

# ***Acinetobacter pneumonia and immune response to this infection***

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## **SUMMARY**

***Acinetobacter pneumonia and immune response to this infection***

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*Acinetobacter spp. are important causes of nosocomial infections and their persistence in the hospital environment may explain some long-term outbreaks. Most strains have intrinsic resistance to some antibiotics and can easily acquire resistance to others, therefore they present an important challenge in treatment. Additionally, ability to produce biofilm participates in their virulence. Even though these bacteria are so clinically important, their pathogenesis or host defense against respiratory A. baumannii infections remains basically unknown. It is claimed that the early recruitment of neutrophils into the lung is critical for initiating an efficient host defense against respiratory infection as well as the increased level of nitric oxide (NO), which plays an important role in the pulmonary host-defense mechanism through the bacteriostatic and bactericidal activity. What is more, the presence of IgA seems important in preventing the development of pneumonia and severity of the infection. This article reviews the epidemiology, host response, and treatment of pneumonia caused by this emerging pathogen.*

**Key words:** *Acinetobacter, immune response, pneumonia*

*Acinetobacter* species are responsible for up to 9% of infections in healthcare facilities worldwide [1, 2, 3], the majority of them affecting the respiratory tract [4]. Besides, they cause bacteremia, meningitis, urinary tract infections and wound infections [5]. *Acinetobacter pneumonia* happens among certain at-risk populations, usually takes place in patients of ICUs (intensive care units), in immunocompromised people, and is characterized with a high mortality rate [6]. Due to its ability to persist for long time *Acinetobacter baumannii* is a serious threat within

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## **STRESZCZENIE**

***Zapalenie płuc spowodowane przez Acinetobacter spp. a odpowiedź układu odpornościowego***

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*Bakterie z rodzaju Acinetobacter coraz częściej powodują zakażenia szpitalne. W dużej mierze jest to warunkowane ich zdolnością do przeżywania w warunkach szpitalnych, co może tłumaczyć powodowanie epidemii wewnątrzszpitalnych. Większość szczepów wykazuje naturalną oporność na niektóre antybiotyki oraz zdolność do jej nabywania na inne, stanowi więc prawdziwe wyzwanie w leczeniu. Co więcej, do wirulencji bakterii przyczynia się również ich zdolność do syntezy biofilmu, który może chronić bakterie zarówno przed działaniem antybiotyków jak i odpowiedzi układu odpornościowego. Pomimo tego, że bakterie te są tak istotne klinicznie, patogenezę zakażeń oraz mechanizmy obrony przed infekcją pozostają słabo poznane. Sądzi się, że wczesna rekrutacja neutrofilów do płuc, podobnie jak podwyższony poziom tlenu azotu (NO) są konieczne do zapoczątkowania skutecznej obrony przed infekcją układu oddechowego. Co więcej, obecność IgA wydaje się być istotna w zapobieganiu zakażeniom i rozwojowi ciężkich postaci zakażeń płuc. Niniejszy artykuł przedstawia epidemiologię, odpowiedź układu odpornościowego oraz leczenie zakażeń płuc powodowanych przez te patogeny.*

**Słowa kluczowe:** *Acinetobacter, układ odpornościowy, zapalenie płuc*

the hospital environment, while community-acquired infections are typically rare [7, 8]. *A. baumannii* infections were often observed in soldiers, as well as in people injured in tsunamis and earthquakes [9, 10]. What is of growing concern is the increase in number of infections caused by multidrug resistant clinical species, which developed several mechanisms of resistance such as alteration of porins, efflux pumps, and beta-lactamases production [11, 12, 13]. The pathogenic mechanisms of *A. baumannii* include also iron acquisition systems [14], adherence

to epithelial cells [15] and biofilm formation [16]. Unfortunately little is known about the immune defense mechanisms against *A. baumannii* or its products [17], but it seems that some *Acinetobacter* strains may play an important role in preventing allergies.

## MICROBIOLOGY

*Acinetobacter spp.* are nonfermentative, nonmotile, aerobic Gram-negative bacteria. They are oxidase-negative, which is crucial to distinguish them from other gram-negative microorganisms, e.g. *Pseudomonas* or *Moraxella*, although there were some problems with identifying them [18]. Most clinical infections, about 80%, was caused by *A. calcoaceticus-A. baumannii* complex (Abc, strains: 1,2,3,13) [18]. Abc strains usually were responsible for infections in immune-compromised hosts where their virulence factors easily enabled colonization and infection. To those factors belonged: exopolysaccharide production (protection from the immune response of the host) and its releasing, typical to thirty percent of Abc strains [19, 20]. Additionally, it was suggested that LPS of *A. baumannii* might contribute to its pathogenicity because of its mitogenic properties and ability to induce synthesis of TNF- $\alpha$  [21]. In addition to those virulence factors, *A. baumannii spp.* might also form biofilm and because of its amounts, were classified into high-, medium- and low-producers [22]. Biofilm was an important factor in pneumonia, as well as in other nosocomial infections such as catheter-mediated urinary tract infections [23]. Its synthesis varied among strains, with a relationship between high biofilm production and serum resistance. It appeared that serum resistance might either support the bacterium in production of biofilm and increased its ability to survive in the presence of the host immune response, or the secreted substances forming biofilm might contribute to serum resistance. It was shown that there was no correlation between the ability of *A. baumannii sp.* to form biofilm, their molecular types, carbapenem resistance or site of isolation of the clinical strains [22]. Similarly, there was no relation of disease severity to biofilm production but it was suggested that biofilm formation may be influenced by its interaction with other bacterial species [24].

## EPIDEMIOLOGY

About 40% of healthy adult people were colonized with *A. baumannii*, with higher frequency among patients and health care workers [25]. Bacteria were isolated from all culturable sites, however, the respiratory tract was the most common site of infection

and colonization. High number of Abc infections were nosocomial, partially due to improper disinfection [26] and the ability of Abc to survive for long periods in the hospital environment (20 days- 4 months), which made them able to cause outbreaks [27, 28]. The frequency of Abc infections has been increasing [5]. The risk factors for *Acinetobacter* hospital-acquired pneumonia (AHAP) and *Acinetobacter* ventilator-associated pneumonia (AVAP) were numerous, e.g. previous neurosurgery, head trauma, and large-volume pulmonary aspiration [29], prior ceftazidime treatment [30], prior sepsis, reintubation, length of mechanical ventilation, length of hospital stay, previous antibiotic use, imipenem or fluoroquinolone exposure [31]. Inappropriate use of antibiotics ended up with worse outcomes in AVAP cases [31, 32]. Especially the previous use of ceftriaxone and ciprofloxacin were identified as risk factors for AVAP, which characterized by high mortality, was also associated with increasing resistance and as follows the use of broad-spectrum antibiotics that generate emerging of multiresistant pathogens [33, 34]. Because ciprofloxacin and ceftriaxon had high digestive elimination (~40% to 50%), they could support digestive colonization and development of AVAP via an endogenous mechanism [35]. Lung transplant recipients (LTRs) were also at high risk for nosocomial *A. baumannii* infections. There was increased mortality and hospital costs associated with this infection [36, 37], while pre-operative colonization was found to be a risk factor for post-transplant pneumonia [38].

Although uncommon, community-acquired pneumonia caused by *A. baumannii* (ACAP) has been well documented [39, 40]. Infections were more frequent in subtropical and tropical regions and more common in the humid, warm months of the year [40, 41]. Risk factors associated with ACAP included cigarette smoking, alcoholism, renal failure, chronic or underlying pulmonary disease, and diabetes mellitus [39, 40].

## IMMUNE RESPONSE IN *A. BAUMANNII* PNEUMONIA

Colonization and infection begins with adherence to host cells and can be followed by biofilm formation. It was revealed that *A. baumannii* biofilm formation on abiotic surfaces depended on the CsuA/BABCDE chaperone-usher pili, but it was not involved in adherence to bronchial epithelial cells or induction of inflammatory cytokine production. Additionally, pili did not induce inflammatory response in bronchial epithelial cells while interacting with this pathogen [42].

It was shown that AbOmpA, a major outer membrane protein of *A. baumannii*, was highly immunogenic. Presence of high concentration of AbOmpA was claimed

to induce apoptosis of dendritic and epithelial cells, which might cause disruption of the mucosal lining and allow for the access of bacteria to deeper tissues. Its lower concentration stimulated expression of CD80, CD86, CD40, CD54, MHC class I and MHC class II and production of IL-12 [43]. AbOmpA made epithelial cells to be more responsive to different ligands by enhancing surface expression of TLR2 and increasing the level of nitric oxide (NO), which plays an important role in the pulmonary host-defense mechanism through the bacteriostatic and bactericidal activity [44, 45]. NO presence appeared to be a crucial first line defense mechanism against *A. baumannii* [17]. Therefore, low concentrations of AbOmpA seemed to control gene expression and stimulate an immune response through TLR2 expression and NO production in respiratory epithelial cells [44].

What is more, it was suggested that some strains of *A. baumannii* were able to resist the killing action of normal human serum and, as a result, cause severe infections. Lipopolysaccharide (LPS) might be partially responsible for this resistance [46]. It was claimed that serum-resistant strains of *A. baumannii* regulated the complement pathway by either avoiding deposition of complement protein C3 or inhibiting the convertase, which cleaves C3 and activate the cascade via binding of C3b [4]. LPS was also shown to be implicated in the pathogenesis of sepsis by inducing synthesis of pro-inflammatory cytokines through binding to CD14 and the TLR4/MD-2 complex. Its neutralization or blocking of CD14 was effective in preventing LPS-induced lethal shock in animals, but failed to be effective in clinical studies. However, it was claimed that inhibition of complement combined with neutralization of CD14 might attenuate the uncontrolled inflammatory reactions [47].

As immune response to infection in lungs is concerned, it was shown that intranasal *A. baumannii* infection in mice model induced local production of TNF- $\alpha$ , IL-1, IL-6, MCP-1, MIP-2, at 4 and 24 h post infection. The extend of mRNA expression in lungs and spleen, noticed at 24 h after infection, as well as cytokine levels in the BAL fluid and serum were comparable to this in the tissue [48]. The high susceptibility of mice after infection with *A. baumannii* was associated with a reduced local proinflammatory cytokine/chemokine (IL-1 $\beta$ , MIP-2 and TNF- $\alpha$ ) response and a significant delay and reduction in the early influx of neutrophils in the lung. Intranasal administration of neutrophil-inducing chemokine MIP-2 enhanced pulmonary neutrophil influx and partially restored host resistance to *A. baumannii* [49]. Depletion of neutrophils significantly decreased levels of cytokines, suggesting that neutrophils play a crucial role in the early proinflammatory cytokine re-

sponse in the lungs. It was implied that the reduced cytokine response did not contribute to the enhanced susceptibility to *A. baumannii* infection, because neutralization of endogenous TNF- $\alpha$  and IFN- $\gamma$  *in vivo* did not intensify the infection [48]. Furthermore, injection of SAA, a major acute-phase protein, also reduced inflammatory response to *A. baumannii* pneumonia and facilitated bacterial replication [50]. The recruitment of large numbers of neutrophils and the neutrophilic inflammatory response in the major airways and the lungs parenchyma of infected mice correlated well with the control and eradication of *A. baumannii* growth in the lungs and spleens [49]. Therefore, the early recruitment of neutrophils into the lung seems critical for initiating an efficient host defense against respiratory *A. baumannii* infection. In other study only these animals which were deficient in CD14 and Toll-like receptor 4 gene developed bacteremia. Because the pulmonary cytokine/chemokine response was decreased the onset of lung inflammation was delayed. On the contrary, deficiency of Toll-like receptor 2 was followed with an earlier cell influx into the lungs together with increased MIP-2 and MCP-1 concentrations. As a result accelerated elimination of bacteria from the pulmonary compartment was shown. These results implied that CD14 and Toll-like receptor 4 play an important role in native sensing of *A. baumannii* via the LPS, causing effective eradication of the bacteria from the lung. On the other hand, Toll-like receptor 2 seems to counteract the strength of innate responses during acute *A. baumannii* pneumonia [51].

What is interesting, it was shown that *Acinetobacter baumannii* strains were able to reduce allergic reactions in mice, to activate mammalian cells *in vitro*, and to induce a T(H)1-polarizing program in dendritic cells. According to the hygiene hypothesis, a microbiologically rich environment, such as a farming environment, might protect against the development of allergies [52]. What is more, there were some trials to use components of *A. baumannii* in preventing diseases. It was shown that vaccines containing AbOmpA, which were tested in a murine melanoma model, significantly delayed tumor growth and improved the survival of animals. Therefore they might be useful in therapy against poorly immunogenic melanoma [53].

## CLINICAL FEATURES

Community-acquired *Acinetobacter pneumonia* (ACAP) is rather rare, and clinically alike AVAP or AHAP caused by other microorganisms [54]. *Acinetobacter pneumonia* did not always present with bacteremia, and the disease could be diagnosed by

the isolation of *A. baumannii* from sputum and bronchoalveolar lavage specimens, as well as from blood cultures [18]. Chronic ACAP typically followed a fulminant and rapid course and had a high mortality rate [40]. The clinical and radiological picture was not distinct and could be difficult to differentiate from CAP caused by other bacteria. It could be supposed that the chronic form of *Acinetobacter* pneumonia could possibly be non-bacteraemic and overlooked [55].

When features of *Acinetobacter* pneumonia are concerned, fever was present in over 80% of cases [39], cough was more common in outpatients (84% vs 49%), sputum production was more frequent in inpatients (93 vs 68%) and only AHAP was associated with small pleural effusions (12%). The ACAP cases had a higher incidence of bacteremia, acute respiratory distress syndrome and death. It was shown that *A. baumannii* triggered a severe systemic inflammatory response syndrome early in the course of the pneumonia, disseminated intravascular coagulation, septic shock, as well as adult respiratory distress syndrome [40]. *Acinetobacter* pneumonia was associated with an increase in burn-related mortality [56]. While comparing patients with infections caused by multidrug-resistant Abc with those with susceptible Abc and those without Abc, a significant increase in length of hospital stay was shown in patients with multidrug-resistant Abc [57].

## TREATMENT

Polymyxin B or E (colistin) (intravenous, inhaled, or intramuscular) remains a good alternative for treatment of Abc [58] because still many hospital *Acinetobacter* strains are sensitive to this drug [59]. It was shown that both intravenous and aerosolised colistin administered in acute pulmonary infections [60] gave significantly higher concentrations in sputum samples than in plasma. What is more, the combination of intravenous and aerosolised colistin was a good therapeutic option for the management of Abc pneumonia, because it might achieve better concentrations in lung parenchyma [61].

High-dose course of ampicillin/sulbactam treatment was shown as effective as colistin monotherapy in the therapy for VAP caused by multi-drug resistance (MDR) *A. baumannii* strains [62, 63] and no significant differences in the mortality rates or in the adverse effects were observed. It was found that sulbactam penetrated very well in the lower respiratory tract and achieved therapeutically active concentrations in the alveolar lining fluid comparable to that in serum [64].

In various studies susceptibility to meropenem was diverse accounting to ca. 30% in Italy or the UK and

35% in Turkey [65]. Extended-infusion treatment with meropenem appeared to be a cost-effective management of HAP caused by MDR *A. baumannii*, being equally clinically effective to conventional drugs [66].

Rifampicin, although successfully used against most carbapenem-resistant *A. baumannii* strains in a neutropenic mouse pneumonia model, gave the poor *in vivo* response of some strains, probably as a result of their high mucin production, which could lead to biofilm formation [67]. Despite the fact that rifampicin resistance was not enhanced by the rifampicin/colistin combination, high-level resistance ( $\geq 64$  mg/L) would be prognostic of poor microbiological and clinical response [68]. It was recommended to add rifampicin to either imipenem or colistin. However, these data require further clinical trials to test treating MDR *A. baumannii* pneumonia with combination regimens [69].

Tigecycline, active against many carbapenemase-producing strains, appeared to be a useful alternative to polymyxins [70, 71]. It showed good *in vitro* activity against carbapenem-resistant strains [72] being found to be active against 44-93.3% of *Acinetobacter spp.* [73, 74, 75]. Exposure to subtherapeutic concentration of tigecycline for short time might support the quick emergence of resistance and be a reason of therapeutic failure [76].

Remaining controversial, combination therapy with rifampin and imipenem in carbapenem-resistant Abc infections appeared to be successful in a mouse model but ended up with therapeutic failure [77]. While multidrug-resistant gram-negative infections were treated with colistin alone or colistin with meropenem no significant difference in clinical outcome or nephrotoxicity were shown [78]. In lung transplant recipients empiric treatment with intravenous imipenem, tigecycline and colistin with aerosolized colistin in addition in cases when there was a high suspicion of pneumonia caused by MDR *Acinetobacter* appeared to have a positive influence on clinical outcome [79]. Therapy of pneumonia caused by *A. baumannii* should be based on antibiogram results. However, until microbiologic data will be known, empirical therapy should be employed taking in consideration probable causative factors as well as the local antibiogram.

## CONCLUSIONS

*Acinetobacter spp.* became an important cause of nosocomial pneumonia, mainly due to rapid adaptation to the hospital environment and multidrug resistance. Even though the pathogenesis of these bacteria is complex and *Acinetobacter* isolates seem highly virulent in immunocompromised and hospitalized

patients, only few virulence factors have been described. Biofilm formation or serum resistance may be particularly important in pathogenesis and their understanding may facilitate effective treatment. However, further study is necessary to analyze mechanisms that induce inflammatory responses to control *A. baumannii* infection.

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