Multidrug Resistance Associated with Acute Kidney Injury Due to Sepsis or Systemic Inflammatory Response Syndrome in Intensive Care Unit Patients

Yoğun Bakım Ünitesi Hastalarında Sepsis veya Sistemik İnflamatuar Sendrom Nedeni ile Gelişen Akut Böbrek Hasarı ile İlişkili Çoğul İlaç Direnci

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ABSTRACT Objective: Sepsis and systemic inflammatory response syndrome (SIRS) are the most common causes of acute kidney injury (AKI) in intensive care unit (ICU) patients. This study aimed to investigate the relationship of infection, the causative microorganisms and their antimicrobial resistance patterns in ICU patients with sepsis/SIRS with the presence of AKI. **Material and Methods:** The microbiological data of 109 ICU patients with sepsis/SIRS with serum creatinine level <2 mg/dl and without known history of renal disease were evaluated retrospectively. **Results:** AKI incidence in sepsis (52%) and in SIRS groups (57%) were similar. In total, 61% of the patients were septic and 157 microorganisms were isolated. The most frequently isolated bacteria was coagulase-negative *Staphylococci* (22%). Isolation rate of *A. baumannii* in samples of patients with AKI was significantly more compared to those of without AKI (p=0.03). although isolation rate of *Pseudomonas aeruginosa* was higher in AKI group, the difference was not statistically significant. Multidrug resistance was more prevalent in *A. baumannii* strains isolated from AKI patients, and foun as 61%. **Conclusion:** The resistant *acinetobacter* infections in ICUs are considered as a the most threatfull problems in most ICUs throughout the world. In our hospital's ICU, incidence of infection due to resistant *A. baumannii* was found in mostly in AKI patients. Since immunosupressed AKI patients are more vulnerable to infection, the proper control of infection and appropiate antibiotic treatment become crucial factors for a better outcome in ICUs, especially in AKI patients.

Key Words: Intensive care units; *acinetobacter* infections; drug resistance, multiple; acute kidney injury

ÖZET Amaç: Sepsis ve sistemik inflammatuar yanıt sendromu (SIYS), yoğun bakım ünitesi hastalarında (YBÜ) akut böbrek hasarı (ABH)'nın en önemli nedenlerindendir. Bu çalışmada, sepsis/SIYS'si olan YBÜ hastalarında enfeksiyonun, etken mikroorganizmaların ve antimikrobiyal direnç paternlerinin ABH varlığı ile ilişkisinin araştırılması amaçlanmıştır. **Gereç ve Yöntemler:** Sepsis/SIYS gelişen, bilinen renal bozukluğu bulunmayan ve serum kreatinin düzeyi <2 mg/dL olan toplam 109 YBÜ hastasının mikrobiyolojik verileri geriye dönük olarak değerlendirildi. **Bulgular:** ABH insidansı, SIYS'lı grupta (%57) ve sepsisli grubta (%52) benzer oranlarda saptandı. Toplam %61 hastada sepsis saptandı ve 157 mikroorganizma izole edildi. En sık izole edilen bakteri koagülaz negatif stafilokok (%22) idi. ABH'ı olan hastalarda ABH olmayanlara kıyasla, *Acinetobacter baumannii* izolasyonu anlamlı derecede daha yüksek oranda bulundu (p=0,03). *Pseudomonas aeruginosa* izolasyonu ise ABH grubunda daha yüksek olmasına rağmen aradaki fark anlamlı bulunmadı. Çoğul ilaç direnci en fazla *A. baumannii*'de gözlendi ve ABH'lı hastadan izole edilen *A. baumannii* izolatlarının %61'inde çoğul ilaç direnci vardı. **Sonuç:** YBÜ'lerindeki dirençli Asinetobakter enfeksiyonları tüm dünyadaki YBÜ'lerinin en korkutucu sorunu olarak kabul edilmektedir. Hastanemiz YBÜ'nde, dirençli *A. baumannii* kaynaklı enfeksiyon yüksek oranda ABH'ı olan hastalarda saptanmıştır. Zaten immunosupresif olan ABH hastaları enfeksiyona daha yatkın olmaları nedeni ile, bu hastalarda enfeksiyon kontrolü ve uygun antibiyotik tedavisi, YBÜ'nde daha iyi bir tedavi sonlanımı için çok önemli faktörleri oluşturmaktadır.

Anahtar Kelimeler: Yoğun bakım üniteleri; *acinetobacter* enfeksiyonları; ilaç direnci, çoklu; akut böbrek hasarı

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Sepsis and systemic inflammatory response syndrome (SIRS) are the most common causes of acute renal failure in intensive care units (ICUs).[1] Avoiding the development of acute kidney injury (AKI) in ICU patients with sepsis is crucial because of its association of vicious negative outcomes.[2,3] Therefore, early control of infection is clearly the key factor to prevent multiorgan failure, including renal impairment, ultimately decreasing morbidity and mortality.

Approximately 37.0-57.2% of ICU patients were reported to be treated for infections.[4] Recently, treatment of infections has become more difficult to deal with, due to the emergence of antibiotic-resistant pathogens; the use of profuse amounts of inappropriate antibiotics might be one of the main reasons why resistance has developed worldwide. European prevelance of infection in intesive care (EPIC) study indicated that in the ICU, 62.8% out of 10,038 patients are treated with one antibiotic, while 51% use more than one antibiotic either for treatment or prophylaxis of infection.[5] Consequently, ICU-acquired infections are considered some of the most threatening nosocomial infections that decrease survival rates and increase the length of stay, rate of complications and hospital expenses.[6]

Up to approximately one third of patients in the ICU developed AKI.[7] The underlying cause of AKI is often multifactorial, but infection plays a well-known crucial role.[1-3,6-8] The considerable impact of nosocomial infections on mortality and length of stay in the ICU has been demonstrated in Turkey.[9,10] However, limited data are available about the epidemiology of infection in patients with AKI in the ICU. Therefore, the present study aimed: i) to evaluate the occurence of AKI in ICU patients with sepsis in comparison to SIRS patients who do not have any infection, and ii) to investigate the relationships of infection, responsible microorganisms and their antibiotic resistance patterns with the development of AKI in our tertiary university hospital in Turkey.

MATERIAL AND METHODS

This is a retrospective subgroup analysis of the patients' clinical and laboratory results in a tertiary University Hospital medical-surgical ICU between 2006 and 2008. All patients with sepsis and SIRS as defined by the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) consensus with initial serum creatinine <2 mg/dl and no history of previous renal disease were included in the study.[11] Based on this consensus, SIRS is defined as a temperature >38 °C or <36 °C, heart rate >90/min, respiratory rate >20/min or $PaCO_2$ <32 torr, and white blood cell count <4.000/mm^3 or >12.000/mm^3 or >10% bands and no evidence of infection and causative pathogens. Sepsis was defined as a condition where the patient met the SIRS criteria and presented with either a documented or a suspected infection.[12]

We excluded those patients with previous history of kidney disease and/or impairment of renal function or a creatinine level >2 mg/dl on admission, surviving less than 24 hours following admission to ICU, and who were younger than 17 years of age. Patients transferred from other hospitals were included if they reached sepsis/SIRS criteria at least 24 hours after admission to our ICU.

In total, 109 patients met the inclusion criteria and were included into this study. Patient's demographic characteristics, laboratory results, treatment schedules, outcomes, and comorbidities were recorded. The patients with malignancy, under chemotherapy or corticosteroid treatment were accepted as immunosuppressed and the patients who had been using oral anti-diabetic or insulin therapy were defined as having diabetes mellitus. The clinical and laboratory parameters of the patients for two weeks or until discharge or death after developing sepsis/SIRS were evaluated retrospectively. The severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score within 24 hours after admission. The sequential organ failure assessment (SOFA) score was also calculated on the day when patients were included into this study.[13,14]

The patients were grouped as Sepsis and SIRS, these both groups were also evaluated for the pres-

ence of AKI. AKI was defined based on the RIFLE (Risk, Injury, Failure, Loss, End stage renal failure) criteria described elsewhere.[15]

Decisions on infection or colonization were based on laboratory and clinical evidence. Nosocomial infections were diagnosed according to the standart definitions of the Centers for Disease Control and Prevention (CDC).[16] In the presence of these criteria, culture positive patients were considered as having infection of the site where the culture samples were obtained.

Blood samples were processed using the BACT/Alert system (Organon, Teknika, Durham, NC, USA). The identification of isolated microorganisms and their antimicrobial susceptibilities were tested using the Vitek-2 automatized system (Biomeréux, France), conventional methods were also used when necessary. Extended-spectrum beta-lactamase (ESBL) producing strains were screened based on ESBL alert of Vitek-2 system. Susceptibility criteria for MIC values were interpreted according to current guidelines from the Clinical Laboratory Standards Institute (CLSI).[17] Coagulase-negative Staphylococci were reported as the cause of a primary blood stream infection only if the patient had fever, chills, or hypotension, no clinical evidence of sepsis at another site and either had two or more positive cultures drawn on seperate occasions or had one positive blood culture and treatment was instituted.

Resistance data were collected only for some frequent pathogens and relevant antibiotics. For gram-negative bacteria, multidrug resistance (MDR) was defined as resistance to any three antibiotics in combination of these categories: quinolones, carbapenems, third generation cephalosporins or aminoglycosides.[18]

The statistical data were performed using SPSS version 13.0 software package (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed with Chi-square or Fisher's exact test where appropiate; Student's t-test was performed to analyze continuous variables. Statistical significance was defined as $p \leq 0.05$.

RESULTS

Over the two-year study period, a total of 109 patients with sepsis/SIRS were followed in the ICU.

The males constituted 58% of the patients. The mean age of the participants was 51.4±18.1 years. Sepsis was identified in 67 patients, and 42 patients were identified as having SIRS. The demographic data, comorbidity factors and outcome of patients with sepsis and SIRS are shown in Table 1. The prevelance of demographic data and comorbidities including AKI was not different in both groups. However, lenght of stay in ICU more than 20 days was higher in the sepsis group ($p<0.001$).

Several clinical features of the AKI and non-AKI patients are shown in Table 2. AKI was detected in 59 patients. AKI was more prevelant in patients older than 50 years of age. Moreover, AKI was associated with significantly higher SOFA scores and higher mortality rates. APACHE II scores were also found higher in AKI group, but the difference was not statistically significant. The distribution of patients according to RIFLE stages were as follows: RIFLE risk in 23 (21%), RIFLE injury in 19 (17%), RIFLE failure in 14 (13%) and RIFLE loss in 3 (3%)

TABLE 1: The clinical features of patients with sepsis and systemic inflammatory response syndrome. Data are presented as n (%) or mean±standard deviation.

	Patients with sepsis n (%)	Patients with SIRS n (%)	p value
Number of subjects (%)	67 (61)	42 (39)	
Demographic data			
Gender (male)	40 (60)	23 (58)	0.611
Age (years)	54.29±17.64	50.33±19.31	0.273
APACHE II Score	19.39±7.81	19.94±6.95	0.728
SOFA Score	9.67±1.80	9.57±2.13	0.793
Comorbidity factors			
Immunosuppression	9 (13)	9 (21)	0.274
Diabetes mellitus	17 (25)	5 (12)	0.088
AKI	35 (52)	24 (57)	0.617
Outcome			
LOS in ICU (>20 days)	36 (53)	4 (10)	<0.001
Mortality	25 (37)	16 (38)	0.935

SIRS: Systemic inflammatory syndrome; APACHE: Acute physiology and chronic health evaluation; SOFA: Sequential organ failure assessment; AKI: Acute kidney injury; LOS: Length of stay; ICU: Intensive care unit.

TABLE 2: The comparison of patients with and without acute kidney injury. Data are presented as n (%) or mean±standard deviation.

	AKI (n=59)	Non-AKI (n=50)	p value
Gender (female)	28 (47)	18 (36)	0.227
Age (>50 years)	39 (66)	22 (44)	0.021
APACHE II score	21.00±8.08	18.15±6.54	0.064
SOFA score	10.10±2.07	9.08±1.58	0.005
Mortality	29 (49)	12 (24)	0.007
LOS in ICU >20 days	19 (32)	21 (42)	0.290
Immunosuppression	12 (20)	6 (12)	0.243
Diabetes Mellitus	16 (27)	6 (12)	0.050
Blood culture (+)	24 (40)	27 (54)	0.165
Culture (+) other than blood	27 (46)	25 (50)	0.659

APACHE: Acute physiology and chronic health evaluation; SOFA: Sequential organ failure assessment; LOS: Length of stay; ICU: Intensive care unit.

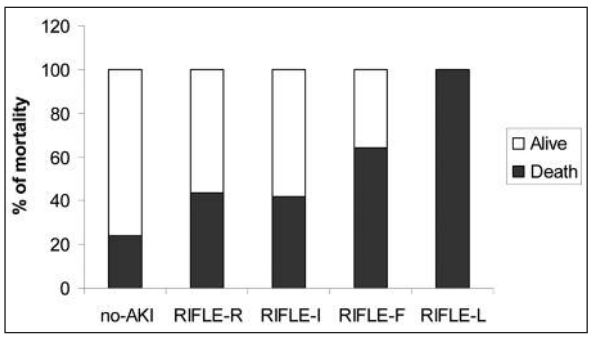

FIGURE 1: The association of renal damage with mortality in ICU patients. AKI: Acute kidney injury; RIFLE: Risk, Injury, Failure, Loss, End stage renal failure; RIFLE-R (Risk); RIFLE-I (Injury); RIFLE-F(Failure); RIFLE-L (Loss).

patients. In patients with AKI, mortality rate increased as the renal damage progressed (Figure 1).

In 2,835 total ICU days, 157 (6%) ICU-acquired infections were detected. Fifteen (25%) out of 67 septic patients experienced more than three infection episodes. The sites of infection were as follows: 45% respiratory tract, 33% bloodstream and 15% urinary tract. Out of 23 urinary tract infections (alone or concomitant), 13 (60%) were found in patients with AKI.

In the AKI group, 85 (10%) of the infection episodes occurred during 867 ICU days, while in the non-AKI group, only 72 (6%) of the episodes observed during 1,268 ICU days ($p<0.001$).

Infections were caused by gram-positive bacteria in 46.2% of patients, gram-negative bacteria in 46.8% and yeasts in 7%. The most frequently isolated bacteria were coagulase-negative staphylococci (CNS) (22%), followed by *Staphylococcus aureus* (17%), *P. aeruginosa* (12%), *A. baumannii* (11%), *Klebsiella pneumoniae* (8%) and *Escherichia coli* (6%) (Table 3). CNS was more predominantly isolated from blood cultures (50%) and *S. aureus* was most commonly isolated microorganism in the respiratory tract (30%) (Table 3). The distribution of most commonly isolated microorganisms in AKI and non-AKI patients is shown in Table 4. The isolation rate of bacteria

TABLE 3: The causative microrganisms by the sites in ICU-aquired infections.

Microorganisms	Bloodstream n (%)	Urinary tract n (%)	Respiratory tract* n (%)	Other n (%)	Total n (%)
Coagulase-negative staphylococci	26 (50)	3 (13)	4 (5)	1(8)	34 (22)
Staphylococcus aureus	4 (8)	--	21 (30)	1(8)	26 (17)
Pseudomonas aeruginosa	--	4 (17)	12 (17)	4 (30)	19 (12)
Acinetobacter baumannii	5 (10)	3 (13)	10 (14)	--	18 (11)
Enterococci and streptococci	6 (12)	3 (13)	5 (7)	1(8)	15 (10)
Klebsiella pneumoniae	1 (2)	3 (13)	5 (7)	3 (23)	12 (8)
Candida spp.	2 (4)	2 (9)	5 (7)	2 (15)	11 (7)
Escherichia coli	1 (2)	4 (17)	3 (5)	1(8)	9 (6)
Enterobacter spp.	4 (8)	1 (5)	1 (1)	--	6 (4)
Others	2 (4)	--	5 (7)	--	7 (5)
Total	51(100)	23 (100)	71(100)	13(100)	157(100)

*: Pneumonic infiltrations, upper and lower respiratory tract infections.

TABLE 4: Mostly isolated microorganisms in AKI and non-AKI patients.

Isolates	Patients with AKI n (%)	Patients with non-AKI n (%)	Total n	p
A. baumannii	14 (71)	4 (29)	18	0.030
P. aeruginosa	11 (56)	8 (42)	19	0.703
K. pneumoniae	8 (67)	4 (33)	12	0.352
E. coli	4 (45)	5 (55)	9	0.562
S. aureus	8 (54)	7 (46)	15	0.970
S. epidermidis	7 (44)	9 (56)	16	0.395
C. albicans	6 (75)	2 (25)	8	0.217
ESBL	5 (50)	5 (50)	10	0.786
MRSA	6 (55)	5 (45)	11	0.959

AKI: Acute kidney injury; ESBL: Extended spectrum betalactamase; MRSA: Methicillin resistant *Staphylococcus aureus.*

other than *A. baumannii* and *P. aeruginosa* were similar in both groups. *A. baumannii* isolates were significantly higher (p=0.030) and *P. aeruginosa* isolates were also higher but the result was not statistically significantly in AKI group compared to non-AKI group (p=0.703).

Among all bacteria isolated, the ESBL-producing bacteria and methicillin-resistant *S. aureus* (MRSA) ratios were 10 (6%) and 11 (7%), respectively. Six of MRSA and 5 of ESBL-producing bacteria were isolated from AKI patients (Table 4).

A total of 99 (91%) patients received antimicrobials during the study period either for treatment or prophylaxis. The most frequently used antibiotics were ampicillin/sulbactam, followed by imipenem, ampicillin, ciprofloxacin, gentamicin, cepha- losporins and piperacillin/tazobactam. Antibiotic resistance was mostly observed in gram-negative strains, especially among *P. aeruginosa* and *A. baumannii*. The resistance of *A. baumannii* against ampicillin/sulbactam and imipenem/meropenem were 94% (17/18) and 89% (16/18), respectively. The resistance against imipenem/meropenem, ceftazidime, cefepime, piperacillin/tazobactam and ciprofloxacin in Pseudomonas isolates were 39/29%, 53%, 44%, 53% and 29%, respectively.

The resistance to quinolones, carbapenems, third generation cephalosporins or aminoglycosides which was described as multi-drug resistance (MDR) was detected as 15 (83%) and 6 (32%) among all isolated *A. baumannii* and *P. Aeruginosa* organisms, respectively. MDR bacteria was observed in 18 (64%) of AKI patients and 10 of non-AKI patients (Table 5). In AKI patients, MDR was predominantly observed in 11 of 15 *A. baumannii* isolates. However, MDR in *P. aeruginosa* was equally observed in both groups (Table 5).

Eleven of AKI patients (61%) and 5 of non-AKI patients (50%) with MDR stayed more than 20 days in ICU (p>0.05). Mortality ratios in AKI and non-AKI patients with MDR were found as 44% and 20%, respectively (p>0.05).

DISCUSSION

The presence of infection in ICU patients was reported as one of the most significant reasons for the development of renal failure.[19] It was observed that the development of AKI in ICU patients with sepsis/SIRS increased the mortality rate and the higher mortality rate also correlated with the stages of renal damage determined by RIFLE criteria as previously reported.[7]

In this study, AKI incidence between sepsis and SIRS groups was similar; however, more infection episodes were observed in patients with AKI

TABLE 5: The infection sites and causative microrganisms resistant to ≥3 classes of antibiotics (third generation cephalosporins, carbapenems, aminoglycosides or quinolones) [multidrug resistant (MDR)] in AKI and non-AKI patients.

MDR bacteria isolated	Patients with AKI n (%)	Patients with non-AKI n (%)	Total number of MDR isolates n
E. faeceium	2 (40)	3 (60)	5
P. aeruginosa	3 (50)	3 (50)	6
A. baumannii	11 (73)	4 (27)	15
E. coli	1 (100)	0	1
K. pneumoniae	1 (100)	0	1
Infection site			
Tracheal aspirate	10 (66)	4 (34)	15
Urine	4 (75)	1 (25)	5
Blood	4 (50)	4 (50)	8
Catheter	0	1 (100)	1
Tissue	1 (100)	0	1

AKI: Acute kidney injury; MDR: Multidrug resistant.

compared to non-AKI group during their ICU stays. Although the most common site of infection was the respiratory tract in all patients, urinary tract infections were foundto be predominantly higher in AKI patients compared to non-AKI patients. There are limited data available about infection in ICU patients with AKI. However, it was reported that nosocomial bloodstream infections in ICU patients with ARF (acute renal failure) treated with renal replacement therapy (RRT) were found as 8.8% which was higher than the patients without RRT (3.5%), and the most frequent sources of the nosocomial bloodsream infections were reported as lungs (26%) while urinary tract was found responsible for only 10% of these infections.[20]

In previous studies, gram-negative bacteria have been reported to be predominant in ICUs of training hospitals in Turkey and in other countries as well.[21,22] However, in recent years we have seen a shift in the pattern of infecting organisms towards gram-positive infections.[23] In our study, infections caused by gram-positive and gram-negative bacteria likely did not differ in prevalence. This result demonstrated that there is an increasing trend of nosocomial bloodstream infections caused by gram-positive bacteria.

A study including 22 Turkish University hospitals and their 56 ICUs showed that infections were mostly caused by *P. aeruginosa* (20.8%), *S. aureus* (18.2%), *Acinetobacter spp.* (18.2%) and *Klebsiella* spp. (16.1%).[23] In contrast, the isolation rates of *P. aeruginosa* and *A. baumannii* were found lower in our study. However, the results from the National Nosocomial Infections Surveillance system reported that the proportion of *A. baumannii* was significantly higher in 2003 compared to 1986.[24] A review by Archibald showed that the types of pathogens encountered in health care institutions in North America, Europe, Asia, and even Africa were largely similar, suggesting that the pathogens' reservoirs, which are often the patients themselves, and the risk factors for hospital-acquired infections, such as invasive devices, which are also similar worldwide.[24]

There is an increasing trend in the prevelance of gram-negative bacteria with multidrug resistance in ICUs in the world.[25] In our study, MDR especially resistant to imipenem was mostly observed in Acinetobacter isolates. Carbapenem have retained anti-Acinetobacter activity better than most other antimicrobial classes.[25] Carbapenems lost their activity against Acinetobacteria due to emerging carbapenemases belonging to beta-lactamase classes B and D in the genus. Major outbreaks of resistant carbapenemase producers have occurred in a few centers in the world.[26-27] The situation is not much different in our country as shown in a recent Turkish retrospective study which claimed that imipenem resistance among Acinetobacter strains increased significantly (from 43% to 72.9%) each year.[28] Similary, highest rates of resistance (100%) of *A. baumannii* was observed against piperacillin-tazobactam, ampicillin-sulbactam and ciprofloxacin, followed by imipenem and cefepime (78%), meropenem and ceftazidime (55%) in a ICU of a Turkish tertiary care hospital.[29] A multicenter surveillance study (Hitit-2) in Turkey demonstrated that in *P. Aeruginosa,* the lowest rate of resistance was observed with piperacillin-tazobactam (18.1%) *and A. baumannii* isolates were highly resistant to all antimicrobial agents, the lowest rate of resistance was observed against cefoperazone/sulbactam (52%) followed by imipenem (55%).[30] In our study, a very high imipenem/meropenem and ampicillin/ sulbactam resistance rates were found in *A. baumannii*. Interestingly, *A. baumannii* with MDR were mostly isolated from AKI patients. It is our opinion, AKI patients, especially the ones with other organ failures, might become immunosuppressed and stay longer in ICU. Consequently, this might lead overuse of antibiotics, particularly carbapenems. This might cause the emergence of MDR and a high mortality, as we found in our study. In addition, mechanical ventilation, central venous catheters, hemodialysis treatment, malignancy and stay in ICU were reported independently as the associated risk factors for the carbapenem resistance of *A. baumannii*.[28]

In conclusion, this study pointed out that there is an alarmingly high rate of resistance to carbapenems, cephalosporins and the beta-lactam-betalactamase inhibitor group of drugs in ICU pa-

tients with AKI in our hospital. MDR was more frequently observed in *A. baumannii* compared to other isolates. No simple explanation was found about the relationship between MDR and AKI sepsis/SIRS cases in ICU; but immunosuppressive uremic condition may be a factor for being vulnarable to infection due to resistant bacteria. Subsequently, this condition may cause inappropriate antibiotic use probably creating the risk for the isolation of MDR organisms. However, further studies are needed to explain why criticall ill cases with AKI were more prone to the infections with MDR bacteria. As this study demonstrated, it is the reality that we have only a few antibiotics left for the treatment of gram-negative bacteria in ICU. Thus, proper infection control measures and the determination of optimal antimicrobial therapy are quite important in critically-ill patients to prevent antimicrobial resistance and to increase the survival rate as well as outcome of the patients.

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REFERENCES

1. Kellum JA. Acute kidney injury. Crit Care Med 2008;36(4 Suppl):S141-5.
2. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. Lancet 2005;365(9457):417-30.
3. Schrier RW, Wang W. Acute renal failure and sepsis. N Engl J Med 2004;351(2):159-69.
4. Reynvoet E, Vandijck DM, Blot SI, Dhondt AW, De Waele JJ, Claus S, et al. Epidemiology of infection in critically ill patients with acute renal failure. Crit Care Med 2009;37(7): 2203-9.
5. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA 1995;274(8):639-44.
6. Vincent JL. Nosocomial infections in adult intensive-care units. Lancet 200;361(9374): 2068-77.
7. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 2006; 10(3):R73.
8. Yegenaga I, Hoste E, Van Biesen W, Vanholder R, Benoit D, Kantarci G, et al. Clinical characteristics of patients developing ARF due to sepsis/systemic inflammatory response syndrome: results of a prospective study. Am J Kidney Dis 2004;43(5):817-24.
9. Yegenaga I, Tuglular S, Ari E, Etiler N, Baykara N, Torlak S, et al. Evaluation of sepsis/systemic inflammatory response syndrome, acute kidney injury, and RIFLE criteria in two tertiary hospital intensive care units in Turkey. Nephron Clin Pract 2010;115(4):c276-82.
10. Meric M, Willke A, Caglayan C, Toker K. Intensive care unit-acquired infections: incidence, risk factors and associated mortality in a Turkish university hospital. Jpn J Infect Dis 2005;58(5):297-302.
11. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20(6): 864-74.
12. Bone RC. Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS). Ann Intern Med 1996;125(8): 680-7.
13. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13(10):818-29.
14. Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998;26(11):1793-800.
15. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8(4):R204-12.
16. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988; 16(3):128-40.
17. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Twentieth Informational Supplement. CLSI Document M100-S21, Wayne, PA: CLSI; 2010; 31(1):42-68.
18. Souli M, Galani I, Giamarellou H. Emergence of extensively drug-resistant and pandrug-resistant Gram-negative bacilli in Europe. Euro Surveill 2008;13(47). pii: 19045.
19. Tozija L, Antova Z, Cakalaroski K, Polenakovic M, Spasovski G. Infection as a risk factor in the outcome of patients with acute renal failure assessed by SOFA score. Prilozi 2006; 27(1):17-27.
20. Hoste EA, Blot SI, Lameire NH, Vanholder RC, De Bacquer D, Colardyn FA. Effect of nosocomial bloodstream infection on the outcome of critically ill patients with acute renal failure treated with renal replacement therapy. J Am Soc Nephrol 2004;15(2):454-62.
21. Esen S, Leblebicioglu H. Prevalence of nosocomial infections at intensive care units in Turkey: a multicentre 1-day point prevalence study. Scand J Infect Dis 2004;36(2):144-8.
22. Gaynes R, Edwards JR; National Nosocomial Infections Surveillance System. Overview of nosocomial infections caused by gram-negative bacilli. Clin Infect Dis 2005;41(6):848-54.

23. Rello J, Ochagavia A, Sabanes E, Roque M, Mariscal D, Reynaga E, et al. Evaluation of outcome of intravenous catheter-related infections in critically ill patients. Am J Respir Crit Care Med 2000;162(3 Pt 1):1027-30.
24. Archibald LK. Gram-negative, hospital-acquired infections: a growing problem. Infect Control Hosp Epidemiol 2004;25(10):809-11.
25. Goel N, Chaudhary U, Aggarwal R, Bala K. Antibiotic sensitivity pattern of gram negative bacilli isolated from the lower respiratory tract of ventilated patients in the Intensive care unit. Indian J Crit Care Med 2009;13(3):148-51.
26. Di Popolo A, Giannouli M, Triassi M, Brisse S, Zarrilli R. Molecular epidemiological investigation of multidrug-resistant Acinetobacter baumannii strains in four Mediterranean countries with a multilocus sequence typing scheme. Clin Microbiol Infect 2011;17(2):197-201.
27. Richet HM, Mohammed J, McDonald LC, Jarvis WR. Building communication networks: international network for the study and prevention of emerging antimicrobial resistance. Emerg Infect Dis 2001;7(2):319-22.
28. Dizbay M, Tunccan OG, Sezer BE, Hizel K. Nosocomial imipenem-resistant Acinetobacter baumannii infections: epidemiology and risk factors. Scand J Infect Dis 2010;42(10):741-6.
29. Bacakoğlu F, Korkmaz Erken P, Taşbakan MS, Başarik B, Pullukçu H, Aydemir S, et al. [Multidrug-resistant Acinetobacter baumannii infection in respiratory intensive care unit]. Bulletin of Microbiology 2009;43(4):575-85.
30. Gur D, Hascelik G, Aydin N, Telli M, Gültekin M, Ogülnç D, et al. Antimicrobial resistance in gram-negative hospital isolates: results of the Turkish HITIT-2 Surveillance Study of 2007. J Chemother 2009;21(4):383-9.