Acinetobacter Infections and Treatment

Özlem Özgür[1], Necmi Aksaray[2]
[1]Clinic of Pediactric Infections Disease, Diyarbakır Pediatric Hospital, *Diyarbakır, Turkey*
[2]Department of Pediactric Infections Disease, Çukurova University Faculty of Medicine, *Adana, Turkey*

Abstract

Acinetobacter baumannii have been a leading cause of nosocomial infections, causing significant morbidity and mortality. It is the most commonly isolated microorganism from clinical specimens. *A. baumannii* has low virulance and causes opportunistic nosocomial infections. The most important features of *A. baumannii* are the ability to persist in the hospital environment and the increased multidrug antibiotic resistance it may present, which compromises the treatment of infections caused by this microorganism. In recent years, there have been reports of multidrug resistant *A. baumannii* outbreaks. *(J Pediatr Inf 2014; 8: 28-32)*

Keywords: *Acinetobacter baumannii*, nosocomial infections, antimicrobial resistance, treatment

Introduction

Acinetobacter spp. increasingly causes nosocomial infections in our country as well, just like over the world. It causes ventilator-related pneumonia especially in patients staying in the intensive care unit, bacteraemia, urinary system infections, meningitis and skin and soft tissue infections (1). Antibiotic resistance of the bacteria hospital-acquired Acinetobacter infections is a serious problem in the treatment. The prevalent use of broad spectrum antibiotics such as aminoglycosides, ureidopenicillins, fluoroquinolones and third generation cephalosporins has caused the development of antibiotic resistance in the Acinetobacter types. *A. baumannii* have natural resistance to the antibiotics such as ampicillin, amoxicillin and first generation cephalosporins (2, 3).

Microbiologic features

Acinetobacter spp are gram-negative coccobacillus that likes to reproduce at 35-37ºC, without flagellums and immobile, oxidase negative, catalase positive and involuntary aerobe. On the bacteriae cell wall, there are polysaccharides with antigenic features, glikokaliks proteins, fimbriae proteins responsible for adhesion to sensitive cells. Acinetobacter-spp bacteria easily reproduce in many mediums such as eosin methylene blue, commonly used in laboratories and blood agar (4).

More than 30 species of Acinetobacter-spp bacteria have been identified. Most of the species are available in the environment and they do not generate illnesses in human beings. Since it is difficult to differentiate the bacteria types according to their phenotypic features, sometimes the term *Acinetobacter calcoaceticus-Acinetobacter baumannii complex* is used. *Acinetobacter baumannii*, *Acinetobacter calcoaceticus* and *Acinetobacter lwoffii* are the most commonly reported Acinetobacter-spp in the clinic literature. Among these types, the most common and important types causing clinic pictures are *A. baumannii* (5, 6).

Epidemiology

Since Acinetobacter-spp bacteria are able to use a great variety of metabolites and carbon sources for their metabolisms and energy needs, are dry-resistant and able to survive in different heat and pH environments, they can freely live in nature as saprophyte and survive on inanimate surfaces (1).

Acinetobacter-spp can colonize as contaminant- saprophyte bacteria on skin and mucous membranes. While Acinetobacter colonization has been detected on skins of 25% of healthy adults, temporary pharyngeal Acinetobacter has

Received: 14.10.2012
Accepted: 08.02.2013
Available Online Date: 12.10.2013

Correspondence Address:
Özlem Özgür
Diyarbakır Çocuk Hastanesi, Çocuk Enfeksiyon Hastalıkları Kliniği, *Diyarbakır, Türkiye*
Phone: +90 505 567 78 01
E-mail: ozlemozgur1978@yahoo.com

DOI:10.5152/ced.2013.38

been found on the skins of 7% of children and adults. Acinetobacter-spp are the most common gram-negative bacteria that hospital personnel carry on their skins. The multiple-resistant Acinetobacter in the stool of intensive care unit patients has been isolated and colonization was detected in the 45% of tracheostomy patients (4, 6).

Even though Acinetobacter prevalence varies according to the type of clinic samples and from country to country, it has noticeably increased in the last 20 years. According to the data of Centers for Disease Control and Prevention and National Nosocomial Infection Surveillance, it was reported that Acinetobacter-spp were responsible agents in the 2.4% of nosocomial sepsis, 2.1% of surgical wound infections, 1.6% of nosocomial urinary system infections and 6.9% of nosocomial pneumonia (7, 8).

Risk factors

While alcoholism, smoking, chronic lung disease, diabetes mellitus and living in tropical climates are the risk factors in community-acquired Acinetobacter infections; elongated hospital stays, surgical intervention, presence of lesions on the body, previously acquired infections, the use of broad spectrum antibiotics, central venous or the presence of urinary system catheter, hospitalization in intensive care unit or burn unit, parenteral nutrition, mechanic ventilation and more importantly deficiencies in the infection control programs implemented at hospitals are the factors increasing the risks in nosocomial infections (9, 10).

Pathogenesis and virulence factors

The fact that Acinetobacter types are able to survive o dry and lifeless surfaces and their ability to adopt to changing environmental conditions is an important factor in pathogenesis. Other factors effective in the virulence Acinetobacter types are as follow (11-14):

Polysaccharide capsule

It is composed of L-rhamnose D-glucose, D-mannose and D-glucuronic acid. It enables the surface of the bacteria to be hydrophilic and helps the bacteria to be protected from phagocytose. Additionally, it also allows the bacteria colonies to cling onto surfaces of invasive instruments such as intravenous catheter and tracheal cannula, and penetrate into deeper tissues.

Sticking to the cells

Surface components in polysaccharide structure, fimbrias in glycoprotein structure and membrane components enable the bacteria to stick to the cell surfaces. OmpA (AbOmpA), which is a surface protein with 38 kDa molecular weight present on the *A.baumannii* cell wall also plays a role in allowing the bacteria to stick to the epithelial surfaces. AbOmpA causes apoptosis of epithelial cells as the reason for the emission of proapoptotic molecules.

Lipopolysaccharide and enzyme production

On the *baumannii* cell wall, there exist various lipopolysaccharides (LPS) whose structures and antigenic features are known. Another factor in the virulence is the enzymes that Acinetobacter produces in great amounts and secretas out of the cell. It was demonstrated in i*n-vivo* and *in-vitro* studies that this caused lipid destruction of the enzymes and had a negative impact on the neutrophils.

Biofilm formation

A. baumannii; formation on surfaces such as steel, polystyrene and glass together with biotic surfaces such as episthelial cells may constitute biofilm. It is thought that important cellular components regarding biofilm formation in Acinetobacter spp are the pili formation systems and OmpA protein released out of the cell.

Other factors effective in pathogenesis

A. baumannii strains have the ability to use different iron resources and an independent iron recovery system enabling the host to colonize. The requirement to be able to use the iron in the environment for the bacteria to reproduce plays a crucial role in the pathogenesis of the infection.

Infections caused by Acinetobacter

Respiratory tract infections

It was reported that Acinetobacter spp cause community-acquired bronchiolitis and tracheobronchitis in children, and tracheobronchitis in healthy adults (1, 15).

The most common infection caused by Acinetobacter spp is pneumonia and Acinetobacter causes both community-acquired and nosocomial pneumonia. Community-acquired pneumonia develops in conditions such as alcoholism and smoking in adults, diabetes mellitus, renal failure and underlying lung disease that weaken host immunity. It reaches greater levels of prevalence in regions with tropical climate. Community-acquired pneumonia caused by Acinetobacter spp is usually sudden-onset and have fulminant progression. Septic shock is seen in 1/3 of the patients. There are many publications in the literature reporting that mortality rate in community-acquired pneumonia varies between 40-60% (16-18).

In the US in 2008, the National Healthcare Safety Network (NHSN) reported that the most important agent in gram negative nosocomial infections was Acinetobacter spp and this bacteria was responsible for the infection in

8.4% of ventilator-related pneumonias (19). In the nosocomial Acinetobacter pneumonia, multilober involvement, cavitation, pleural effusion and bronchopulmonary fistula formation were observed. In the nosocomial Acinetobacter pneumonia, mortality is reported to between 35-70%. The existence of bacteremia or sepsis symptoms and presence of previous colonization is a negative is a sign of poor prognosis in nosocomial Acinetobacter pneumonia (1, 17).

Bacteremia

Acinetobacter spp cause 1.5% to 2.5% of the nosocomial bacteremia. Nosocomial Acinetobacter bacteremia is frequently associated with respiratory tract infections and intravenous catheter use and is less frequently associated with urinary tract, lesions, skin and abdomen infections (7, 20, 21). In about 1/3 of the patients with Acinetobacter bacteremia, septic shock develops. Mortality rate in Acinetobacter bacteremia is between 20 to 60%. Mortality of Acinetobacter pneumonia-caused bacteremia is higher than mortality of intravenous catheter-caused bacteremia (39% vs. 4%) (21-23).

Endocarditis

Acinetobacter-caused endocarditis might rarely develop on the natural and prosthetic cardiac valves. Acinetobacter-caused endocarditis has an acute onset and serious progression. Endocarditis developing on the natural cardiac valves may have greater mortality than prosthetic cardiac valves (24, 25).

Central nervous system infections

Nosocomial *Acinetobacter meningitis* is rare. Neurosurgery interventions, cerebrospinal fluid leakage, intracranial haemorrhage and prior antibiotic use are risks factor in the development of Acinetobacter-caused meningitis. However, Acinetobacter meningitis has a high mortality (20-30%) and leaves serious neurological sequels in the patients (26-28).

Nosocomial Acinetobacter spp meningitis is rare and is generally seen in hot climates. In nosocomial meningitis, the bacteria are generally not highly resistant (29).

In nosocomial meningitis, most of the patients have the symptoms of fever and meningeal irritation, and these symptoms may be accompanied by seizure. Pleocytosis dominated by neutrophil is present in the cerebrospinal fluid. Cerebrospinal fluid has low level of glucose and high level of protein (27). In gram staining, Acinetobacter spp may morphologically be confused with *N. meningitidis* (1).

Skin-Soft tissue and bone infections

Acinetobacter types may colonize in surgical and traumatic lesions, and may cause serious soft tissue infections, and develop into osteomyelitis. Acinetobacter-caused soft tissue infections may be related to prosthetic material and may develop into infections requiring broadly spectrum debridement. Acinetobacter may also cause skin infections such as community-acquired and nosocomial cellulite and furuncle. It may cause cellulite formation at the catheter insertion site and may only heal by the removal of catheter (1, 30).

Urinary tract infection

Acinetobacter-caused urinary tract infections are not frequent; however, Acinetobacter may frequently colonize in the urinary system, especially in the presence of catheter. Prevalence of catheter-caused urinary system infections is reported to be 1.2% (19).

Other infections

Acinetobacter spp may colonize in the eyes as well. It may cause corneal ulcerations, endophthalmitis and periorbital cellulite. It may cause infection in the eye after surgery or trauma (31, 32).

Acinetobacter spp may cause nosocomial sinusitis. This picture has been linked to the development of nosocomial pneumonia. Mechanical ventilation is a risk factor for nosocomial sinusitis (33).

Acinetobacter spp may cause septic arthritis, pancreatitis, hepatic abscess and peritonitis (1, 34).

Treatment of acinetobacter infections

It is important to be able to differentiate between colonization and infection before the treatment. In the infections caused by antibiotic-resistant Acinetobacter, broad spectrum cephalosporins, beta-lactam/beta-lactamase inhibitors, carbapenems may be used on their own or combined with antipseudomonal florokinolons or aminoglycosides. Duration of treatment may vary depending on the location of the infection and its severity (1).

It was demonstrated that sulbactam, a beta-lactam inhibitor, the carbapenem-resistant *A. baumannii,* had over 90% in-vitro efficiency and was comparable with imipenem. However, in Acinetobacter infections, the use of antibiotics with sulbactam on their own are not recommended due quick-developing resistance (35, 36).

The antibiotics likely to be used for multiple-drug resistant Acinetobacters are limited. The Polymyxin group antibiotics (Polymyxin B and Polymyxin E) with *in-vitro* efficiency, and tigesiklin and combined antibiotics may be an option in the treatment of multiple-drug resistant Acinetobacter infections. Quick resistance may develop against tigesiklin and the clinical experience of this drug for the treatment of *A. baumannii* is rare (37).

If there is a carbapenem-sensitivity for Acinetobacter-caused meningitis, carbapenem may be used on its own

or may be given intrathecally or interventricularly together with aminoglycoside. If there is carbapenem resistance, intravenous colistin may be used on its own or may be given intrathecally or interventricularly together with colistin or aminoglycoside. Colistin may also be used combined together with intravenous rifampicin (38). In antibiotic-resistant Acinetobacter meningitis, tigesiklin is not recommended due to its pharmacodynamic characteristics (39).

Another issue that has been under discussion recently is that beta-lactam antibiotics, especially those such as cefepime, piperacillin- tazobactam and carbapenems (meropenem, imipenem, and doripenem) are to be given with long-term infusion. The serum concentrations of drugs given with long-term infusion stay longer above the minimum inhibitor concentration (MIK) value and ensures more bactericidal effect over the sensitivity-reduced bacteria. While imipenem and meropenem serum are half-life less than four hours and the benefit of infusions longer than three hours are limited, the long-term infusion of doripenem increases drug effectiveness since serum's half-life is long (37, 40).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ö.Ö., N.A; Design - Ö.Ö., N.A; Supervision - N.A.; Funding - Ö.Ö.; Materials - Ö.Ö.; Data Collection and/or Processing - Ö.Ö.; Literature Review - Ö.Ö.; Writing - Ö.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Allen DM, Hartman BJ. Acinetobacter species. In: Mandell GL, Bennet JE, Doun R, (eds). Pirinciples and practise of Infectious Diseases. 7th ed. Philadelphia: Elsevier Churchill Livingstone; 2009: 222. p. 2881-5.
2. Manchanda V, Sanchaita S, Singh NP. Multidrug Resistant Acinetobacter. Journal of Global Infectious Diseases 2010; 2: 291-304. [CrossRef]
3. Maragakis LL, Perl TM. Acinetobacter baumannii: epidemiology, antimicrobial resistance, and treatment options. Clin Infect Dis 2008; 46: 1254-63. [CrossRef]
4. Schreckenberger PC, Daneshvar MI, Weyant RS, Hollis DG. Acinetobacter, Achromobacter, Chryseobacterium, Moraxella, Methylobacterium, and other nonfermentative gram-negative rods. In: Murray PR, Baron EJ, Jorgensen JH, et al. (eds) Manual of Clinical Microbiology, 8th ed., Washington, DC: ASM Press, 2003.p.749-79.
5. Ganacho-Montero J, Amaya-Villar R. Multiresistant Acinetobacter baumannii infections: epidemiology and management. Curr Opin Infect Dis 2010; 23: 332-9. [CrossRef]
6. Munoz-Price LS, Weinstein RA. Acinetobacter Infection. N Engl J Med 2008; 358: 1271-81. [CrossRef]
7. Gaynes R, Edwards JR; National Nosocomial Infections Surveillance System. Overview of nosocomial infections caused by gram negative bacilli. Clin Infect Dis 2005;41: 848-54. [CrossRef]
8. National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance (NNIS) System Reports, data summary from January 1992 through June 2004, issued Oct 2004. Am J Infect Control 2004; 32: 470-85. [CrossRef]
9. Anstey NM, Currie BJ, Withnall KM. Community-acquired Acinetobacter pneumonia in the northern territory of Australia. Clin Infect Dis 1992; 14: 83-91. [CrossRef]
10. Lortholary O, Fagon J-Y, Hoi AB, et al. Nosocomial acquisition of multi-resistant Acinetobacter baumannii: Risk factors and prognosis. Clin Infect Dis 1995; 20: 790-6. [CrossRef]
11. Joly-Guillou ML. Clinical impact and pathogenicity of Acinetobacter. Clin Microbiol Infect 2005; 11: 868-73. [CrossRef]
12. Tomaras AP, Dorsey CW, McQueary CN, Actis LA. Molecular basis of Acinetobacter virulence and pathogenecity, In: Gerischer U (ed), Acinetobacter Molecular Biology. Norfolk, UK: Caistr Academic Pres; 2008. p.265-97.
13. Gaddy JA, Actis L. Regulation of Acinetobacter baumannii biofilm formation. Future Microbiol 2009; 4: 273-8. [CrossRef]
14. Dorsey CW, Beglin MS, Actis LA. Detection and analysis of iron uptake components expressed by Acinetobacter baumannii clinical isolates. J Clin Microbiol 2003; 41: 4188-93. [CrossRef]
15. O'Connell CJ, Hamilton R. Gram-negative rod infections: II. Acinetobacter infections in general hospital. N Y State J Med 1981; 81: 750-3.
16. Anstey NM, Currie BJ, Hassell M,. Community-acquired bacteremic Acinetobacter pneumonia in tropical Australia is caused by diverse strains of Acinetobacter baumannii, with carriage in the throat of at-risk groups. J Clin Microbiol 2002; 40: 685-6. [CrossRef]
17. Leung WS, Chu CM, Tsang KY, et al. Fulminant communityacquired Acinetobacter baumanii pneumonia as a distinct clinical sydrome. Chest 2006; 120: 102-9. [CrossRef]
18. Chen MZ, Hsueh PR, Lee LN,. Severe community-acquired pneumonia due to Acinetobacter baumannii. Chest 2001; 120:1072-7. [CrossRef]
19. Hidron AI, Edwards JR, Patel J, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. Infect Control Hosp Epidemiol 2008; 29: 996-1011. [CrossRef]
20. Cisneros JM, Rodriquez- Bano J. Nosocomial bacteremia due to Acinetobacter baumannii: epidemiology, clinical features and treatment. Clin Microbiol Infect 2002; 8: 687-93. [CrossRef]
21. Chen HP, Chen TL, Lai CH, et al. Predictors of mortality in Acinetobacter baumannii bacteremia. J Microbiol Immunol Infect 2005; 38: 127-36.
22. Seifert H, Strate A, Pulverer G. Nosocomial bacteremia due to Acinetobacter baumannii. Clinical Features, epidemiology and predictors of mortality. Medicine (Baltimore) 1995; 74: 340-9. [CrossRef]
23. Grupper M, Sprecher H, Mashiach T, et al. Attributable mortality of nosocomial Acinetobacter bacteremia. Infect Control Hosp Epidemiol 2007; 28: 293-8. [CrossRef]

24. Gradon JD, Chapnick EK, Lutwick LI. Infective endocarditis of a native valve due to Acinetobacter: case report and review. Clin Infect Dis 1992; 14: 1145-8. [CrossRef]
25. Malik AS. Acinetobacter endocarditis in Children: a case report and review of the literatüre. Infection 1995; 23: 306-8. [CrossRef]
26. Chen SF, Chan WN, Lu CH, et al. Adult Acinetobacter meningitis and its comparison with non-Acinetobacter gram- negative bacterial meningitis. Acta Neurol Taiwan 2005; 14: 131-7.
27. Chen HP, Lai CH, Chan YJ, et al. Clinical significance of Acinetobacter species isolated from cerebrospinal fluid. Scand J Infect Dis 2005; 37: 669-75. [CrossRef]
28. Siegman-Igra Y, Bar- Yosef S, Gorea A, et al. Nosocomial acinetobacter meningitis secondary to invasive procedures: report of 25 cases and review. Clin Infect Dis 1993; 17: 843-9. [CrossRef]
29. Chang WN, Lu CH, Huang CR, et al. Community- acquired Acinetobacter menengitis in adults. Infection 2000; 28: 395-7. [CrossRef]
30. Davis KA, Moran KA, McAllister CK, et al. Multidrug-resistant Acinetobacter extremity infections in soldiers. Emerg Infect Dis 2005; 11: 1218-24. [CrossRef]
31. Levy J, Oshry T, Rabinowitz R, et al. Acinetobacter corneal graft ulcer and endophthalmitis: report of two cases. Can J Ophthalmol 2005; 40: 79-82. [CrossRef]
32. Lindbohm N, Moilanen JA, Vesaluoma MH et al. Acinetobacter and Staphyloccoccus aureus ulcerative keratitis after laser insitu keratomileusis treated with antibiotics and phototherapeutic keratectomy. J Refract Surg 2005; 21: 404-6.
33. Bert F, Lambert- Zechovsky N. Sinusitis in mechanically ventilated patients and its role in the pathogenesis of nosocomial pneumonia. Eur J Clin Microbiol Infect Dis 1996; 15: 533-44. [CrossRef]
34. Valdez JM, Asperilla MO, Smego RA. Acinetobacter peritonitis in patients receiving continuous ambulatory perinoneal dialysis. South Med J 1991; 84: 607-10.
35. Tatman-Otkun M, Gürcan S, Ozer B, et al. Annual trends in antibiotic resistance of nosocomial Acinetobacter baumannii strains and the effect of synergistic antibiotic combinations. New Microbiol 2004; 27: 21-8.
36. Jellison TK, Mckinnon PS, Rybak MJ. Epidemiology, resistance, and outcomes of Acinetobacter baumannii bacteremia treated with imipenem-cilastatin or ampicillin-sulbactam. Pharmacotherapy 2001; 21: 142-8. [CrossRef]
37. Fishbain J, Peleg AY. Treatment of Acinetobacter Infections. Clinical Infectious Diseases 2010; 51: 79-84. [CrossRef]
38. Kim BN, Peleg AY, Loidise TP, et al. Management of meningitis due to antibiotic-resistant Acinetobacter species. Lancet Infect Dis 2009; 9: 245-55. [CrossRef]
39. Doan TL, Fung HB, Mehta D, et al. Tigecycline: a glycylcycline antimicrobial agent. Clin Ther 2006; 28: 1079-106. [CrossRef]
40. Van Wart SA, Andes DR, Ambrose PG, et la. Pharmacokinetic-pharmacodynamic modeling to support doripenem dose regimen optimization for critically ill patients. Diagn Microbiol Infect Dis 2009; 63: 409-14. [CrossRef]