RATE AND PATTERN OF ANTIBIOTIC RESISTANCE IN MICROBIOLOGICAL CULTURES OF SEPSIS PATIENTS IN A LOW-MIDDLE-INCOME COUNTRY'S ICU

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Abstract

Background: In this prospective, observational study, the rate of antibiotic resistance in cultures sampled from sepsis patients was determined in an intensive care unit of a low-middle income country.

Methods: Critically ill patients suffering from bacterial sepsis were eligible for enrollment. Aside from demographic, disease-related and sepsis-specific parameters, the type of microbiological sample and cultured microorganism as well as the resistance pattern (extensively resistant bacteria, multi-drug resistant bacteria) were documented. Descriptive statistical methods, parametric and non-parametric tests were used.

Results: 215 sepsis patients were included. 193 of the 410 cultured organisms (47.1%) showed antibiotic resistance [extensively resistant bacteria, n = 90 (11%); multi-drug resistant bacteria, n = 103 (25.1%)]. 51.6% of the patients were infected by ≥1 resistant bacteria. Bacteria with an exceptionally high rate of antibiotic resistance were Acinetobacter baumannii (90%), Enterobacter spp (60%) and coagulase-negative Staphylococci (60%). Patients infected with resistant bacteria more often received inadequate empirical antibiotic therapy (36.9 vs. 13.5%, p <0.001), required mechanical ventilation (66.7 vs. 42.3%, p <0.001) and renal replacement therapy (28.8 vs. 9.6%, p <0.001) more frequently, and had a longer stay in the intensive care unit [5 (3-9.5) vs. 5 (2-8)%, p <0.001] than patients with sepsis due to non-resistant bacteria. There was a trend towards a higher mortality in patients with resistant bacteria (43.2 vs. 31.7%, p = 0.09).

Conclusion: Resistant bacteria were detected in up to 50% of microbiological samples from critically ill sepsis patients in the intensive care unit of a low-middle-income country. Antibiotic resistance appears to be a relevant problem of sepsis management in a resource-limited setting.

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Introduction

While sepsis receives most attention in the medical literature and public in high-income countries, the majority of worldwide deaths due to sepsis occur in middle- and low-income countries[1]. Reasons for this are multiple, ranging from the additional burden of tropical infectious diseases, low hygienic standards, a high prevalence of HIV/AIDS and tuberculosis as well as resource-limited health care systems with insufficient infection prevention and management facilities[2].

Independent of the causative pathogen of sepsis, timely and adequate empirical antibiotic therapy is crucial for survival[3]. Antibiotic resistance is an important factor influencing the adequacy of both empirical and targeted antibiotic therapy[4]. The rate of antibiotic resistance drastically varies for different bacteria and between geographic regions. Due to uncontrolled antibiotic use, availability of only a restricted amount of antibiotic agents, particularly high antibiotic resistance rates have been observed in resource-limited heath care systems[5]. So far, only scarce data on the incidence and clinical relevance of antibiotic resistance patterns in critically ill sepsis patients treated in middle-and low-income countries have been published.

In this prospective observational study, the rate of antibiotic resistance in cultures sampled from critically ill sepsis patients was determined in an intensive care unit of a low-middle income country. Furthermore, the influence of antibiotic resistance on clinical outcome was assessed. We hypothesized that antibiotic resistance was frequent and relevantly affected clinical outcome in this study population.

Methods

This analysis was designed as a prospective observational study. During the time from Jan 1, 2011 until Aug 31, 2012, the study was conducted in an eight bed multidisciplinary intensive care unit of a tertiary university teaching hospital in Ulaanbaatar, the capital city of Mongolia. The study protocol was approved by the Ethics Committee of the Central State University Hospital/Mongolian Medical University (protocol number, 83/4 24 june 2010). Considering that only anonymous data were collected, no blood or tissue samples were taken and the patients' management was not changed by the study. Written informed consent was waived.

Description of the Study Setting

The study setting is an intensive care unit typical for many low-middle-income countries with part-time intensivist staffing, possibilities to provide basic organ support (mechanical ventilation and intermittent hemodialysis for renal replacement) but with restricted and inconsistent supply of drugs and disposable materials. The hospital-based microbiological laboratory processes 100-120 microbiological sample tests per day. During the study period, the principal method used for bacterial cultures and determination of antibiotic resistance was API strip, ATB strip and the disc diffusion method, respectively. The laboratory is limited by only a restricted number of staff as well as intermittent shortages of material resources.

Patients

Critically ill patients who suffered from bacterial sepsis, confirmed by a positive microbiological culture, were eligible for study enrollment. Exclusion criteria were: sepsis without microbiological confirmation, lack of an antibiogram, sepsis due to viral or fungal infection, infections with mycobacteria (n = 31 during the study period), and patient age <18 years. Patients suffering from viral, fungal or mycobacterial infection were excluded because no testing for antimicrobial resistance of these organisms could be performed in the study hospital during the observation period.

Data

The following data were collected in each study patient: age, gender, the McCabe classification[6], admission diagnosis, the Simplified Acute Physiology Score II[7], type of infection, presence of severe sepsis or septic shock, presence of multiple organ dysfunction, adequacy of empirical antibiotic therapy, availability of adequate antibiotic agent(s), need for mechanical

ventilation or renal replacement therapy, intensive care unit length of stay and mortality. The type of microbiological sample and cultured microorganism as well as the resistance pattern were documented for each positive culture.

Definitions

Sepsis, severe sepsis and septic shock were defined according to the most recent ACCP/SCCM criteria[8]. Multiple organ dysfunction was defined as the presence of two or more organ dysfunctions as defined by an organ Sequential Organ Failure Assessment Score count of two or higher. The pattern of antibiotic resistance was defined as suggested by the joint initiative of the European Centre for Disease Prevention and Control as well as the Centers for Disease Control and Prevention[9]. Accordingly, resistant bacteria were grouped into extensively resistant and multidrug-resistant bacteria. Extensive drug resistance was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories. Multidrug resistance was defined as non-susceptibility to at least one agent in three or more antimicrobial categories. For five bacteria [Staphylococcus aureus, Enterococcus *spp*, Enterbacteriacae (other than Salmonella and Shigella), Pseudomonas aeruginosa and Acinetobacter *spp*] pre-defined resistance profiles and antibiotic susceptibility categories were applied. For all other bacteria, those antibiotic categories intrinsically active against the bacterium and for which resistance testing was available were considered. Resistance or non-susceptibility was defined using breakpoint criteria as suggested by the Clinical Laboratory Standards Institute[10].

We did not apply the definition of pandrug-resistance, since not all antibiotic agents which are commonly tested in high-income countries to define pandrug-resistant bacteria, were available and tested in the study laboratory.

Statistical Analysis

The primary endpoint was to identify the rate of bacterial resistance per sample and critically ill sepsis patient. Secondary endpoints were to compare intensive care unit mortality, adequacy of empirical antibiotic therapy, need for mechanical organ support, presence of multiple organ dysfunction and length of stay in the intensive care unit between study patients with and without resistant bacteria.

Following plausibility testing, study variables were tested for normality distribution using the Shapiro Wilk's test. Descriptive statistics were applied to identify the rate of bacterial resistance. Comparisons of study variables between patients with and without resistant bacterial infections were performed using the Student's *t*- (continuous normally distributed variables) or the Mann-Whitney *U*-test (continuous, non-normally distributed variables) as well as the Fisher's Exact test (categorical data), as appropriate. *P*-values <0.05 were considered to indicate statistical significance. Data are given as median values with interquartile ranges, if not otherwise indicated.

Results

During the study period, 1,284 patients were admitted to the study intensive care unit. Two-hundred-fifteen of these had no exclusion criteria present and suffered from sepsis confirmed by 410 positive microbiological cultures. Table 1 presents details of the study population. Hundred-ninety-three of the 410 cultured organisms (47.1%) revealed antibiotic

Fig. 1

Identification of resistant bacteria in microbiological cultures over time during the observation period

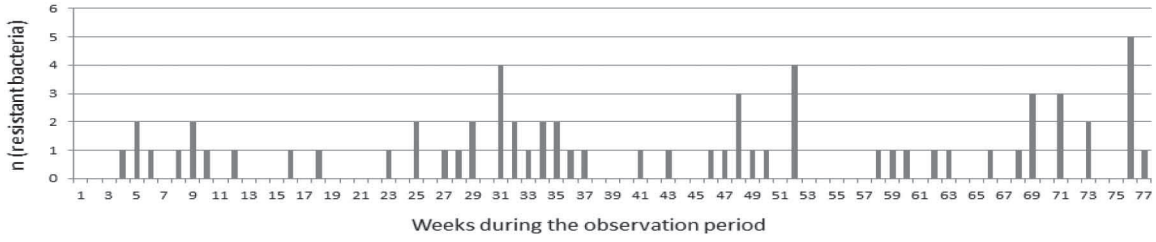

Table 1
Characteristics of the Study Population

n		215
Age	*(years)*	51 (37-67)
Male gender	*n (%)*	104 (48.4)
McCabe Classification	*n (%)*	
0		70 (32.6)
1		92 (42.8)
2		49 (22.8)
3		4 (1.9)
Admission Diagnosis	*n (%)*	
Medical		89 (41.4)
Surgical		83 (38.6)
Neurological		13 (6)
Traumatological		6 (2.8)
Other		24 (11.2)
SAPS II	*(pts)*	41 (33-50)
Type of Infection	*n (%)*	
Community-acquired		161 (74.9)
Hospital-acquired		54 (25.1)
Severe Sepsis	*n (%)*	64 (29.8)
Septic Shock	*n (%)*	104 (48.4)
Multiple Organ Failure	*n (%)*	73 (34)
Mechanical Ventilation	*n (%)*	118 (54.9)
Renal Replacement Therapy	*n (%)*	81 (37.7)
Intensive Care Unit Length of Stay	*days*	6 (3-10)
Intensive Care Unit Mortality	*n (%)*	81 (37.7)
Data are presented as median values with interquartile range, if not otherwise indicated.		

Table 2. Characteristics of Microbiological Samples and Resistance Patterns

n		410
Samples per patient	*n*	1 (1-2)
Type of sample	*n (%)*	
Sputum		136 (33.2)
Urine		78 (19)
Cerebrospinal fluid		36 (8.8)
Catheter tip		32 (7.8)
Wound swab		31 (7.6)
Other		97 (23.7)
Microorganisms	*n (%)*	
Staphylococcus aureus		111 (27.1)
Escherichia coli		71 (17.3)
Enterobacter spp		65 (15.9)
Acinetobacter baumannii		30 (7.3)
Pseudomonas aeruginosa		28 (6.8)
Streptococcus pyogenes		22 (5.4)
Enterococcus faecium		21 (5.1)
Klebsiella spp		19 (4.6)
Other		43 (10.5)
Drug-Resistance per Patient	*n (%)*	111 (51.6)
Extensive Drug Resistance		49 (22.8)
Multi-Drug Resistance		62 (28.8)
Drug-Resistance per Sample	*n (%)*	193 (47.1)
Extensive Drug Resistance		90 (22)
Multi-Drug Resistance		103 (25.1)
Drug-Resistance per Microorganism	*n (%)*	
Acinetobacter baumannii		27 (90)
Enterobacter spp		39 (60)
Coagulase-negative Staphylococcus		3 (60)
Klebsiella spp		10 (52.6)
Pseudomonas aeruginosa		14 (50)
Escherichia coli		33 (46.5)
Enterococcus faecium		9 (42.9)

resistance. Characteristics of microbiological samples with resistance patterns are given in Table 2. Resistant bacteria were mostly observed in clusters during the study period (Fig. 1).

Sepsis patients infected with resistant bacteria more often received inadequate empirical antibiotic therapy, required mechanical ventilation and renal replacement more frequently, suffered from multiple organ dysfunction more often and had a longer stay in the intensive care unit than patients with sepsis due to non-resistant bacteria. Except for a lacking difference in the presence of multiple organ dysfunction and the length of intensive care unit stay in patients with extensively resistant bacteria, similar inter-group differences were observed between patients with and without extensively resistant bacteria as well as between patients with and without multidrug-resistant bacteria.

Discussion

In this prospective observational study, approximately half of the microbiological cultures sampled from critically ill sepsis patients in a Mongolian intensive care unit revealed resistant

Table 3. Differences between Patients with and without Resistant Microorganisms

		Patients with Resistant Microorganisms	Patients without Resistant Microorganisms	*p*-value
n		111	104	
Inadequate Empirical Antibiotic Therapy	*n* (%)	41 (36.9)	14 (13.5)	<0.001*
Unavailability of Adequate Antibiotic	*n* (%)	8 (7.2)	1 (1)	0.04*
Mechanical Ventilation	*n* (%)	74 (66.7)	44 (42.3)	<0.001*
Renal Replacement Therapy	*n* (%)	32 (28.8)	10 (9.6)	<0.001*
Multiple Organ Failure	*n* (%)	44 (39.6)	29 (27.9)	0.08
Intensive Care Unit Length of Stay	*days*	5 (3-9.5)	5 (2-8)	<0.001*
Intensive Care Unit Mortality	*n* (%)	48 (43.2)	33 (31.7)	0.09
		Patients with XDR Microorganisms	**Patients without XDR Microorganisms**	***p*-value**
n		49	104	
Inadequate Empirical Antibiotic Therapy	*n* (%)	16 (32.7)	14 (13.5)	0.005*
Unavailability of Adequate Antibiotic	*n* (%)	2 (4.1)	1 (1)	0.24
Mechanical Ventilation	*n* (%)	34 (69.4)	44 (42.3)	0.002*
Renal Replacement Therapy	*n* (%)	16 (32.7)	10 (9.6)	0.001*
Multiple Organ Failure	*n* (%)	14 (28.6)	29 (27.9)	1
Intensive Care Unit Length of Stay	*days*	5 (2-8)	5 (2-8)	0.09
Intensive Care Unit Mortality	*n* (%)	21 (42.9)	33 (31.7)	0.21
		Patients with MDR Microorganisms	**Patients without MDR Microorganisms**	***p*-value**
n		62	104	
Inadequate Empirical Antibiotic Therapy	*n* (%)	25 (40.3)	14 (13.5)	<0.001*
Unavailability of Adequate Antibiotic	*n* (%)	6 (9.7)	1 (1)	0.01*
Mechanical Ventilation	*n* (%)	40 (64.5)	44 (42.3)	0.007*
Renal Replacement Therapy	*n* (%)	16 (25.8)	10 (9.6)	0.008*
Multiple Organ Failure	*n* (%)	30 (48.4)	29 (27.9)	0.01*
Intensive Care Unit Length of Stay	*days*	5 (3-10)	5 (2-8)	<0.001*
Intensive Care Unit Mortality	*n* (%)	27 (43.5)	33 (31.7)	0.14

XDR, extensively drug resistant; MDR, multi-drug resistant. *, significant difference between groups.
Data are given as median values with interquartile range, if not indicated otherwise.

bacteria. Extensively resistant bacteria were observed in 22% and multidrug-resistant bacteria in 25.1% of microbiological cultures, respectively. In total, 51.6% of the study patients were infected by one or more resistant bacteria. Bacteria with an exceptionally high rate of antibiotic resistance (≥60%) were Acinetobacter baumannii, Enterobacter *spp* and coagulase-negative Staphylococci. Sepsis patients infected with resistant bacteria received inadequate empirical antibiotic therapy, mechanical ventilation, renal replacement therapy more frequently and suffered from multiple organ dysfunction more often than sepsis patients without resistant bacteria. The length of stay in the intensive care unit was longer in sepsis patients with resistant bacteria but the mortality rate in the intensive care unit did not significantly differ between groups despite a trend towards a higher fatality rate in sepsis patients infected with resistant bacteria.

A 47.1% rate of resistant bacteria in microbiological cultures sampled from sepsis patients is high. Even when taking extensively resistant bacteria not into account, a 25.1% rate of multidrug-resistant bacteria is striking both from a clinical point of view and in comparison with reports of intensive care units in high-income countries[11,12]. Since the microbiological laboratory of the study hospital did not routinely test resistance against all antibiotic agents active against the cultured bacterium in their antibiograms due to resource limitations, the true rate of antibiotic resistance is likely to be underestimated and the rate of pan-drug resistance could not be evaluated. Our results need to be further relativized when considering that frequently resistant microbes causing sepsis in Mongolia such as mycobacteria and fungi were not analyzed in this study for reasons stated above. Compared to other middle- and low-income settings, our study showed similar results as reported by other authors[12-16]. So far, however, none of these studies specifically evaluated the rate of resistant bacteria in critically ill sepsis patients.

Particularly high resistance rates with 50% or more of the cultures being resistant were found for five specific bacteria, four of which were gram-negative. Almost all cultures of Acinetobacter baumannii revealed antibiotic resistance. This is particularly relevant for our setting, since Acinetobacter baumannii was detected in 7.3% of all study samples. Extremely high resistance rates of Acinetobacter *spp* have been reported in the literature[17,18] and are explained by the bacterium's ability to mutate rapidly and spontaneously during therapy[19]. Similar observations were made in other low-and middle-income settings as well as high-income countries for Enterobacter *spp*, Klebisella *spp* and Pseudomonas aeruginosa[20-22].

Reasons for the high resistance rate observed in this population cannot be determined by our results. Other authors have suggested that irrational use of a restricted selection of antibiotics, even in patients with no infectious disease, plays an important causative role[5]. In most middle- and low-income countries over-the-counter availability of antibiotic agents with widespread unprescribed use is a key problem[23]. This is also the case in Mongolia[24]. In addition, common use of antibiotics for non-medical reasons contributes to an

extent that has not yet been quantified and analyzed in these settings.

Fig. 1 shows that most samples culturing resistant bacteria were detected in clusters during the study period. Although this can partly be explained by the fact that repeated samples were taken in sepsis patients with resistant bacteria, it may also indicate that patient-to-patient transmission within the study ICU could have played a role. Hand hygiene is a crucial measure to prevent patient-to-patient transmission of infectious pathogens and is notoriously under-respected in resource-limited health care systems[25,26].

In our study population, sepsis patients infected with resistant bacteria had a higher morbidity as reflected by a more frequent need for mechanical ventilation and renal replacement therapy as well as more frequent multiple organ dysfunction. One reason for this observation could be the higher rate of inadequate empirical antibiotic therapy in these patients. Inadequate empirical antibiosis has repeatedly been identified as a relevant risk factor for increased morbidity and mortality in critically ill sepsis patients[3,27]. Despite these data on an increased fatality rate in case of inappropriate empirical antibiotic therapy, we observed a trend but no significant difference in intensive care unit mortality between sepsis patients with and without resistant bacteria. Including 215 patients, our sample size was too small to detect a significant mortality difference. Indeed, a *post hoc* power analysis suggests that a beta-level of merely 41% was achieved to detect an absolute 11.5% mortality difference at an alpha-level of 5%. While studies from high-income countries report controversial data on the mortality effects of resistant bacteria in sepsis[28,29], there are almost no data on this aspect from resource-limited settings[30]. However, as our data indicate the association between resistant bacteria and mortality may be different in resource-limited settings. While antibiotic agents active against resistant bacteria are routinely available in high-income countries, this is typically not true for middle- and low-income settings where the majority of new generation and back-up antibiotics are not or only inconsistently available[31,32]. Therefore, unlike in high-income countries, infection with resistant bacteria in middle- and low-income countries is likely to be equivalent to inadequate antibiotic therapy and thus likely to negatively affect patient outcome. Accordingly, in eight of our study patients infected with resistant bacteria the adequate antibiotic agent was not available. Seven of these patients died during their stay in the intensive care unit.

Our study suffers from relevant limitations that need to be taken into account when interpreting its results. First, due to the unavailability of laboratory resources, no specifications of antibiotic resistance could be performed. Thus, we cannot report on the incidence of key resistance factors such as production of extended spectrum or other beta-lactamases (e.g. AmpC or metallo-beta-lactamase-1). Neither could we test for antibiotic resistance genes as well as presence of certain enzymes characterizing resistant bacterial strains. In addition, both mycobacteria and fungi, which frequently exhibit resistance in resource-limited settings, were not included in our analysis. Finally, it was impossible to evaluate the true pathogenic relevance of all microbiological samples. Therefore, it we cannot exclude that a certain number of resistant bacteria which were cultured in this study population rather reflected colonization than true infection.

In conclusion, resistant bacteria were detected in up to 50% of microbiological samples from critically ill sepsis patients in the intensive care unit of a low-middle-income country. Antibiotic resistance appears to be a relevant problem of sepsis management in a resource-limited setting.

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