence it is possible that a microorganism with a high avidity for iron and siderophores, such as A. baumannii, might be more easily targeted and killed by antibiotics of this class. As a bonus, resistance might appear by downregulating siderophore uptake but only at the expense of in vivo fitness.

8. Host resistance factors

Like A. baumannii virulence factors, host factors important for protection against A. baumannii infection are still largely unexplored. It is generally recognized that immunocompromised individuals are much more likely to become infected by A. baumannii, an opportunistic pathogen by most definitions (1). As such, the host innate immune system is generally successful in controlling the pathogen and that only when it fails does the infection progress, such as upon barrier disruption, severe stress or immunosuppressive drug treatment. Identification of host immune cells and molecules that are critical for resistance could help us better deal with these deadly infections by monitoring those factors and boosting or supplementing them as the need arises.

Infections with A. baumannii are characterised by an acute, rapid progression. The host appears to either control the infection or becomes overwhelmed by it. This implies that innate immunity plays a major role in the control of this pathogen. Indeed, CD14 and TLR4, members of the innate immune system and the LPS sensing pathway, have been shown to be essential for resistance to A. baumannii infection in a knockout mouse model, while TLR2 appeared to counteract the robustness of the induced innate immunity (65).

The importance of LPS sensing would be consistent with a strong, protective pro-inflammatory reaction against the pathogen. Paradoxically, trauma and postsurgical patients mounting a strong systemic acute-phase response are more susceptible to A. baumannii infections (66-68). Experimentally, an acute-phase response elicited in mice with turpentine or by direct injection of exogenous serum amyloid A protein reduced pulmonary inflammation and neutrophil migration during A. baumannii pneumonia (69). This treatment ultimately led to enhanced susceptibility in the mice. This phenomenon might explain part of the immunosuppression that permits the microbe to successfully infect hospital patients. Hence, control of A. baumannii probably requires a targeted and self-limiting inflammatory response.

Major effectors of the innate inflammatory response, neutrophils play a critical role in the control of A. baumannii infection, as would be expected when dealing with extracellular bacteria. They are rapidly recruited to the lungs after infection and contribute to its
resolution. Early animal models of *A. baumannii* pneumonia used cyclophosphamide to render mice neutropenic (24, 27) which might have increased the magnitude of bacterial replication *in vivo*, although this was not addressed directly. The role of neutrophils was not formally investigated until much later when it was found that antibody-mediated depletion of neutrophils resulted in an acute lethal infection in mice that was associated with enhanced bacterial burdens in the lung and extrapulmonary dissemination to the spleen (28). Conversely, enhanced pulmonary recruitment of neutrophils by intranasal supplementation of the chemoattractant MIP-2 promoted clearance of the pathogen (28).

The importance of neutrophils and of the regulation of their trafficking was reinforced when it was shown that A/J mice are more susceptible to *A. baumannii* compared to C57BL/6 mice due to a delayed and weaker neutrophil recruitment (70). Strain differences in host responses are common and may lead to genetic studies uncovering novel resistance factors. However, the choice of strains, route of infection and measurements might be of prime importance since another study did not report differences between their experimental mouse strains when doing intraperitoneal injections (25) while a third found differences in mortality but not in lung bacteriology when comparing three murine strains (27).

The role of neutrophils was further investigated at the molecular level to determine what effector functions were required for clearance of *A. baumannii*. It was found that NADPH phagocyte oxidase expressed in neutrophils played a major role in extrapulmonary dissemination of *A. baumannii* whereas the contribution of inducible nitric oxide synthase (NOS2) was minor (71). This is consistent with evidence that NOS2 may be predominantly restricted to the control of intracellular pathogens (72). Other factors suspected to play a role such as sex, IL-17A and the chemokine KC (CXCL1) were also ruled out (25). Still unresolved is the role of the lung macrophages and epithelial cells in the initial recognition of the pathogen and subsequent recruitment of neutrophils. Are these cell types and others involved in recruiting neutrophils to the site of infection? Is infection of epithelial cells essential for the translocation of the pathogen into the circulation? Many of the initial steps of *A. baumannii* infection remain unexplored.

In the bloodstream, *A. baumannii* would encounter other hurdles to infection and dissemination. Blood contains a number of innate immune components that can restrict bacterial growth and even kill a large proportion of infecting microorganisms. Human serum is bactericidal or bacteriostatic to most strains of *A. baumannii* and this was shown to be mediated by complement (29, 45). The alternative complement pathway is responsible for killing the bacteria (45, 51). Interestingly, serum resistance in some strains was explained by the binding of Factor H, an inhibitor of this pathway, to *A. baumannii* outer membrane proteins, including AbOmpA (45). However, this is not a universal phenomenon since binding to Factor H was not observed in another set of serum-resistant isolates (51).

There is clearly a substantial amount of variability in both the serum sensitivity of the pathogen and the bactericidal activity of sera from different individuals (38, 73). This could be due to past exposures and the presence of circulating antibodies. Lifelong exposure to *Acinetobacter* species from the environment might confer some low level of immunity to the pathogen. Indeed, both active and passive immunization using an inactivated whole cell vaccine are very effective at preventing *A. baumannii* infection in mice (74). This could explain why blood from naïve mice does not show any inhibitory activity towards *A. baumannii* (unpublished observations) and would suggest that blood does not contain
significant natural defences against the pathogen, a state that could prove detrimental to the susceptible, naïve host.

9. Conclusion

*Acinetobacter baumannii* presents an array of features that make it a particularly troublesome pathogen. Similar to other emerging gram-negative bacilli like *Pseudomonas aeruginosa* and *Klebsiella pneumonia*, its quick rise in the past decades is probably the result of an ability to rapidly evolve and acquire new genetic material for virulence and antibiotic resistance. The multidrug resistance of several isolates of *A. baumannii* can be traced back to multiple events including downregulation of porins, expression of drug-inactivating enzymes and target alterations (75). Furthermore, the ability of *A. baumannii* to form biofilms allows it to persist on abiotic surfaces, a first step in disease transmission. When it finds an appropriate niche, such as the lung, it rapidly multiplies and creates a localized infection or colonization. If this infection is not contained effectively because of treatment failure or ineffective host defense mechanism, bacteremia will rapidly progress which may prove fatal.

Fast-growing in nature and able to overwhelm host defences, *A. baumannii* has a limited but effective set of virulence factors. One of them, AbOmpA, appears to simultaneously mediate host cell invasion, serum resistance and iron uptake, three potential prerequisites to virulence. This protein could therefore be a prime candidate for therapies targeting virulence mechanisms. Phospholipase D and recA are other candidates with an even wider spectrum that could benefit treatments of other infections. Other strategies targeting iron acquisition by the microbe could also prove successful. On the host side, boosting the activity of innate immunity such as neutrophils, or at least maintaining their proper numbers and function, could help slow or halt the progress of the pathogen.

Given the wide variation in the clinical success, biofilm formation, disease pathogenesis and antibiotic resistance profiles of *A. baumannii* isolates, it is currently difficult to pinpoint which steps and factors are really essential for virulence and which merely modulate it. More research needs to be conducted to better understand pathogenesis, preferably in experimentally controlled conditions involving characterised hosts and bacteria. Given enough information, the ultimate goal would be to predict the course and outcome of the disease when encountering an unknown isolate, in order to take appropriate measures. Another benefit would be to identify new therapeutic targets to supplement and perhaps replace the shrinking arsenal of chemotherapeutic agents at our disposal.

10. Acknowledgements

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11. References


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Pulmonary infections are notorious in causing considerable morbidity and mortality. Caused by bacteria, viruses or fungi, respiratory infections require distinct knowledge of recent advances in pathogenesis. Progress in the understanding of immunopathogenesis of Acinetobacter baumannii infection will explain how an atypical organism establishes infection. The chapter regarding pulmonary nontuberculous mycobacterial infections in the State of Para depicts a unique study in an endemic region for tuberculosis in North of Brazil. The diagnosis and treatment of latent tuberculosis is a formidable challenge. Thus, new developments in diagnosis and treatment of latent tuberculosis are included in this book. Challenging in their diagnosis, nontuberculous mycobacterial pulmonary diseases require special education for management. The problems of respiratory infections in the immunocompromised host are increasing in numbers and in resilience to treatment. Therefore, the chapter describing the host immune responses against pulmonary fungal pathogens comes as a necessary section in this book. The insight brought forth from this book can be valuable for both clinicians and scientists.

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