Original Article

A Study of Multidrug-Resistant, Colistin-Only-Sensitive Infections in Intubated and Mechanically Ventilated Patients Over 2 Years

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Abstract

Background and Aims: Multidrug-resistant, Gram-negative infections are increasingly common in the intensive care unit (ICU). This study compares the occurrence and outcome of colistin-only-sensitive (COS) infections among mechanically ventilated patients at a tertiary hospital ICU. **Methods:** The study included adult patients admitted over a period of 2 years, who were intubated and mechanically ventilated for more than 48 h. They were divided into two groups, those with COS infections and those without, and their GCS and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, ICU length of stay, leukocyte count, and mortality were compared. COS patients were divided into neurosurgery, neurology, respiratory, and sepsis with bacteremia groups. The COS organisms in each group, their sources, ICU length of stay, ventilator-free days, and mortality were analyzed. **Results:** Three hundred and one patients were selected, of whom 41 (13.6%) had COS infections. COS patients had a longer ICU length of stay than non-COS patients ($P = 0.001$) but comparable APACHE II and GCS scores, leukocyte count, and mortality. The sepsis group accounted for 8 out of 15 (53%) deaths among COS patients ($P = 0.03$). *Acinetobacter baumannii* accounted for 61% of the COS infections, *Klebsiella pneumonia*: 24.4%, *Pseudomonas aeruginosa*: 12.2%, and *Escherichia coli:* 2.4%. Endotracheal secretion cultures accounted for 65.8% of COS isolates, urine cultures 17%, pus cultures 7.3%, and blood cultures 4.9%. ICU length of stay, ventilator-free days, and mortality were similar between each COS organism. **Conclusion:** Intubated patients with multidrug-resistant, COS infections have a longer stay in ICU than non-COS patients. COS infections associated with bacteremia have high mortality.

Keywords: Colistin-only-sensitive, multidrug-resistant, polymyxin only sensitive

Introduction

Resistance to multiple antibiotics is an increasingly common and difficult to treat problem, especially in infections caused by the so-called ESKAPE organisms comprising the Gram-positive cocci, *Enterococcus faecium,* and *Staphylococcus aureus*, and the Gram-negative bacilli *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa,* and *Enterobacter* species. These Gram-negative bacteria have fewer new and developmental antibiotics active against them, owing mainly to the diminishing industry focus on antibacterial drug research and development.[1] These bacteria produce the extended-spectrum beta-lactamase (ESBL) and carbapenemase enzymes which render them resistant to cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems, the main antibiotic classes for the treatment of Gram-negative infections. These enzymes are coded for by genes, carried by snippets of DNA called plasmids, which easily spread from bacterium to bacterium and allow for the rapid and alarming spread of Gram-negative resistance.[2]

This has forced health-care providers to resort to older antibiotics. Colistin is one such bactericidal agent, discovered about 50 years ago but abandoned 20 years later

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in most countries, because of frequent reports of serious nephrotoxicity and neurotoxicity.[3] However, recent studies have shown that colistin is more efficacious and much less toxic than suggested by the older studies, leading to a surge in its popularity.[4-6]

An isolate is defined as colistin-only-sensitive (COS) if it is resistant to all antipseudomonal agents, namely, cephalosporins, antipseudomonal penicillins, carbapenems, monobactams, quinolones and aminoglycosides, except colistin.[7] This study compares various parameters between COS-infected patients and non-COS patients, including Glasgow Coma Scale scores, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, total leukocyte count, intensive care unit (ICU) length of stay, and mortality. It also looks at the occurrence of Gram-negative infections sensitive only to colistin, among various groups of intubated and mechanically ventilated patients and their impact on ICU length of stay, ventilator-free days and mortality.

Methods

Design

This is a cross-sectional epidemiological study conducted at a tertiary care, referral ICU. It included all adult patients who were intubated and mechanically ventilated, for 2 days or more, over a 2-year period from January 2014 to December 2015. It was cleared by the institutional ethics committee. Patients <17 years of age were excluded from the study. The study population was divided into two groups, those patients infected with COS organisms and those without (non-COS). The COS group was further divided into four main groups according to the primary cause for ICU admission, namely, postoperative neurosurgery cases, neurology patients, including stroke and meningitis, respiratory patients with pneumonia, and sepsis patients with proven bacteremia. These groups were chosen as they represented the majority of patients requiring invasive mechanical ventilation and having a longer stay in ICU.

Data collection

Data were retrieved from the electronic medical records and daily case sheets, including demographics, lowest GCS score in the first 24 h, white blood cell count at admission, APACHE II score, reason for ICU admission, ICU length of stay, ventilator-free days, and mortality. The COS organism, the isolate which grew the organism, and the route of administration of colistin were noted.

Statistical analysis

Data were analyzed using the statistical software SPSS (IBM SPSS Statistics for Windows, Version 20.0. IBM Corporation, Armonk, NY, USA). APACHE II scores, GCS scores, total leukocyte count, ICU length of stay, and ventilator-free days were summarized in terms of median and interquartile range. $P < 0.05$ was considered as statistically significant.

Results

Of a total of 301 patients who were intubated and mechanically ventilated for more than 2 days, 41 (13.6%) had a COS infection. Over half of them were >61 years of age. Males were twice more affected than females.

Table 1 shows the COS and non-COS patients and their various parameters. COS patients had a longer ICU length of stay as compared to non-COS patients (average of 10 days vs. 6.5 days, $P = 0.001$). The two groups had similar APACHE II scores (20 vs. 23, $P = 0.245$), lowest GCS scores in the first 24 h (7 vs. 5, $P = 0.659$), total leukocyte count at admission (15.2×10^3 cells/mm^3 vs. 13.2×10^3 cells/mm^3, $P = 0.242$), and mortality (36.6% vs. 38.1%, $P = 0.887$).

The various multidrug-resistant (MDR) organisms sensitive only to colistin, their occurrence among the four groups of intubated patients, and their sources are listed in Tables 2 and 3. Neurosurgical patients were the group most commonly affected by COS organisms, accounting for 13 of the 41 COS patients (31.7%). Sepsis patients accounted for 29.3% of the COS infections, respiratory patients 21.9%, and neurology 17% ($P = 0.150$).

Acinetobacter baumannii was the most common COS organism, accounting for 61% of cultures, followed by *Klebsiella pneumonia*, *Pseudomonas aeruginosa,* and *Escherichia coli*, accounting for 24%, 12%, and 2%, respectively ($P = 0.150$). Endotracheal secretion cultures were the most common source of COS organisms accounting for 66% of the isolates ($P = 0.059$). Urine, pus, and blood were the other sources, accounting for 17%, 7%, and 5% of the cultures, respectively.

The overall mortality of the COS-infected patients was 37%, with 15 deaths recorded in the study population of 41 patients. Of these, 8 deaths (53%) occurred in the sepsis

Table 1: Comparison of Acute Physiology and Chronic Health Evaluation II score, Glasgow Coma Scale score, white blood cell count, intensive care unit length of stay and mortality between colistin-only-sensitive and noncolistin-only-sensitive patients

Parameter	COS patients ($n=41$)	Non-COS patients ($n=260$)	*P*
APACHE II score, median (IQR)	20.0 (17.5-26.5)	23.0 (17.0-30.0)	0.245
GCS score, median (IQR)	7.0 (3.00-12.5)	5.0 (3.0-10.3)	0.659
WBC count, median (IQR)	15.2 (10.9-20.4)	13.2 (8.2-19.6)	0.242
ICU LOS, median (IQR)	10.0 (7.5-16.0)	6.5 (4.0-11.0)	0.001
Mortality (%)	36.6	38.1	0.887

APACHE: Acute Physiology and Chronic Health Evaluation, GCS: Glasgow Coma Scale, WBC: White blood cell, ICU: Intensive care unit, COS: Colistin-only-sensitive, IQR: Interquartile range, LOS: Length of stay

group ($P = 0.030$). ICU length of stay and ventilator-free days were not impacted by a specific COS organism [Table 4]. Mortality did not differ significantly between the 4 COS organism groups [Table 5].

Discussion

There are numerous studies that describe the epidemiology, morbidity, and mortality associated with MDR infections in ICU.[8-10] Endotracheal intubation and mechanical ventilation have been shown to be independent risk factors for developing nosocomial infections in the ICU.[11,12] However, the literature search has not shown any studies that compare infections by various MDR organisms among intubated patients.

In the present study, 41 of 301 patients (13.6%) who were intubated and mechanically ventilated for more than 2 days developed MDR COS infections. These patients had a lower APACHE II score, higher GCS score, higher total leukocyte count, and lower mortality than the non-COS patients, although these were non-significant findings. The COS group, however, had a longer stay in ICU ($P = 0.001$). This is a finding corroborated by many other studies; however, these studies were on non-intubated patients.[13-15]

The neurosurgery patients were observed to be the most vulnerable to MDR organisms, accounting for about 32% of the total MDR infections. Sepsis patients were the second-most commonly affected, followed by respiratory and neurology patients. There are a few studies looking into increased rates of sepsis in patients with neurological injury. This phenomenon has been described as spinal cord injury-induced immune deficiency syndrome (SCI-IDS),[16] characterized by a significant fall in CD14+ monocytes, CD3+ T-lymphocytes and CD19+ B-lymphocytes and MHC class II (HLA-DR) + cells in the 1st week following spinal cord injury, and central nervous system (CNS) injury-induced immunodepression, where there is suppression of cell-mediated immunity as a

Table 2: Distribution of colistin-only-sensitive organisms among various groups of mechanically ventilated patients

COS organism	Neurosurgery (*n*=13), *n* (%)	Neurology (*n*=7), *n* (%)	Respiratory (*n*=9), *n* (%)	Sepsis (*n*=12), *n* (%)	Percentage of total patients (*n*=41), *n* (%)
Acinetobacter baumannii	11/13 (84.6)	1/7 (14.3)	5/9 (55.6)	8/12 (66.7)	25/41 (61.0)
Pseudomonas aeruginosa	1/13 (7.7)	2/7 (28.6)	1/9 (11.1)	1/12 (8.3)	5/41 (12.2)
Klebsiella pneumoniae	1/13 (7.7)	4/7 (57.1)	3/9 (33.3)	2/12 (16.7)	10/41 (24.4)
Escherichia coli	0/13 (0.0)	0/7 (0.0)	0/9 (0.0)	1/12 (8.3)	1/41 (2.4)
Percentage of total COS patients	13/41 (31.7)	7/41 (17)	9/41 (21.9)	12/41 (29.3)	

χ^2=13.28, *P*=0.150. COS: Colistin-only-sensitive

Table 3: Source of colistin-only-sensitive organisms among various groups of mechanically ventilated patients

Culture	Neurosurgery (*n*=13), *n* (%)	Neurology (*n*=7), *n* (%)	Respiratory (*n*=9), *n* (%)	Sepsis (*n*=12), *n* (%)	Percentage of total cultures (*n*=41), *n* (%)
Endotracheal secretions	12/13 (92.3)	4/7 (57.1)	8/9 (88.9)	5/12 (41.7)	27/41 (65.8)
Urine	1/13 (7.7)	1/7 (14.3)	1/9 (11.1)	4/12 (33.3)	7/41 (17)
Blood	0/13 (0.0)	0/7 (0.0)	0/9 (0.0)	2/12 (16.7)	2/41 (4.9)
Pus	0/13 (0.0)	2/7 (28.6)	0/9 (0.0)	1/12 (8.3)	3/41 (7.3)

χ^2=16.42, *P*=0.059

Table 4: Intensive care unit length of stay and ventilator-free days among various colistin-only-sensitive organisms

	Acinetobacter baumannii (*n*=25)	*Pseudomonas aeruginosa* (*n*=5)	*Klebsiella pneumoniae* and *Escherichia coli* (*n*=11)	*P*
ICU LOS in days, median (IQR)	15.0 (7.5-19.5)	12.0 (7.0-15.0)	9.0 (5.0-15.0)	0.256
Ventilator free days, median (IQR)	4.0 (2.5-8.0)	6.0 (2.0-8.5)	5.0 (2.0-6.0)	0.738

ICU: Intensive care unit, IQR: Interquartile range, LOS: Length of stay

Table 5: Mortality in colistin-only-sensitive organism group and percentage of total mortality

Mortality	*Acinetobacter baumannii* (*n*=25), *n* (%)	*Pseudomonas aeruginosa* (*n*=5), *n* (%)	*Klebsiella pneumoniae* (*n*=10), *n* (%)	*Escherichia coli* (*n*=1), *n* (%)	*P*
Mortality within COS organism group	11/25 (44.0)	1/5 (20.0)	3/10 (30.0)	0/1 (0)	0.450
Percentage of overall mortality of COS group (*n*=15)	11/15 (73.3)	1/15 (6.7)	3/15 (20)	0/15 (0)	0.450

χ^2=1.59, *P*=0.450. COS: Colistin-only-sensitive

result of CNS injury.[17] However, the group of patients most commonly affected by MDR infections may vary from hospital to hospital. In another Indian study on nosocomial infections in the ICU, cardiovascular and respiratory patients were the most affected, followed by neurological and surgery patients.[12]

The most common organisms causing nosocomial infections in the ICU is another parameter that varies between hospitals and countries. The prevalent MDR organisms in India are *Acinetobacter, Klebsiella,* and *Pseudomonas*.[12,18,19] In this study, *Acinetobacter* was by far the most common MDR organism isolated, accounting for two-thirds of the infections, followed by *K. pneumoniae* and *Pseudomonas*, a finding similar to another study in a North Indian ICU.[18] Dasgupta *et al*. reported *Pseudomonas*, *E. coli*, Candida species, and *K. pneumoniae* as the most common isolates at an East Indian ICU.[12] In a study at a South Indian ICU, the most common organism was *Klebsiella*, followed by *E. coli*, *Acinetobacter,* and *Pseudomonas*.[19] In the SOAP study conducted in European ICUs, *Staphylococcus aureus*, *Pseudomonas* species, and *Escherichia coli* were the common organisms.[9] In an American study, the most common organisms were MRSA, *Pseudomonas,* and *Klebsiella*.[11]

In this study, ventilator-associated pneumonia (VAP) was the most common infection associated with MDR organisms, with endotracheal secretions accounting for two-thirds of the positive cultures. This finding is corroborated in other studies as well.[8,9,12] Urosepsis was the second-most common infection, as in other studies.[10-12] Blood and pus were the other sources of COS organisms.

It was also noted that cultures sent at admission either showed no growth or grew sensitive organisms. MDR organisms were generally isolated when the second or third culture samples had been sent, after an average of 7 days in ICU, indicating a hospital-acquired infection, with longer ICU length of stay for such patients being a risk factor.

Infections with MDR organisms when compared to non-MDR ones, contribute to greater hospitalization costs, poorer clinical outcomes, and higher mortality. The longer stay in both ICU and wards and greater expenditure on infection prevention and control result in the increased costs.[20]

A. baumannii was associated with a longer length of stay in ICU and fewer ventilator-free days, than the other COS organisms. It also had higher mortality, with death occurring in 44% of patients infected with this organism. It accounted for 73% of the mortality seen among COS patients. However, these findings were nonsignificant. This high mortality is also seen in other studies on *Acinetobacter*.[21,22] The ability of this organism to acquire and rearrange genetic determinants of antibiotic resistance as well as resist desiccation and persist on hospital materials and medical devices contributes to its high virulence.[23]

Patients with *K. pneumoniae* infection also had high mortality of 30% and contributed to a mortality of 20% within the COS patient group. A recent meta-analysis has shown significantly more deaths among carbapenem-resistant Enterobacteriaceae than in carbapenem-susceptible Enterobacteriaceae.[24] Patients with *Pseudomonas* infection had 20% mortality. In contrast, in the SOAP study, *Pseudomonas* species was the only microorganism independently associated with increased mortality rates.[9]

There are multiple factors leading to the acquisition and spread of MDR infections. Duration of mechanical ventilation more than 7 days and prior use of broad-spectrum drugs (third-generation cephalosporins, fluoroquinolones, and imipenem) were significant risk factors for VAP caused by MDR organisms.[25,26] Other risk factors for early-onset VAP by MDR organisms, especially *Acinetobacter*, include emergency intubation, aspiration, and a GCS score of 9 or less. Head trauma, neurosurgery, acute respiratory distress syndrome, and large-volume aspiration are in particular risk factors in the acquisition of *Acinetobacter*.[27] The use of carbapenems and third-generation cephalosporins appear to be related to the development of an MDR *A. baumannii*, whereas carbapenems and fluoroquinolones are implicated in MDR *Pseudomonas aeruginosa*.[28] Other risk factors include age more than 60 years and hospitalization in the past 4–12 months,[29] length of ICU stay,[8] and a positive fluid balance.[9]

There are four main mechanisms behind the emergence and further spread of resistant strains: (1) induction, (2) selection, (3) introduction, and (4) dissemination.[30] Antibiotic therapy may lead to the induction of resistance by mutation and also select and favor overgrowth of preexisting resistant flora. An increasing number of health-care workers and patients in the community, already colonized with resistant bacteria, have contributed to the increase in MDR microorganisms in the ICU. Finally, a delayed diagnosis resulting in a time lag to the initiation of appropriate antibiotics leads to the further dissemination of these microorganisms.[14] Resistance and its rapid evolution, however, make efforts to ensure initially appropriate antibiotic therapy (IAAT) more difficult, and IAAT is a key determinant of outcome in severe infection.[31]

The recognition of these risk factors can help to identify patients more likely to develop ESBL-producing infection, thus improving the approach to empiric antimicrobial treatment selection. Novel diagnostic techniques such as polymerase chain reaction, matrix-assisted laser desorption/ionization (MALDI), time-of-flight mass spectrometry, or chromogenic ESBL detection assays can significantly reduce the lag time between culture acquisition and ESBL status recognition, thereby enabling the earlier implementation of appropriate antibiotic therapy.[14]

The identification of these risk factors is also useful in preventing further outbreaks of by these organisms. This assumes greater importance as it is difficult to identify the actual source of the outbreaks. Risk factors such as antibiotic use and high numbers of device days have to be reduced or eliminated.

Basic infection prevention measures such as contact isolation of patients and strict compliance with hand hygiene measures are the other major preventative steps. Consultation with an infectious disease specialist with knowledge of the prevalence of MDR bacteria and the most recent antibiotic guidelines in the hospital significantly increases the administration of microbiologically correct antibiotic therapy.[32]

Colistin is a bactericidal antibiotic belonging to the class of polymyxins, which has been re-introduced to tackle MDR Gram-negative infections.[33] The initial site of action of colistin is the lipopolysaccharides and phospholipids in the outer cell membrane of Gram-negative bacteria. It binds to these membrane lipids and displaces the cations calcium and magnesium from the phosphate groups in the lipids.[6] This results in disruption of the outer cell membrane, leakage of intracellular contents, and bacterial death.

A. baumannii can rapidly develop resistance to polymyxin antibiotics by complete loss of this initial binding target, the lipid A component of lipopolysaccharide (LPS).[34] Resistance to colistin is associated with ICU length of stay, duration of mechanical ventilation, surgical procedures, inappropriate colistin use, use of monobactams, and duration of use of third-generation cephalosporins.[35]

Conclusion

Intubated and mechanically ventilated patients with multidrug resistant, Colistin-only-sensitive, Gram-negative infections may be expected to have a longer ICU length of stay than those with antibiotic sensitive infections. The most common infection noted with COS organisms was VAP. Those patients with bacteremia due to these organisms may have a high mortality.

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Conflicts of interest

There are no conflicts of interest.

References

1. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, *et al*. Bad bugs, no drugs: No ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis 2009;48:1-2.
2. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, *et al*. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: A molecular, biological, and epidemiological study. Lancet Infect Dis 2010;10:597-602.
3. Koch-Weser J, Sidel VW, Federman EB, Kanarek P, Finer DC, Eaton AE. Adverse effects of sodium colistimethate. Manifestations and specific reaction rates during 317 courses of therapy. Ann Intern Med 1970;72:857-68.
4. Michalopoulos AS, Tsiodras S, Rellos K, Mentzelopoulos S, Falagas M*E. coli*stin treatment in patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria: The renaissance of an old antibiotic. Clin Microbiol Infect 2005;11:115-21.
5. Garnacho-Montero J, Ortiz-Leyba C, Jiménez-Jiménez FJ, Barrero-Almodóvar AE, García-Garmendia JL, Bernabeu-WittelI M, *et al*. Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: A comparison with imipenem-susceptible VAP. Clin Infect Dis 2003;36:1111-8.
6. Falagas ME, Kasiakou SK. Colistin: The revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clin Infect Dis 2005;40:1333-41.
7. Falagas ME, Blizniotis IA, Kasiakou SK, Samonis G, Athanassopoulou P, Michalopoulos A. Outcome of infections due to pandrug-resistant (PDR) Gram-negative bacteria. BMC Infect Dis 2005;5:24.
8. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, *et al*. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302:2323-9.
9. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, *et al*. Sepsis in European intensive care units: Results of the SOAP study. Crit Care Med 2006;34:344-53.
10. Pradhan NP, Bhat SM, Ghadage DP. Nosocomial infections in the medical ICU: A retrospective study highlighting their prevalence, microbiological profile and impact on ICU stay and mortality. J Assoc Physicians India 2014;62:18-21.
11. Sonti R, Conroy ME, Welt EM, Hu Y, Luta G, Jamieson DB. Modeling risk for developing drug resistant bacterial infections in an MDR-naive critically ill population. Ther Adv Infect Dis 2017;4:95-103.
12. Dasgupta S, Das S, Chawan NS, Hazra A. Nosocomial infections in the intensive care unit: Incidence, risk factors, outcome and associated pathogens in a public tertiary teaching hospital of Eastern India. Indian J Crit Care Med 2015;19:14-20.
13. Sostarich AM, Zolldann D, Haefner H, Luetticken R, Schulze-Roebecke R, Lemmen SW. Impact of multiresistance of gram-negative bacteria in bloodstream infection on mortality rates and length of stay. Infection 2008;36:31-5.
14. Mauldin PD, Salgado CD, Hansen IS, Durup DT, Bosso JA. Attributable hospital cost and length of stay associated with health care-associated infections caused by antibiotic-resistant gram-negative bacteria. Antimicrob Agents Chemother 2010;54:109-15.
15. Shorr AF. Review of studies of the impact on Gram-negative bacterial resistance on outcomes in the intensive care unit. Crit Care Med 2009;37:1463-9.
16. Riegger T, Conrad S, Schluesener HJ, Kaps HP, Badke A, Baron C, *et al*. Immune depression syndrome following human spinal cord injury (SCI): A pilot study. Neuroscience 2009;158:1194-9.
17. Meisel C, Schwab JM, Prass K, Meisel A, Dirnagl U. Central nervous system injury-induced immune deficiency syndrome. Nat Rev Neurosci 2005;6:775-86.
18. John J, Thomas SM, Mathai AS, Rajkumar A. A prospective study on incidence and microbiological profile of ventilator associated pneumonia in the intensive care unit of a tertiary care centre. Int J Contemporary Med Res 2017;4:1840-3.
19. Porwal R, Gopalakrishnan R, Rajesh NJ, Ramasubramanian V. Carbapenem resistant Gram-negative bacteremia in an Indian intensive care unit: A review of the clinical profile and treatment outcome of 50 patients. Indian J Crit Care Med 2014;18:750-3.
20. Maslikowska JA, Walker SA, Elligsen M, Mittmann N, Palmay L, Daneman N, *et al*. Impact of infection with extended-spectrum β-lactamase-producing *Escherichia coli* or *Klebsiella* species on outcome and hospitalization costs. J Hosp Infect 2016;92:33-41.
21. Falagas ME, Blizniotis IA, Siempos II. Attributable mortality of *Acinetobacter baumannii* infections in critically ill patients: A systematic review of matched cohort and case-control studies. Crit Care 2006;10:R48.
22. Sunenshine RH, Wright MO, Maragakis LL, Harris AD, Song X, Hebden J, *et al*. Multidrug-resistant *Acinetobacter* infection mortality rate and length of hospitalization. Emerg Infect Dis 2007;13:97-103.
23. McConnell MJ, Actis L, Pachón J. *Acinetobacter baumannii*: Human infections, factors contributing to pathogenesis and animal models. FEMS Microbiol Rev 2013;37:130-55.
24. Falagas ME, Tansarli GS, Karageorgopoulos DE, Vardakas KZ. Deaths attributable to carbapenem-resistant *Enterobacteriaceae* infections. Emerg Infect Dis 2014;20:1170-5.
25. Trouillet JL, Chastre J, Vuagnat A, Joly-Guillou ML, Combaux D, Dombret MC, *et al*. Ventilator-associated pneumonia caused by potentially

drug-resistant bacteria. Am J Respir Crit Care Med 1998;157:531-9.
26. Akça O, Koltka K, Uzel S, Cakar N, Pembeci K, Sayan MA, *et al*. Risk factors for early-onset, ventilator-associated pneumonia in critical care patients: Selected multiresistant versus nonresistant bacteria. Anesthesiology 2000;93:638-45.
27. Baraibar J, Correa H, Mariscal D, Gallego M, Vallés J, Rello J. Risk factors for infection by *Acinetobacter baumannii* in intubated patients with nosocomial pneumonia. Chest 1997;112:1050-4.
28. Falagas ME, Kopterides P. Risk factors for the isolation of multi-drug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*: A systematic review of the literature. J Hosp Infect 2006;64:7-15.
29. Cardoso T, Ribeiro O, Aragão IC, Costa-Pereira A, Sarmento AE. Additional risk factors for infection by multidrug-resistant pathogens in healthcare-associated infection: A large cohort study. BMC Infect Dis 2012;12:375.
30. Bonten MJ, Mascini EM. The hidden faces of the epidemiology of antibiotic resistance. Intensive Care Med 2003;29:1-2.
31. Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillamet C, Kollef MH. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: A retrospective cohort study. Crit Care 2014;18:596.
32. Kerremans JJ, Verbrugh HA, Vos MC. Frequency of microbiologically correct antibiotic therapy increased by infectious disease consultations and microbiological results. J Clin Microbiol 2012;50:2066-8.
33. Michalopoulos AS, Falagas ME. Colistin: Recent data on pharmacodynamics properties and clinical efficacy in critically ill patients. Ann Intensive Care 2011;1:30.
34. Moffatt JH, Harper M, Harrison P, Hale JD, Vinogradov E, Seemann T, *et al*. Colistin resistance in *Acinetobacter baumannii* is mediated by complete loss of lipopolysaccharide production. Antimicrob Agents Chemother 2010;54:4971-7.
35. Matthaiou DK, Michalopoulos A, Rafailidis PI, Karageorgopoulos DE, Papaioannou V, Ntani G, *et al*. Risk factors associated with the isolation of colistin-resistant gram-negative bacteria: A matched case-control study. Crit Care Med 2008;36:807-11.