OLGU SUNUMU/CASE REPORT
Yoğun Bakım Dergisi 2010;9(3):164-167

Colistin-Resistant *Acinetobacter baumannii* Isolated from Ventilator-Associated Pneumonia: A Case Report from Turkey

Ventilatör-İlişkili Pnömoniden İzole Edilen Kolistin Dirençli *Acinetobacter baumannii*: Türkiye'den Bir Olgu Sunumu

Gülbin AYGENCEL[1], Murat DİZBAY[2], Arzu ÇİFTÇİ[2], Melda TÜRKOĞLU[1]

[1] **Gazi Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Yoğun Bakım Bilim Dalı, Ankara, Türkiye**
Division of Intensive Care, Department of Internal Medicine, Faculty of Medicine, University of Gazi, Ankara, Turkey

[2] **Gazi Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Ankara, Türkiye**
Department of İnfectious Diseases and Clinical Microbiology, Faculty of Medicine, University of Gazi, Ankara, Turkey

ABSTRACT

Multidrug-resistant Acinetobacter baumannii is one of the most important pathogens in intensive care units related to morbidity and mortality. Colistin is being used increasingly as "salvage" therapy for these patients. However, resistance to colistin in A. baumannii has recently been reported. We herein present a case in which ventilator-associated pneumonia due to A. baumannii developed in one of our patients in the intensive care unit. Colistin was initiated in the patient; however, resistance was observed during the treatment. Our aim in presenting this case is to attract attention to the potential risks of multidrug-resistant Acinetobacter infections in Turkey.

Key Words: *Acinetobacter baumannii, Ventilator-associated pneumonia, Colistin, Resistance.*

Received: 01/02/2010 • Accepted: 14/10/2010

ÖZET

Çoklu ilaç dirençli Acinetobacter baumannii yoğun bakım ünitelerinde morbidite ve mortaliteden sorumlu önemli bir patojendir. Kolistin bu olgularda "kurtarıcı" tedavi olarak kullanılmaya başlanmıştır. Fakat A. baumannii'de kolistine direnç yakın dönemde rapor edilmiştir. Burada yoğun bakım ünitemizde yatan bir olguda A. baumannii'ye bağlı gelişen ventilatör ilişkili pnömoni sunulmuştur. Hastaya kolistin tedavisi başlanmış; fakat tedavi sırasında kolistine direnç geliştiği gözlenmiştir. Bu olguyu sunarken çoklu ilaç direnci Acinetobacter infeksiyonlarının Türkiye'de de potansiyel bir risk olduğuna dikkat çekilmeye çalışılmıştır.

Anahtar Kelimeler: *Acinetobacter baumannii, Ventilatör ilişkili pnömoni, Kolistin, Direnç*

Geliş Tarihi: 01/02/2010 • Kabul Ediliş Tarihi: 14/10/2010

INTRODUCTION

Acinetobacter species have increasingly been recognized as hospital-acquired pathogens mainly in immunocompromised patients and patients in intensive care units (ICUs) (1). *Acinetobacter* spp. can cause a multitude of infections, including pneumonia, bacteremia, meningitis, urinary tract infections, and skin and soft tissue infections, and mortality rates associated with these infections are quite high. Emergence of pan-drug-resistant (PDR) or multidrug-resistant (MDR) *A. baumannii* strains has become a serious clinical problem in many parts of the world (2). Antimicrobial options for the treatment of MDR *A. baumannii* are limited, including polymyxins (e.g. colistin), unusual drugs (e.g. sulbactam) or drugs with which there is presently little clinical experience (e.g. tigecycline). Colistin is being used increasingly as salvage therapy for this pathogen (3). Unfortunately, resistance to colistin has emerged with its increasing use, and there is a recent observation of heteroresistance to colistin among clinical strains of MDR *A. baumannii* (4).

In this study, we present a patient who developed ventilator-associated pneumonia (VAP) due to *A. baumannii* in our ICU, for which colistin treatment was initiated; however, resistance was observed during treatment. In view of this case, we would like to emphasize the likelihood of colistin resistance in *Acinetobacter* infections.

CASE REPORT

An 82-year-old female patient with a history of atrial fibrillation and who used warfarin (Coumadin®) due to a cerebrovascular event presented to the emergency service of Gazi University Hospital with a complaint of gastrointestinal bleeding. Having performed replacement and endoscopy, she was hospitalized in the internal medicine clinic for follow-up. On the fifth day of her admission, she arrested, was intubated, and was transferred to our ICU for further follow-up and treatment. On her initial endotracheal aspirate (ETA) culture, methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated and linezolid treatment was started. On her fifth day of intubation, she was extubated. The patient was then transferred back to the internal medicine clinic; however, on the fourth day of her observation in the clinic, she developed acute respiratory failure. Therefore, she was intubated and re-admitted to the ICU. On the second day of her admission in the ICU, *A. baumannii* (ETA: 3×10^5 colony, susceptible to only colistin and netilmycine, mean inhibitory concentration (MIC): 0.5 µg/mL for CT) was isolated in the ETA culture. The patient then received colistin (intravenous and inhalation route). On the seventh day of her admission, she was again extubated, but this time her extubation period lasted for five days. Due to her increasing secretion and respiratory problems, she had to be intubated a third time. Following the third intubation, a tracheostomy was performed and she was assessed with regard to her daily weaning trial, but the patient could not be totally withdrawn from the mechanical ventilation. On the 15^{th} day of her admission to the ICU, she developed fever again, and on the ETA culture, *A. baumannii* (ETA: 7×10^4 colony, susceptible only to NET, MIC: > 32 µg/mL for CT) was isolated once again. Therefore, netilmycine and rifampin were administered; however, on the 21^{st} day of her admission in the ICU, the patient died due to sepsis and septic shock.

Isolates were collected from ETA cultures from the patient. *A. baumannii* isolates growing on ETA cultures were tested for antimicrobial susceptibility by disk diffusion method. Isolates resistant to at least three different antibiotics, including carbapenems, aminoglycosides, quinolones, piperacillin/tazobactam, cefepime, ceftazidime, and cefoperazone/sulbactam, were considered as MDR *A. baumannii*. *A. baumannii* strains from VAP were identified using a BBL Crystal Enteric/Nonfermenter ID Kit (Becton Dickinson, Sparks, MD).

The in vitro antimicrobial susceptibility for colistin was also confirmed by Etest (AB BIODISK, Solna, Sweden). Large (150 mm) agar plates with Mueller-Hinton medium (Becton Dickinson) were inoculated with suspensions of the strains equivalent to 0.5 McFarland standard, and Etest strip of colistin was applied. After incubation for 24 hours at 35°C, MICs were read and interpreted according

to the manufacturer's instructions and Clinical and Laboratory Standards Institute (CLSI 2008) recommendations. According to CLSI 2008 recommendations, colistin susceptibility criterion for *A. baumannii* is MIC ≤ 2 µg/mL and resistance criterion is MIC ≥ 4 µg/mL (5).

DISCUSSION

In the last two decades, *A. baumannii* has become an important nosocomial pathogen in Turkey as well as throughout the world and is a leading problem in treatment due to its MDR (6). Carbapenems, quinolones, aminoglycosides, and combinations with sulbactam are commonly used in the treatment of these infections. Unfortunately, resistance rates for these antibiotics are increasing. In various studies performed in ICUs from Turkey, carbapenem resistance in *A. baumannii* was reported to be between 55% and 63% (6-8).

Increasing carbapenem resistance due to OXA-type carbapenemase or, more rarely, metallo-beta-lactamases, among *A. baumannii* isolates has led clinicians to look for new therapeutic alternatives. Many carbapenemase-producing *A. baumannii* isolates are resistant to all available agents except polymyxins (9,10). Tigecycline, which is active against most carbapenemase-producing strains, may be a useful alternative to polymyxins. Tigecycline, a new semi-synthetic tetracycline, has provided hope for the treatment of *A. baumannii* infections, including carbapenem-resistant isolates. However, *A. baumannii* isolates showing reduced susceptibility to tigecycline have recently been identified (6,11,12). Furthermore, tigecycline was not approved for the treatment of VAP, so there is presently little clinical experience with this drug.

Colistin, an old antibiotic from the polymyxin group, is very effective against MDR *A. baumannii* isolates, but the emergence of resistance has occasionally been experienced. Moreover, unfavorable pharmacokinetic properties and possible adverse effects (e.g. nephrotoxicity and neurotoxicity) restrict its clinical use (4,13). In addition, colistin is not available in Turkey and can only be obtained abroad.

Colistin is one agent reliably active against many *Acinetobacter* isolates. Heteroresistance to colistin among *Acinetobacter* isolates has been previously described in some reports, and preliminary in vitro data indicate that the emergence of heteroresistant populations may be amplified by colistin exposure. In other words, it is possible that the heteroresistant proportion of the bacterial population might be selected and become predominant during colistin therapy, leading to treatment failure. Monotherapy with colistin has been described as a risk factor for the selection of heteroresistant isolates. Careful monitoring for emerging resistance during prolonged colistin therapy is warranted (14,15).

Heteroresistance to colistin in clinical isolates of *A. baumannii* that are apparently susceptible to colistin is considered on the basis of MICs. The detection of hetero-colistin-resistant *A. baumannii* in the clinical isolates provides a strong warning that if colistin is used inappropriately, there may be substantial potential for the rapid development of resistance and therapeutic failure. Monotherapy with colistin for treatment of infections caused by hetero-colistin-resistant *A. baumannii* may be problematic. We believe that resistance to this last-resort antibiotic should be monitored in global and local surveillance programs and that every effort should be made to increase its life span by ensuring that it is used judiciously and in appropriate dosage regimens (15-17).

Hernan et al. showed the high presence of colistin heteroresistant strains with endemic infections in an ICU (18). Thus, combination therapy has become the ultimate resource to treat MDR and PDR *A. baumannii* infections, but its actual efficacy is unclear from a microbiological and clinical viewpoint (19).

In our case, VAP due to *A. baumanii* developed in the patient on her admission to the ICU, and colistin, to which her isolate was sensitive, was administered initially as a monotherapy. During administration of colistin, the study conducted by Dizbay et al. in our hospital in 2008 (in which colistin resistance was found as 0% and tigecycline resistance as 25.8%) and the MIC value for colistin were taken into consideration (6). However, as also indicated in other similar previous studies, resistance under colistin monotherapy developed in our patient. Since the infection could not be cont-

rolled, she died due to sepsis. This case rekindled our interest in the fact that *Acinetobacter* infections can also lead to major problems in Turkey, as have been experienced worldwide, due to this existing and rapidly spreading resistance problem in the treatment.

CONCLUSION

A. baumannii has emerged recently as an important pathogen frequently isolated from VAP worldwide. MDR *A. baumannii*-related infections and outbreaks have become a health problem in many countries as well as in Turkey.

There is no simple answer to the treatment of *Acinetobacter* infections. A high prevalence of MDR in *A. baumannii* limits the therapeutic options in the treatment. Eradication of *Acinetobacter* spp. requires adherence to good infection control practices and prudent antibiotic use, as well as effective antimicrobial therapy. Although colistin appears to be a good choice, adverse reactions and unavailability of colistin limit its wide usage in Turkey. Moreover, potential risk of resistance limits its usage worldwide.

REFERENCES

1. *Chastre J. Infections due to Acinetobacter baumannii in the ICU. Semin Respir Crit Care Med 2003;24:69-78.*
2. *Jain R, Danziger LH. Multidrug-resistant Acinetobacter infections: an emerging challenge to clinicians. Ann Pharmacother 2004;38:1449-59.*
3. *Murray CK, Hospenthal DR. Treatment of multidrug resistant Acinetobacter. Curr Opin Infect Dis 2005;18:502-6.*
4. *Linden PK, Paterson DL. Parenteral and inhaled colistin for treatment of ventilator-associated pneumonia. Clin Infect Dis 2006;43(Suppl 2):S89-94.*
5. *Clinical and Laboratory Standards Institute, Performance Standards for Antimicrobial Susceptibility Testing: 18th informational supplement, CLSI M100-S18. Wayne, PA: Clinical and Laboratory Standards Institute, 2008.*
6. *Dizbay M, Altuncekic A, Sezer BE, Ozdemir K, Arman D. Colistin and tigecycline susceptibility among multidrug-resistant Acinetobacter baumannii isolated from ventilator-associated pneumonia. Int J Antimicrob Agents 2008;32:29-32.*
7. *Aksaray S, Dokuzoguz B, Guvener E, Yucesoy M, Yuluğ N, Kocagöz S, et al. Surveillance of antimicrobial resistance among gram-negative isolates from intensive care units in eight hospitals in Turkey. J Antimicrob Chemother 2000;45:695-9.*
8. *Eser OK, Ergin A, Hascelik G. Antimicrobial resistance and existence of metallo-beta-lactamase in Acinetobacter species isolated from adult patients. Mikrobiyol Bul 2009;43:383-90.*
9. *Lopez-Hernandez S, Alarcon T, Lopez-Brea M. Carbapenem resistance mediated by beta-lactamases in clinical isolates of Acinetobacter baumannii in Spain. Eur J Clin Microbiol Infect Dis 1998;17:282-5.*
10. *Heritier C, Dubouix A, Poirel L, Marty N, Nordmann P. A nosocomial outbreak of Acinetobacter baumannii isolates expressing the carbapenem-hydrolyzing oxacillinase OXA:58. J Antimicrob Chemother 2005;55:115-8.*
11. *Livermore DM. Tigecycline: what is it, and where should it be used? J Antimicrob Chemother 2005;56:611-4.*
12. *Reid GE, Grim SA, Aldeza CA, Janda WM, Clark NM. Rapid development of Acinetobacter baumannii resistance to tigecycline. Pharmacotherapy 2007;27:1198-201.*
13. *Li J, Nation RL. Old polymyxins are back: is resistance close? Clin Infect Dis 2006;43:663-4.*
14. *Li J, Rayner CR, Nation RL, Owen RJ, Spelman D, Tan KE, et al. Heteroresistance to colistin in multidrug-resistant Acinetobacter baumannii. Antimicrob Agents Chemother 2006;50:2946-50.*
15. *David MD, Gill MJ. Potential for underdosing and emergence of resistance in Acinetobacter baumannii during treatment with colistin. J Antimicrob Chemother 2008;61:962-4.*
16. *Ko KS, Suh JY, Kwon KT, Jung SI, Park KH, Kang CI, et al. High rates of resistance to colistin and polymyxin B in subgroups of Acinetobacter baumannii isolates from Korea. J Antimicrob Chemother 2007;60:1163-7.*
17. *Reis AO, Luz DA, Tognim MC, Sader HS, Gales AC. Polymyxin-resistant Acinetobacter spp. isolates: what is next? Emerg Infect Dis 2003;9:1025-7.*
18. *Hernan RC, Karina B, Gabriela G, Marcela N, Carlos V, Angela F. Selection of colistin-resistant Acinetobacter baumannii isolates in postneurosurgical meningitis in an intensive care unit with high presence of heteroresistance to colistin. Diagn Microbiol Infect Dis 2009;65:188-9.*
19. *Yoon J, Urban C, Terzian C, Mariano N, Rahal JJ. In vitro double and triple synergistic activities of polymyxin B, imipenem and rifampin against multidrug-resistant Acinetobacter baumannii. Antimicrob Agents Chemother 2004;48:753-7.*

Yazışma Adresi/Address for Correspondence

Doç. Dr. Gülbin AYGENCEL

Gazi Üniversitesi Tıp Fakültesi
İç Hastalıkları Anabilim Dalı,
Yoğun Bakım Bilim Dalı 06510
Beşevler, Ankara-Türkiye

E-posta: aygencel@hotmail.com