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BLOODSTREAM INFECTIONS AND ANTIMICROBIAL RESISTANCE OF RESPONSIBLE PATHOGENS IN UKRAINE: RESULTS OF A MULTICENTER STUDY (2013-2015)

Aidyn G. Salmanov[1], Yuriy V. Voronenko[1], Sergiy O. Vozianov[1], Yelizaveta Ye. Shunko[1], Maryna Ye. Mamenko[1], Olga M. Verner[1], Vasyl M. Mykhalchuk[1], Stanislav V. Vydyborets[1], Volodymyr O. Shkorbotun[1], Halyna V. Beketova[1], Olena M. Okhotnikova[1], Nadiya V. Goryainova[2], Olena A. Oshlianska[1], Olga Laksha[1], Olena Bielova[1], Volodymyr Yo. Shuba[1], Tetyana M. Osadcha[3]

[1]SHUPYK NATIONAL MEDICAL ACADEMY OF POSTGRADUATE EDUCATION, KYIV, UKRAINE
[2]STATE INSTITUTE OF HAEMATOLOGY AND TRANSFUSIOLOGY OF NAMS OF UKRAINE, KYIV, UKRAINE
[3]NATIONAL PEDAGOGICAL M. DRAGOMANOV UNIVERSITY, KYIV, UKRAINE

ABSTRACT

Introduction: Bloodstream infections (BSIs) are associated with high morbidity and mortality worldwide. However data of BSI from Ukraine are scarce.

The aim: To obtain the first national estimates of the current incidence of BSI and antimicrobial resistance of responsible pathogens, and associated mortality in Ukraine.

Materials and methods: A retrospective multicenter cohort study was conducted at the 14 hospitals of Ukraine between January 2013 to December 2015. Definitions of BSIs were adapted from the CDC. The identification and antimicrobial susceptibility of cultures were determined, using automated microbiology analyzer. Some antimicrobial susceptibility test used Kirby - Bauer antibiotic testing.

Results: Among 20,544 patients, 3816 (18.6%) BSIs were observed. The rate of health care associated BSI was 92.4%. Death was reported in 68.4% BSI cases. The predominant pathogens were: *Klebsiella pneumoniae* (25.1%), *Escherichia coli* (17.5%), *Staphylococcus aureus* (9.9%), *Pseudomonas aeruginosa* (8.9%), and *Acinetobacter* spp.(8.5%). The overall proportion of extended spectrum beta-lactamase (ESBL) production among Enterobacteriaceae was 24.8% and of methicillin-resistance in *S. aureus* (MRSA) 38.2%. Vancomycin resistance was observwd in 9.2% of isolated enterococci (VRE). Carbapenem resistance was identified in 33.1% of *P.aeruginosa* isolates and 63.2% of *A. baumannii* isolates. Resistance to third-generation cephalosporins was observed in 14.2% *K. pneumoniae* and *E.coli* 55% isolates.

Conclusions: Healthcare-associated BSIs and antimicrobial resistance of responsible pathogens together with their associated impact on mortality, presents a significant burden to the Ukraine hospital system. Surveillance of BSIs may help to delineate the requirements for infection prevention and control.

KEY WORDS: Bloodstream Infections, Healthcare-associated infection, Mortality, Pathogens, antimicrobial resistance

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INTRODUCTION

Bloodstream infections (BSIs) is associated with major morbidity and mortality [1-4]. Despite the great advances in medical science in the past century, BSI remains a growing public health concern in the modern world. BSI is among the top seven causes of death in many European and North American countries [2]. With an a case fatality rate of 20–50%, BSI have been declared the third most common cause of death in Germany [5]. The incidence of BSI has been demonstrated to vary significantly among regions, and this is in part related to blood culturing rates, population demographic differences and risk factor distribution in regions [1].

Bacterial resistance to antibiotics is increasing and creates a therapeutic challenge for clinicians when treating patients with BSI. Increasing rates of bacterial resistance leads many clinicians to empirically treat critically ill patients with broad-spectrum antibiotics, which can perpetuate the cycle of increasing resistance [6, 7]. Conversely, inappropriate initial antimicrobial therapy can lead to treatment failures and adverse patient outcomes [8].

Nosocomial BSI has particular importance from the public health standpoint. Optimizing the management and empirical antimicrobial therapy may reduce the burden of nosocomial BSI, but prevention is the key element [2]. A thorough knowledge about local epidemiology of resistance may contribute to limiting resistance and may have a significant role in designing effective antimicrobial stewardship policies [9].

BSIs can be caused by a wide variety of microorganisms, commonly *Escherichia coli, Klebsiella* spp., *Staphylococcus aureus, Enterococcus* spp., *Pseudomonas aeruginosa,* other bacteria, and yeast [2-4, 6, 9]. Microorganisms enter the bloodstream through various portals, including dissemination from a previous or concomitant infection and access via surgical sites, intravenous catheters, and other vascular access devices [10].

Among the infection prevention initiatives, surveillance of BSIs is the cornerstone to decrease infection rates in hospitalized patients, and it is considered to be the best way to assure patient safety. Continuous monitoring of BSI rates can be used to assess effectiveness of interventions and provides information which may be used for benchmarking comparison.

To identify BSIs prevention targets and reduce thus disparities between countries, ongoing surveillance is necessary. However, the epidemiology of BSI in Ukraine and associated treatment outcomes are not well studied. National network for the surveillance of HAIs is not in Ukraine. Resources are severely limited in country, creating difficulties implementing surveillance and establishing effective measures for infection control and BSI prevention. However, efforts to improve infection control training and begin HAI surveillance have been underway. Previous reports of BSIs in Ukraine were limited [3, 4].

THE AIM

The objective of this study was to obtain the first national estimates of the current incidence of BSI and antimicrobial resistance of responsible pathogens, and associated mortality in Ukraine.

MATERIALS AND METHODS

STUDY DESIGN AND DATA COLLECTION

This is a retrospective, cohort study of patients with bloodstream infection (BSI) admitted to the 14 regional (tertiary) hospitals (50% adult (3600 beds) and 50% pediatric, total 1200 beds) that are similar in terms of technical equipment (ICU, haematology, surgery) highly specialized personnel, laboratory facilities) of Ukraine between January 1st, 2013 and December 31st, 2015. These hospitals provide care to individuals living within its catchment area (total 24 147 586 populations) and regularly take referrals from other (primary and secondary) hospitals.

All participating hospitals were required to have at least one full-time infection prevention and control professional (doctors), a clinical microbiology laboratory with the capacity to process cultures, and a data collection and reporting manager. The study included all positive blood cultures with recognized bacterial pathogens among patients who were hospitalized during the study period and additional clinical information from a subgroup of patients whose patient records were available to the investigators. Only the first bacteremic episode for each patient was included in the analysis. A standard data collection form was created to extract demographic and clinical data, microbiology (isolated pathogens and their antibiograms) and outcome information from routine patient records.

DEFINITIONS

In our study the CDC (Centers for Disease Control and Prevention, Atlanta, Georgia, USA) definition of BSI was used [11]. Clinically significant bacteremia was defined as at least one positive blood culture together with clinical features compatible with BSI. When the clinical information was not available for judgment, the same organism(s) isolated within 48 h of another positive culture was considered as the same episode. A case of community-acquired BSI (CABSI) was defined as a patient with a positive blood culture from a blood sample drawn < 48 h after hospitalization. Patients were classified as having healthcare-associated hospital-onset BSI (HABSI) when the culture was obtained 48 hours or more after admission. Fatal cases were defined as patients who died in hospital. These data were only available from patients whose clinical records were available.

ETHICS

The Shupyk National Medical Academy of Postgraduate Education ethics committee approved the waiver of informed consent to participate in this study due to its retrospective design. All patient data were anonymised prior to the analysis. According to the Health Research Act of Ukraine, quality assurance projects, surveys and evaluations that are intended to ensure that diagnosis and treatment produce the intended results do not require ethical approval or patient consent.

MICROBIOLOGICAL METHODS

Microbial isolates were identified using standard microbiological techniques, including automated microbiology testing (Vitek-2; bioMe´rieux, France), and antibiotic susceptibility testing was performed by using the disk diffusion method according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI). Some antimicrobial susceptibility test used Kirby - Bauer antibiotic testing.

STATISTICAL ANALYSIS

The prevalence of BSIs was reported as the percentage of the total number of patients. BSIs were analysed by type of infection (CABSI and HABSI), which were mutually exclusive. The analysis of statistical data was performed using Microsoft Excel for Windows. Results are expressed as median (range), meanstandard deviation for continuous variables, and number and corresponding percentage for qualitative variables. The primary endpoint was the epidemiology of the micro-organisms isolated in blood samples and their resistance to antibiotics. Comparisons were undertaken using Student's t-test and Pearson's chi-squared test or Fisher's exact test for categorical variables as appropriate. 'Statistical significance was defined as $P<0.05$.

RESULTS

PATIENT CHARACTERISTICS

During the study period (January 2013 and December 2015), 3816 of 20,544 patients were found to have BSIs.

Table 2. Distribution of responsible pathogens (n=3872) of bloodstream infections (BSIs) in Ukrainian hospitals (2013-2015)

Types of micro-organisms[a]	Total no. (%) of isolates	95% CI
Gram-positive cocci	1022 (26.4)	25.7 – 27.1
Staphylococcus aureus	382 (9.9)	9.4 – 10.4
CoNS	265 (6.8)	6.4 – 7.2
Staphylococcus haemolyticus	58 (1.5)	1.3 – 1.7
Streptococcus spp.	213 (5.5)	5.1 – 5.9
S. pneumoniae	135 (3.5)	3.2 – 3.8
S. viridans[b]	51 (1.3)	1.1 – 1.5
Beta-hemolytic streptococci	27 (0.7)	0.6 – 0.8
Enterococcus spp.	87 (2.2)	2.0 – 2.4
Other gram-positive bacteria	17 (0.4)	0.3 – 0.5
Gram-negative bacilli	2752 (71.1)	70.4 – 71.8
Enterobacteriaceae	1989 (51.4)	50.6 – 52.2
Klebsiella pneumoniae	973 (25.1)	24.4 – 25.8
Escherichia coli	678 (17.5)	16.9 – 18.1
Serratia marcescens	103 (2.7)	2.4 – 3.0
Enterobacter spp.	97 (2.5)	2.3 – 2.7
Enterobacter aerogenes	56 (1.4)	1.2 – 1.6
Enterobacter cloacae	82 (2.1)	1.9 – 2.3
Non-Enterobacteriacae	763 (19.7)	19.1 – 20.3
Stenotrophomonas maltophilia	63 (1.6)	1.4 – 1.8
Pseudomonas aeruginosa	334 (8.9)	8.4 – 9.4
Acinetobacter spp.[c]	328 (8.5)	8.1 – 8.9
Other gram-negative bacteria	28 (0.7)	0.6 – 0.8
Fungi	98 (2.5)	2.3 – 2.7
Candida albicans	81(2.1)	1.9 – 2.3
Nonalbicans fungi	17 (0.4)	0.3 – 0.5
Total no. of isolates	3872 (100.0%)	

Notes: BSIs, bloodstream infections; CoNS, coagulase-negative staphylococci; CI, confidence interval.
aUsed 'The Bergey's Manual of Determinative Bacteriology', 9th Edn.
bCases with Viridans group infection had at least two positive blood culture or single positive blood culture plus vegetation on echocardiography.
cIncluding 30 cases with A. baumannii, and 10 cases with A. lwoffii.

The prevalence of BSIs was 18.6%. Among these patients, 7.6% (289/3816) CABSI and 92.4% (3527/3816) HABSI were observed. Of the cases of BSIs identified, 2611/3816 (68.4%) died before discharge. The age of the patients was ≤ 28 days to ≥ 76 years. From the confirmed cases of BSIs, 1788/3816 (46.9%) were male and 2078/3816 (53.1%) female. Sensitivity analysis of gender showed no differences between cases with and without clinical outcome (p = 0.053). BSI rate was highest in the age group of ≤28 days (34.1%; 1298/3816) followed by those in the age group of 29 days – 3 years (16.3%; 619/3816). Most patients (86.4%; 3297/3816) had HABSI. Table 1 shows the demographic data of patients with BSI.

HABSI were reported as catheter-related in 41.9% (1478/3527) and secondary to another infection site in 28.9% (1020/3527). For 29.2% (1029/3527) of the bloodstream infections, the origin was unknown, either after clinical ascertainment of possible sources of the infection (17.1%; 603/3527), or because data were missing (12.1%; 426/3527).

MICRO-ORGANISMS CAUSING BSI

A total of 3872 specimens isolated from 3816 patients with BSI. Gram-positive organisms accounted for 26.4% (1022/3872) of all BSIs and gram-negative organisms accounted 71.1% (2752/3872), respectively. Enterobacteriaceae were the most frequently isolated group of organisms among patients with BSI (51.4%, 1989/3872) with the predominant Enterobacteriaceae being *Klebsiella pneumoniae*

Table 1. Demographics data of patients with bloodstream infections (BSI) in Ukraine (2013-2015)

Characteristics	Total		CABSI		HABSI	
	n	%	*n*	%	*n*	%
All	3816	100.0	519	13,6	3297	86.4
Sex						
Male	1788	46.9	225	43,4	1563	47.4
Female	2028	53.1	294	56,6	1734	52.6
Age						
≤28 days	1298	34.1	0	0	1298	100.0
29 days – 3 years	619	16.3	16	2,6	603	97.4
4 – 12 years	214	5.7	13	6,1	201	93.9
13 – 21 years	168	4.5	13	7,7	155	92.3
22 – 30 years	191	5.1	13	6,8	178	93.2
31 – 39 years	233	6.2	32	13,7	201	86.3
40 – 48 years	119	3.2	33	27,7	86	72.3
49–57 years	160	4.3	12	7,5	148	92.5
58 – 66 years	172	4.6	7	4,7	165	95.3
67 – 75 years	291	7,70	7	2,7	284	97.6
≥75 years	351	9,30	3	0,9	348	99.1

Notes: CABSI, community-acquired bloodstream infections; HABSI, healthcare-associated bloodstream infections.

(25.7%, 973/3872) and *Escherichia coli* (17.5%, 678/33872), followed by *P. aeruginosa* (8.9%; 334/3872), and *Acinetobacter* spp.(8.5%; 328/3872). Among Gram-positive isolates, *S. aureus* was the leading pathogen (9.9%; 382/3872), followed by Coagulase-negative staphylococci (CoNS) (6.8%; 265/3872). Anaerobes were not isolated. *Candida albicans* and nonalbicans fungi accounted for 2.1% (81/3872) and 0.4% (17/3872) of all BSI episodes (Table 2).

The proportions of CABSI and HABSI caused by Enterobacteriaceae were not statistically different (48.1% vs 51.9%, p = 0.23), similar for non-enterobacteriaceae Gram-negative bacteria (19.7% vs 28.2%, p = 0.132). In contrast, Gram-positive bacteria were more frequently identified in CABSI (29.2% vs 14.3%, p = 0.011) and *Acinetobacter* species were more common in HABSI.

ANTIMICROBIAL RESISTANCE

The overall proportion of extended spectrum beta-lactamases (ESBL) production among Enterobacteriaceae was 24.8%. The prevalence of ESBL production among *E. coli* isolates was significantly higher than in *K. pneumoniae* (44.4%, vs 12.4%, p < 0.001). Methicillin/oxacillin resistance was observed in 38.2% *S. aureus* and 44.2% CoNS isolates. Vancomycin resistance was reported in 9.2% of isolated enterococci (VRE). Carbapenem resistance was reported for 33.1% of *P.aeruginosa* isolates and 63.2% of *A. baumannii* isolates. Resistance to third-generation cephalosporins was reported in 14.2% *K. pneumoniae* and *E.coli* 55% isolates.

There was no difference in the proportion of ESBL production in community versus hospital setting among *E. coli* isolates (53.5% vs 55.3%, p = 1.0). In *K. pneumoniae* isolates, the proportion of ESBL production were higher in HABSI (21.3% vs 6.2%, p = 0.039). Compared with *K. pneumoniae*, *E. coli* isolates were also more frequently resistant to aminoglycosides (23.3%, vs 13.0%, p = 0.031) and fluoroquinolones (31.7% vs 8.3%, p < 0.001).

K. pneumoniae isolates associated with HABSI more frequently showed antibiotic resistance compared to CABSI isolates, though statistical significance was only reached for quinolones, while the pattern of resistance among *E. coli* isolates did not differ between the hospital and community. MRSA rates differed between community and hospital settings, though this did not reach statistical significance (p = 0.074).

IMPACT OF BSI ON INPATIENT MORTALITY

Of the BSI case-patients identified, 2611/3816 (68.4%) died before discharge. Case fatality of BSIs was assessed in the clinical dataset only. Overall case fatality rates among patients infected with Gram-negative and Gram-positive bacteria were 78.7%, and 21.3%, respectively. There was no case of death among patients with mix infections. Case fatality rate in CABSI (27.5%) was lower, but not statistically different from HABSI (36.4%) (p < 0.05). In the most frequent isolates of *P. aeruginosa*, *Acinetobacter* spp., *E. coli, K. pneumoniae,* and *S. aureus*, case-fatality rates were 37.9%, 36.3%, 26.8%, 23.6% and 12.4%. The pathogen-specific hospital mortality rate was significantly greater for *P. aeruginosa* and *Acinetobacter* spp. compared to Enterobacteriaceae (p < 0.001 and p = 0.008, respective-

ly). BSIs caused by *E coli* and *Klebsiella* spp. had relatively low mortality, ESBL-producing isolates were associated with a significantly increased mortality. In addition, the mortality rate of carbapenem-resistant gram-negative bacteria (*P. aeruginosa*, *Acinetobacter* spp. and *K. pneumoniae*) was high.

DISCUSSION

This study presents the first national estimates of the current prevalence of BSIs and antimicrobial resistance of responsible pathogens in Ukraine. During the study period (2013-2015) the prevalence of BSIs was 18.6%. Among these patients, 7.6% community-acquired and 92.4% healthcare associated infection were observed. Death was reported in 68.4% BSI cases.

The BSI prevalence by European countries ranged from 4.9% in Latvia to 19.0% in Cyprus. Bloodstream infections were highest in Greece at 18.9%, 16.1% in Netherlands, and 15.8% in Italy and Belgium at 14.0% [12]. The prevalence rate of BSIs in our study was 18.6%. The similar prevalence rate of 16% BSIs was observed in Pakistan [13].

The most frequently reported pathogens of BSIs were common all countries with some rank differences. In our study the predominant pathogens were *K. pneumoniae* (25.1%), *E. coli* (17.5%), *S. aureus* (9.9%), *P. aeruginosa* (8.9%), and *Acinetobacter* spp.(8.5%). *E.coli* is one of the most frequent pathogens causing CABSI and HABSI [14,15]. The highest percentage of *E. coli* was observed in France (26.6%) and the lowest in Cyprus (3.9%). *E. coli* was one of the three most common microorganisms in most of the European countries, except in Cyprus, Denmark, Greece, Romania and UK-Northern Ireland [12]. *S. aureus* is the most significant cause of gram-positive bacteremia in the worldwide [17]. *S. aureus* was most common in Malta (26.5%) and least common in Greece (3.0%). The percentage of enterococci varied between 4.5% in the Czech Republic and Norway and more than 20% of all microorganisms in Denmark and Sweden. *P. aeruginosa* ranged from 0% in Iceland and Latvia to 16.8% in Greece. *Klebsiella* spp. (79.0% of which were *K. pneumoniae*) varied from less than 4% in Iceland, Sweden, UK-England, UK-Northern Ireland and UK-Wales to 17.6% in Greece. The highest percentages of *Candida* spp. were reported from Denmark (19.4%), Iceland (10.8%) and Sweden (10.3%). The percentage of *Enterobacter* spp. was 6% or more in Belgium, Estonia, the Netherlands, Poland and Slovenia. No *Acinetobacter* spp. were reported from nine countries, but in four countries (Latvia, Romania, Bulgaria and Greece), the percentage of these bacteria ranged from 10.6% to almost 17% [12].

During last years, in worldwide clinicians have witnessed a growing incidence of BSIs along with resistance against commonly used antimicrobials [3-10, 12, 13]. Four European countries (Cyprus, Italy, Portugal and Romania) reported the most than 60% of meticillin-resistance in *S. aureus* (MRSA) isolates [12]. Sensitivity varies among MRSA strains, ranging 26–100% in US and 0–92% worldwide [16]. In 2017, 14.9% of *E. faecium* isolates in the European hospitals were reported to be resistant to vancomycin. In 2017, national percentages ranged from 0.0% to 43.9% [18]. In European countries the highest percentage of non-susceptibility to third-generation cephalosporins among Enterobacteriaceae isolates was observed in Greece (63.9%) and Latvia (71.4%) [12]. EARS-Net data indicated that in the EU mean resistance rate *E.coli* isolates was reported for aminopenicillins (58.7%), followed by fluoroquinolones (25.7%), third-generation cephalosporins (14.9%) and aminoglycosides (11.4%) [18]. Three countries reported over 20% of Enterobacteriaceae isolates resistant to carbapenem with the highest level (39.9%) being reported from Greece. Non- susceptibility to carbapenems in *K.pneumoniae* was higher than 50%, Greece (66.7%) and Lithuania (66.7%). The percentage of *P.aeruginosa* non- susceptibility isolates varied from 6.3% in Bulgaria to almost 49.4% in Greece [12]. In the EU, 30.8% of the *P. aeruginosa* isolates reported to EARS-Net for 2017 were resistant to at least one of the antimicrobial groups under regular surveillance (piperacillin ± tazobactam, fluoroquinolones, ceftazidime, aminoglycosides and carbapenems). Carbapenem resistance *P. aeruginosa* was reported in >40% of isolates in Slovakia (47.0%), Latvia (57.1%) and Romania (63.4%). [18]. In EARS-Net database, in 15 countries in the EU from where susceptibility rates for *A. baumannii* were reported >30% of all isolates were resistant to carbapenems (33.4%), fluoroquinolones (37.6%) and aminoglycosides (32.4%). Carbapenem resistance was reported in >60% of isolates in Poland (67.4%), Spain (68.2%), Cyprus (76.0%), Italy (78.7%), Latvia (79.4%), Bulgaria (80.4%), Romania (87.4%), Lithuania (88.5%), Greece (94.8%) and Croatia (86.2%) [18]. In our study the overall proportion of extended spectrum beta-lactamase (ESBL) production among Enterobacteriaceae was 24.8% and of methicillin-resistance in *S. aureus* (MRSA) 38.2%. Vancomycin resistance was observwd in 9.2% of isolated enterococci (VRE). Carbapenem resistance was identified in 33.1% of *P.aeruginosa* isolates and 63.2% of *A.baumannii* isolates. Resistance to third-generation cephalosporins was observed in 14.2% *K. pneumoniae* and *E.coli* 55% isolates.

BSIs are associated with high mortality worldwide. In North America and Europe, the nosocomial BSI case fatality rate ranges from 12 to 32% [2]. Our study shows a death rate of 68.4%; this rate appears higher than those reported by several international studies [2, 5, 19-21]. HABSIs are known to have a higher attributable mortality than infections acquired outside the hospital [23]. Mortality estimates vary with country, and overall in-hospital mortality has been estimated as 15.3% in Ireland [20], 40.0% in Brazil [20], and 28.9% in Vietnam [21]. The differences in mortality rates may be caused by differences in the distribution of pathogens and in the delivery of health care. The prevalence of AMR in Enterobacteriaceae was higher in Brazil [20] and Vietnam [21] than in other countries, and fungal BSIs were a significant contributor to mortality in some reports [20, 22].

In our study, CABSIs had a low mortality risk. BSIs caused by *E coli* and *Klebsiella* spp. had relatively low mortality, ESBL-producing isolates were associated with a significantly

increased mortality. In addition, the mortality rate of carbapenem-resistant gram-negative bacteria (*P. aeruginosa, Acinetobacter* spp. and *K. pneumoniae*) was high. The results suggest that antimicrobial resistance has a poor prognosis in BSIs. Further study is needed to investigate the effect of antimicrobial resistance on patient prognosis.

This study highlights the predominance of Gram negative bacteria and the emergence of multidrug-resistant organisms. Our results confirm some facts reported in many publications like the resistance to antibiotics and mortality.

STUDY LIMITATIONS

The limitations of this study include its retrospective design and conduct at a 58.3% region (14 from 24) in Ukraine. The results may not be representative of other regions of Ukraine with different distributions of antimicrobial resistance of responsible pathogens of BSIs. However, there are no national surveillance data in Ukraine, which compelled us to rely entirely on data from the only existing national retrospective study of BSIs. This investigation provides valuable data as a first study for national surveillance of BSI and potential comparison with data from other countries.

CONCLUSION

Healthcare-associated BSIs and antimicrobial resistance of responsible pathogens together with their associated impact on mortality, presents a significant burden to the Ukraine hospital system. Strategic planning and implementation of BSI surveillance is required in Ukraine.

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Authors' contributions:
According to the order of the Authorship

ORCID numbers:
Aidyn G. Salmanov - 0000-0002-4673-1154
Yuriy V. Voronenko - 0000-0003-4945-1817
Sergiy O. Vozianov - 0000-0003-3782-0902
Yelizaveta Ye. Shunko - 0000-0002-4883-2549
Maryna Ye. Mamenko - 0000-0001-7487-2993
Olga M. Verner - 0000-0002-7588-5742
Vasyl M. Mykhalchuk - 0000-0002-5398-4758
Stanislav V. Vydyborets - 0000-0003-0546-4325
Volodymyr O. Shkorbotun - 0000-0003-0769-6242
Halyna V. Beketova - 0000-0002-1362-0060
Olena M. Okhotnikova - 0000-0003-2498-0560
Nadiya V. Goryainova - 0000-0003-2123-4140
Olena A. Oshlianska - 0000-0002-2525-4491
Olga Laksha - 0000-0001-6241-4813
Olena Bielova - 0000-0002-3534-9590
Volodymyr Yo. Shuba - 0000-0003-4896-5269
Tetyana M. Osadcha - 0000-0001-5632-8716

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CORRESPONDING AUTHOR
Aidyn Salmanov
Shupyk National Medical Academy of Postgraduate Education,
St. Dorohozhytska 9, 04112, Kyiv, Ukraine
tel: +380667997631
e-mail: mozsago@gmail.com

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