Short Communication

# Bacterial resistance in the intensive care unit of developing countries: Report from a tertiary hospital in Kazakhstan

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## ARTICLE INFO

## ABSTRACT

*Objectives:* The aim of this study was to describe the patterns of antimicrobial resistance (AMR) of bacterial isolates causing hospital-acquired infections (HAIs) in the intensive care unit (ICU) of a tertiary hospital in Kazakhstan.
*Methods:* This was a retrospective analysis of AMR in the ICU of the National Research Center for Oncology and Transplantation (Astana, Kazakhstan) during the year 2015.
*Results:* During the study period, 546 patients were admitted to the ICU, of whom 135 (24.7%) developed at least one HAI. Most HAIs caused by Gram-positive bacteria were due to *Enterococcus faecalis*, which were resistant to aminoglycosides in >70% cases. Gram-negative bacteria were isolated in ca. 50% of cases, thus representing the greatest burden of HAIs. Very high resistance rates to ceftriaxone, cefotaxime and cefuroxime were observed. Moreover, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* were resistant to carbapenems in <20% and in ca. 45% of cases, respectively.
*Conclusion:* This study demonstrates the urgent need to implement more rational use of antimicrobials in Kazakhstan, which can be done only by establishing a proactive surveillance system along with an appropriate infection control programme.

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## 1. Introduction

Hospital-acquired infections (HAIs) are caused by infectious agents that have been encountered by patients in the hospital setting; therefore, the definition includes all infections that are not present or incubating at the time of admission to the hospital. Practically, infections manifesting >48 h after hospital admission are usually considered to be HAIs [1].

HAIs are an important cause of increased morbidity and mortality and represent a serious clinical issue, especially in the intensive care unit (ICU) where their incidence is 5–10 times greater than in general wards [2].

According to the 2016 report of the European Centre for Disease Prevention and Control (ECDC), which refers to the year 2014, ca. 8% of patients staying in the ICU for >2 days presented with at least one ICU-related HAI [3]. In developing countries, the burden of HAIs is more significant, and in Kazakhstan we previously described an incidence of ca. 20% in the ICU of the National Research Center for Oncology and Transplantation (NRCOT) located in Astana [4].

The consequences of HAIs for patients are worsened by the fact that bacteria in the hospital setting are more likely to develop antimicrobial resistance (AMR) and, especially in ICUs, these bacteria are frequently multidrug-resistant. Thus, the emergence of AMR in the ICU leads to long-term sequelae and/or increases mortality rates as well as healthcare costs [5].

According to the ECDC, in European ICUs 25% of *Staphylococcus aureus* isolates were methicillin-resistant *S. aureus* (MRSA), and Gram-negative bacterial resistance to third-generation cephalosporins and carbapenems was 17–44% and 28–64%, respectively,

depending on the different bacterial species [3]. Such an issue may become even more concerning in developing countries where specific and efficient surveillance systems are still lacking and where rational policies for antimicrobial therapy are difficult to implement for economic reasons [6]. Regarding Kazakhstan specifically, currently there are no documents regarding the surveillance on AMR. Here we report clinical data regarding the emergence of AMR in bacteria causing HAIs in the ICU of a tertiary hospital in Astana.

## 2. Materials and methods

This study was carried out the 12-bed ICU of NRCOT of University Medical Center, a tertiary-care hospital in Astana, Kazakhstan.

Laboratory data were retrospectively collected from all patients with ICU-related HAIs from 1 January 2015 to 31 December 2015. This study was approved by the Human Research and Ethics Committee of Nazarbayev University School of Medicine (Astana, Kazakhstan).

All adult (age ≥ 18 years) ICU patients developing HAIs were included in this study. These were patients admitted to the ICU because of major surgical and medical procedures of different types (oncological, gynaecological, orthopaedic, vascular, abdominal and thoracic).

According to the guidelines provided by the Healthcare Infection Control Practices Advisory Committee (HICPAC) [7], laboratory investigations (including total blood cell count, complete biochemistry and coagulation panel) were routinely performed in all high-risk ICU patients with underlying chronic diseases and/or primary/secondary immunodeficiency in order to diagnose HAIs as soon as possible. Moreover, chest radiography, deep tracheal aspirate and bronchoalveolar lavage were performed if ventilator-associated pneumonia (VAP) was suspected. Cultures from peripheral blood, tips of removed intravascular catheters, urine and urinary/wound catheters were variably obtained according to the clinical suspicion of bloodstream infection, urinary tract infection or surgical site infection, respectively. Microbiological samples were cultured and identified both using standard microbiological methods (such as Gram stain and analysis of colony morphology and biochemical properties) and

mass spectrometry (VITEK® MS). Isolated bacteria were tested for antimicrobial susceptibility by the Kirby–Bauer disk diffusion method according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) [8].

## 3. Results

During the 12-month study period, 546 patients were admitted to the ICU, of whom 135 (24.7%) developed at least one HAI. The overall HAI-related mortality rate was 5.11%.

The following types of HAI were diagnosed: VAP ($n = 42$); urinary tract infection ($n = 25$); bloodstream infection ($n = 25$); and surgical site infection ($n = 45$). In all cases it was possible to isolate the causative bacteria from one or more biological samples.

Overall, the most frequent pathogens were *Enterococcus faecalis* (20%), *Klebsiella pneumoniae* (15%), *Pseudomonas aeruginosa* (14%), *Escherichia coli* (10%), *Acinetobacter baumannii* (8%), *S. aureus* (4%), *Staphylococcus epidermidis* (4%), *Streptococcus mitis* (4%) and *Streptococcus haemolyticus* (4%). *Candida* spp. were isolated in 9–10% of cases, whereas other less frequent bacteria (*Citrobacter* spp., *Staphylococcus saprophyticus*, *Enterococcus cloacae*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*) were isolated in the remaining samples.

The patterns of AMR for the most frequent Gram-positive and Gram-negative bacteria implicated in HAIs are reported in Tables 1 and 2, respectively.

Briefly, the data showed very high rates of resistance to ceftriaxone (66.7%), cefotaxime (66.7%) and cefuroxime (75.0–88.9%) among Enterobacteriaceae. Moreover, 55.6% of *E. coli* and 25.0% of *K. pneumoniae* were also resistant to cefepime. However, no significant resistance to amikacin or carbapenems has yet emerged in these bacteria. Unfortunately, the situation is different for *P. aeruginosa* and *A. baumannii* with rates of resistance to the aforementioned classes of antibiotics of >15% and >40%, respectively, in addition to very high rates of resistance to third-generation cephalosporins. Regarding Gram-positive bacteria, the most striking finding is the isolation of strains resistant to aminoglycosides in >70–100% of cases; however all main bacterial species (namely *S. haemolyticus*, *E. faecalis* and *S. aureus*) have not yet developed resistance to vancomycin or linezolid.

**Table 1**
Antimicrobial resistance in Gram-positive bacteria in the intensive care unit of a tertiary hospital in Kazakhstan, expressed as a percentage of total isolates for each bacterial species.[a]

| Antimicrobial agent | Resistance (%) | | |
|---|---|---|---|
| | *Streptococcus haemolyticus* ($n = 5$) | *Enterococcus faecalis* ($n = 28$) | *Staphylococcus aureus* ($n = 5$) |
| Gentamicin | 100 | 71.4 | – |
| Ciprofloxacin | 0 | 25.0 (6/24) | – |
| Levofloxacin | 0 | 25.0 (6/24) | – |
| Ampicillin | – | 7.1 | – |
| Amoxicillin | – | 0 | – |
| Tetracycline | 25.0 (1/4) | 33.3 (9/27) | 20.0 |
| Doxycycline | 25.0 (1/4) | – | 20.0 |
| SXT | 0 | – | 0 |
| Penicillin | 100 | 13.0 (3/23) | 100 |
| Oxacillin | 100 | – | 0 |
| Erythromycin | 100 | – | 20.0 |
| Clarithromycin | 100 | – | 20.0 |
| Azithromycin | 100 | – | 20.0 |
| Clindamycin | 100 | – | – |
| Vancomycin | 0 | 0 (0/24) | 0 |
| Linezolid | 0 | 0 (0/24) | 0 |
| Moxifloxacin | 0 | – | – |
| Chloramphenicol | 100 (4/4) | – | – |
| Norfloxacin | – | 25.0 (6/24) | – |
| Nitrofurantoin | – | 25.0 (6/24) | – |

SXT, trimethoprim/sulfamethoxazole.
[a] Antimicrobial resistance data were not available for some antibiotics for all of the isolates; in these cases, the total number of isolates is given in parenthesis.

**Table 2**
Antimicrobial resistance in Gram-negative bacteria in the intensive care unit of a tertiary hospital in Kazakhstan, expressed as a percentage of the total isolates for each bacterial species.[a]

| Antimicrobial agent | Resistance (%) | | | |
| --- | --- | --- | --- | --- |
| | *Pseudomonas aeruginosa* (n = 17) | *Escherichia coli* (n = 18) | *Klebsiella pneumoniae* (n = 18) | *Acinetobacter baumannii* (n = 9) |
| Piperacillin | 64.7 | 90.0 (9/10) | 25.0 (4/16) | 44.4 |
| Ceftazidime | 70.6 | – | – | – |
| Gentamicin | 41.2 | 20.0 (2/10) | – | 44.4 |
| Tobramycin | 0 | 50.0 (5/10) | – | – |
| TZP | 35.3 | 0 | 0 (0/16) | 44.4 |
| Cefepime | 64.7 | 55.6 | 25.0 (4/16) | 88.9 |
| Ticarcillin | 82.4 | – | – | – |
| Imipenem | 11.8 | 0 | 0 (0/16) | 44.4 |
| Aztreonam | 64.7 | – | – | – |
| Amikacin | 23.5 | 0 | 0 (0/16) | 44.4 |
| Ciprofloxacin | 17.6 | 44.4 | 8.3 (1/12) | 44.4 |
| Levofloxacin | 17.6 | 44.4 | 9.1 (1/11) | 44.4 |
| Meropenem | 17.6 | 0 | 0 | 44.4 |
| Ampicillin | – | 100 | 100 (16/16) | – |
| Cefazoline | – | 100 | 75.0 (12/16) | – |
| Amoxicillin | – | 100 | 100 (16/16) | – |
| SAM | – | 80.0 (8/10) | 50.0 (8/16) | 77.8 |
| Ceftriaxone | – | 66.7 | 66.7 | 88.9 |
| Cefotaxime | – | 66.7 | 66.7 | 88.9 |
| Cefuroxime | – | 88.9 | 75.0 (12/16) | – |
| AMC | – | 100 | 75.0 (12/16) | – |
| TCC | – | 100 | 27.8 | |

TZP, piperacillin/tazobactam; SAM, ampicillin/sulbactam; AMC, amoxicillin/clavulanic acid; TCC, ticarcillin/clavulanic acid.

[a] Antimicrobial resistance data were not available for some antibiotics for all of the isolates; in these cases, the total number of isolates is given in parenthesis.

## 4. Discussion

To our knowledge, this is the first study from Kazakhstan reporting data on the AMR of bacteria responsible for ICU-related HAIs. Kazakhstan is a middle-income, developing country. For economic reasons, the use of antibiotics (e.g. imipenem, meropenem, linezolid and aztreonam) has been introduced only recently and in limited supplies; moreover, microbiological analysis of bacterial susceptibility to antibiotics still presents some technical difficulties, e.g. it was not possible to test for extended-spectrum β-lactamase (ESBL) production by the bacterial isolates. Therefore, specific surveillance systems for HAIs and a rational policy for the use of antibiotics in the hospital setting are still lacking and must be fully implemented [4,6]. This is a very important issue for Kazakhstan: indeed, in this study the rate of ICU-related HAIs was at least three times greater than in European countries (24.7% vs. 8.0%).

The ECDC provides annual epidemiological reports for countries that are members of the European Community regarding ICU-related HAIs, which also includes data on the patterns of AMR. In September 2011, all 53 countries of the World Health Organization (WHO) European Region adopted the European strategic action plan on AMR; however, the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) network could involve only a few countries and Kazakhstan was not able to participate. Therefore, these kinds of epidemiological data have not been available for Kazakhstan so far [3,6]. The current study first provides data on AMR in ICUs. Indeed, only two reports on this topic are available from Kazakhstan. Azizov et al. described the antimicrobial susceptibility of nosocomial *A. baumannii* strains isolated in some tertiary hospitals in Central Kazakhstan [9]. Very recently, Shalekenov et al. reported the patterns of antimicrobial susceptibility and the molecular genetic mechanisms of resistance of Gram-negative bacteria isolated in the Department of Urology of one hospital in Almaty, Kazakhstan [10]. However, neither of these studies were focused on the ICU.

Very briefly, the latest ECDC report highlighted that: (i) 25% of *S. aureus* isolates were MRSA; (ii) resistance to third-generation cephalosporins was reported in 17% of *E. coli* isolates, 44% of

*Klebsiella* spp. isolates and 44% of *Enterobacter* spp. isolates; and (iii) carbapenem resistance was reported in 8% of *Klebsiella* spp. isolates, 28% of *P. aeruginosa* isolates and 64% of *A. baumannii* isolates [3]. These findings can be a good comparison for the data in the current study.

*Staphylococcus* spp. were implicated in <10% HAIs in the ICU in the current study, and the incidence of MRSA strains was very low. Most HAIs caused by Gram-positive bacteria were due to *E. faecalis* (20%), which was resistant to aminoglycosides in >70% of cases. Such a high rate of isolation of *Enterococcus* spp. can be explained by the preponderance of patients undergoing abdominal surgery (including hemicolectomy due to colorectal cancer) in the study cohort. Indeed, several studies have reported *Enterococcus* spp. as being a common causative pathogen of HAI following major surgical intervention on the gastrointestinal tract [11,12].

Conversely, Gram-negative bacteria were isolated in ca. 50% of cases, thus representing the greatest burden of HAIs.

Third-generation cephalosporins represent the first approach against *E. coli* and *K. pneumoniae* infections. The current data showed significant resistance rates to ceftriaxone, cefotaxime and cefuroxime. Moreover, >50% of *E. coli* and 25% of *K. pneumoniae* isolates were also resistant to cefepime. This concerning finding can be explained by considering the higher use of these antibiotics owing to their greater availability in Kazakhstan compared with other antibiotic classes such as carbapenems, which are reserved for other types of infections in our local context, as described below.

Carbapenems (imipenem, meropenem) represent the most important antibiotics to treat HAIs sustained by two dangerous opportunistic agents, namely *P. aeruginosa* and *A. baumannii* [13]. Compared with the ECDC data, in the ICU in the current study the resistance rates to imipenem and meropenem were lower: *P. aeruginosa* was resistant in 11.8% and 17.7% of cases (vs. 28%), respectively, and *A. baumannii* has a similar resistance pattern (44.4% vs. 64%) against both antibiotics. At first glance this result may be comforting, but it is really the contrary if we consider that carbapenems have been available for only a few years in Kazakhstan and, as mentioned, their use is quite selective. As

mentioned, this phenomenon probably relied on inaccurate policies of antimicrobial use that might have been also due to an inconsistent supply of antimicrobial agents and to the lack of resources to obtain a routine and complete analysis of the patterns of antimicrobial susceptibility.

These warnings are consistent with what has also been evidenced in other developing countries. Very recently, Tran et al. described the patterns of AMR in ICU patients admitted in a tertiary hospital in Vietnam, focusing their attention on VAP: *P. aeruginosa* and *A. baumannii* were essentially resistant to ceftazidime, ceftriaxone, piperacillin, imipenem, meropenem, ertapenem, ciprofloxacin and levofloxacin; moreover, high rates (>70%) of ceftriaxone- and ceftazidime-resistant *Klebsiella* spp. were also observed [14].

In conclusion, this study demonstrates the urgent need to implement more rational use of antimicrobials in Kazakhstan, which can be done only by establishing a proactive surveillance system along with an appropriate programme of infection control.

## Funding

## Competing interests

None declared.

## Ethical approval

This study was approved by the Human Research and Ethics Committee of Nazarbayev University School of Medicine (Astana, Kazakhstan).

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