ORIGINAL ARTICLE

Epidemiology, Management, and Outcomes of Sepsis in ICUs among Countries of Differing National Wealth across Asia

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Abstract

Rationale: Directly comparative data on sepsis epidemiology and sepsis bundle implementation in countries of differing national wealth remain sparse.

Objectives: To evaluate across countries/regions of differing income status in Asia *1*) the prevalence, causes, and outcomes of sepsis as a reason for ICU admission and *2*) sepsis bundle (antibiotic administration, blood culture, and lactate measurement) compliance and its association with hospital mortality.

Methods: A prospective point prevalence study was conducted among 386 adult ICUs from 22 Asian countries/regions. Adult ICU participants admitted for sepsis on four separate days (representing the seasons of 2019) were recruited.

Measurements and Main Results: The overall prevalence of sepsis in ICUs was 22.4% (20.9%, 24.5%, and 21.3% in low-income countries/regions [LICs]/lower middle-income countries/regions [LMICs], upper middle-income countries/regions, and high-income countries/regions [HICs], respectively; $P < 0.001$). Patients were younger and had lower severity of illness in LICs/LMICs. Hospital mortality was 32.6% and marginally significantly higher in LICs/LMICs than HICs on multivariable generalized mixed model analysis (adjusted odds ratio, 1.84; 95% confidence interval, 1.00–3.37; $P = 0.049$). Sepsis bundle compliance was 21.5% at 1 hour (26.0%, 22.1%, and 16.2% in LICs/LMICs, upper middle-income countries/regions, and HICs, respectively; $P < 0.001$) and 36.6% at 3 hours (39.3%, 32.8%, and 38.5%, respectively; $P = 0.001$). Delaying antibiotic administration beyond 3 hours was the only element independently associated with increased mortality (adjusted odds ratio, 2.53; 95% confidence interval, 2.07–3.08; $P < 0.001$).

Conclusions: Sepsis is a common cause of admission to Asian ICUs. Mortality remains high and is higher in LICs/LMICs after controlling for confounders. Sepsis bundle compliance remains low. Delaying antibiotic administration beyond 3 hours from diagnosis is associated with increased mortality.

Clinical trial registered with www.ctri.nic.in (CTRI/2019/01/016898).

Keywords: sepsis; epidemiology; mortality; sepsis bundle

Sepsis is a state of life-threatening organ dysfunction caused by a dysregulated host response to infection (1). It is responsible for 20% of all global deaths (2), and mortality rates remain high at 30–45% (2–4). Although sepsis epidemiology, including its prevalence, causes, and outcomes, differs among countries/regions (4, 5), most data are obtained from high-income countries/regions (HICs), which constitute only 13% of the world's population (6). Asia is strikingly underrepresented, despite being the world's largest continent and comprising territories from every national wealth group, thus facilitating a direct comparison of

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Availability of data and material: The data sets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

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epidemiology across different territorial incomes. The MOSAICS I (Management Of Severe sepsis in Asia's Intensive Care unitS I) study, conducted in 2009, provided some data, but participation from low-income countries/regions (LICs) and lower middle-income countries/regions (LMICs) was limited (7). Likewise, fewer than 5% of the study population in the international EPIC III (Extended Study on Prevalence of Infection in Intensive Care), conducted in 2017, was from LICs/LMICs (5). Although 217 Asian ICUs participated, the vast majority were in China. Importantly, EPIC III focused on the prevalence of infection rather than sepsis (1, 5).

The MOSAICS I study highlighted poor compliance rates to the then 6-hour resuscitation bundle for severe sepsis in 2009: 2.3%, 6.9%, and 10.0% in LICs, middle-income countries, and HICs, respectively. However, both the definition and the management of sepsis have evolved tremendously in the past decade (1, 8–10). Although the 2018 update of the Surviving Sepsis Campaign guidelines recommended a sepsis bundle comprising antibiotic administration, blood cultures, and lactate measurement within 1 hour of sepsis recognition (10), its feasibility in resource-limited countries remains in question (4). Concerns were also raised regarding how the recommendation lacked the backing of strong evidence and whether it could result in the premature diagnosis of sepsis and antibiotics misuse (11–15). To address these issues, the latest 2021 Surviving Sepsis Campaign guidelines recommended a tiered approach in which antibiotics are administered within 1 hour for possible septic shock or a high likelihood of sepsis and within 3 hours for possible sepsis without shock (16). It was acknowledged, however, that such recommendations were made on the basis of scarce data from resource-limited settings.

Given the gaps in the current literature, an update of Asia's sepsis epidemiology and sepsis bundle compliance, with an impetus to involve more LICs/LMICs over the different seasons, is timely. We thus conducted the MOSAICS II (Management Of Sepsis in Asia's Intensive Care unitS II) study with the aims of evaluating *1*) the prevalence, causes, and outcomes of sepsis as a reason for ICU admission in Asia, stratified by country/region income status and *2*) sepsis bundle compliance and its association with 90-day hospital mortality.

Methods

Study Design

This was an observational, cross-sectional, point prevalence study among Asian ICUs (defined as any unit capable of providing invasive mechanical ventilation and organ support that is recognized to be an ICU by its hospital). A steering committee of national coordinators invited ICUs in their respective countries/regions to participate. Where available, we used databases of ICUs, directors, and intensivists from national critical care societies and networks. We supplemented these with regional and personal snowball sampling. Each ICU had one representative. Participation was voluntary. The study was approved by institutional review boards according to local regulations, with most waiving the need for informed consent. The National Healthcare Group Domain-Specific Review Board approved the study (2018/00354), with a waiver of the requirement to obtain informed consent because of the noninterventional study design.

Participants

We included all adult ICUs, except neurosurgical, coronary, and cardiothoracic ICUs. We enrolled patients on four days (the first Wednesday of the month) representing the different seasons of 2019 (January 9 [February 27 in India, Indonesia, and Japan because of delayed ethics approval], April 3, July 3, and October 9). We included all patients aged ⩾18 years who were admitted to ICUs for sepsis and who were still in the ICUs from 00:00 to 23:59 of the study days (*see* Figure E1 in the online supplement). We defined sepsis as infection with a Sequential

At a Glance Commentary

Scientific Knowledge on the Subject: Epidemiological studies of sepsis are predominantly from high-income countries/regions (HICs), with few low-income countries/regions (LICs) and lower middle-income countries/regions (LMICs). Although diarrheal and tropical diseases are common causes of death in LICs/LMICs, these are rarely discussed in existing studies.
Controversy arose with the 2018 Surviving Sepsis Campaign recommendation of a 1-hour target for the sepsis bundle, which was based on limited evidence. Also, some elements of the bundle may not be feasible in resource-limited settings.
The MOSAICS I (Management of Severe Sepsis in Asia's Intensive Care Units) study demonstrated poor compliance with a 6-hour sepsis bundle target in Asian ICUs.

What This Study Adds to the Field: This is the largest point prevalence study on sepsis in ICUs across LICs/LMICs, upper middle-income countries/regions, and HICs. Although the study highlights similarities in sepsis epidemiology among countries/regions of differing national wealth, nosocomial pathogens were more commonly isolated in upper middle-income countries/regions and HICs. Tropical diseases do not appear to substantially burden ICUs in all resource settings.
Antibiotic administration within 3 hours was consistently the only bundle element associated with reduced 90-day hospital mortality. The results show marked improvement in compliance to sepsis bundles compared with the MOSAICS I study.

Organ Failure Assessment score ⩾2 from baseline (assumed to be zero if without prior organ dysfunction) (1).

Data Collection

ICU representatives primarily used password-protected online case report forms, which were translated into six other languages, though hard-copy forms were provided to those with limited Internet access. Representatives also completed a questionnaire to describe their centers' characteristics (hospital and ICU type, open or closed ICU model, university affiliation status, presence of accredited training program, nurse:patient ratio, and intensivist:patient ratio among the closed ICUs) and microbiology-processing capabilities (ability to process routine and acid-fast bacilli cultures; perform PCR and serological testing for dengue, influenza, and tuberculosis; perform blood film identification for malaria; and test for galactomannan).

The case report form contained four sections. The first section focused on baseline characteristics (demographics, comorbidities, and details of admission). The second section comprised parameters upon ICU admission, including vital signs, laboratory parameters, illness severity scores (Sequential Organ Failure Assessment score, systemic inflammatory response syndrome criteria, and the Acute Physiology and Chronic Health Evaluation II score), site of infection, and microbiology. Only microorganisms detected via cultures, serology, molecular, and/or histological investigations and deemed to be true pathogens rather than commensals or contaminants were recorded. The third section captured the timing of sepsis bundle elements and surgical source control referencing Time 0, determined as follows: *1*) time of triage in the emergency department (ED) for those presenting with sepsis to the ED, *2*) time of clinical documentation of deterioration in the general wards or other non-ED areas for those who developed sepsis after hospital admission, and *3*) time of ICU admission for those in which the first two time points could not be determined from the clinical documentation. The bundle elements were based on the Surviving Sepsis Campaign's 2018 update: antibiotic administration, blood cultures, lactate measurement, fluid administration (volume administered in the first and third hours from Time 0), and vasopressor initiation (10). Timings beyond 24 hours from Time 0 were excluded. The fourth section concerned life-sustaining treatments provided during the ICU stay. In addition, each ICU recorded the total number of ICU patients on each study day (*see* Figure E1). We checked the data for implausible outliers and missing fields and contacted ICU representatives for clarification.

Outcome Measures

We followed all patients till hospital discharge, till death in the ICU/hospital, and up to 90 days after enrollment, whichever was earliest. The main outcome measure was 90-day hospital mortality. Secondary outcome measures were compliance with the sepsis bundle elements, 90-day ICU mortality, and ICU and hospital lengths of stay (LOSs).

Statistical Analysis

We expressed categorical variables as frequency (percentage) and continuous variables as median (interquartile range [IQR]) or mean (SD). We compared categorical variables using the χ^2 test or Fisher exact test and continuous variables using one-way ANOVA and linear regression analysis. We used the Bonferroni correction for pairwise comparisons. We grouped countries/regions on the basis of their 2019 gross national income per capita, as defined by the World Bank (17): LICs/LMICs, upper middle-income countries/regions (UMICs), and HICs (*see* Table E1).

Thereafter, we used different multivariable generalized linear mixed models to study *1*) the association of different countries/regions' income classifications with 90-day hospital mortality and *2*) the association of bundle compliance with 90-day hospital mortality. To account for confounding, we used directed acyclic graphs to determine independent variables that could themselves have associations with mortality (*see* Tables E2 and E3 and Figures E2 and E3). ICU practices may differ among ICUs and countries/regions. Thus, we sought to account for these differences and nesting effects by defining the individual ICU and country/region as random effects.

We categorized patients into five groups according to the time of completion of each bundle element: 0–60 minutes, 61–120 minutes, 121–180 minutes, >180 minutes and <24 hours, and not administered within 24 hours of Time 0. We deemed elements completed within 1 hour before Time 0 as being completed at 0 minutes. Although we focused on antibiotic administration, blood cultures, and lactate measurement for all patients with sepsis, we included fluid administration and vasopressor initiation for patients who were hypotensive within the first hour of Time 0 who subsequently required vasopressors within 24 hours. These patients were defined as having septic shock. In a separate model, we categorized patients

according to the different permutations of completion within 1 hour or lack thereof of individual bundle elements (i.e., antibiotic administration and/or blood cultures and/or lactate measurement). In the third model, we repeated the latter analysis using a cutoff of 3 hours.

We used the meologit command in Stata Release 15 (StataCorp LLC) and set statistical significance at $P < 0.05$.

Results

ICUs

A total of 386 ICUs from 22 Asian countries/regions (9 LICs/LMICs, 5 UMICs, and 8 HICs) participated. Among the ICUs, 131 were from LICs/LMICs, 151 from UMICs, and 104 from HICs (*see* Table E4). The majority were from urban areas (87.0%), were university affiliated (57.3%), and had accredited training programs (56.2%). Most were mixed or medical ICUs. The most common nurse:patient ratio was 1:2. Closed units with patient care directed by intensivists accounted for 62.2% of ICUs.

Patients

We received 5,030 case report forms, of which 50 were excluded as they did not fulfill the inclusion criteria or were duplicates. Thus, 4,980 patients were included (Table 1). The median age was 64 (IQR, 51–76) years, with patients in LICs/LMICs and UMICs being significantly younger than those in HICs. The majority of patients were male (61.4%) with medical admissions (81.7%). More patients were admitted from EDs in LICs/LMICs than in UMICs and HICs. Further information, stratified by seasons, is available in Table E5. Patients from LICs/LMICs had lower Acute Physiology and Chronic Health Evaluation II scores than those from UMICs and HICs. Overall, 38.5% of patients had septic shock.

Prevalence of Sepsis

Of the 386 ICUs, 320 provided data on the total number of patients during the study dates. The prevalence of sepsis was 22.4% (4,683 of 20,929): 20.9% (1,261 of 6,021) in LICs/LMICs, 24.5% (1,858 of 7,579) in UMICs, and 21.3% (1,564 of 7,329) in HICs. Prevalence was higher in January/February (25.7% [1,421 of 5,538]) compared with

Table 1. Baseline Characteristics of the Study Population

Characteristic	All (*n* = 4,980)	Low- to Lower Middle-Income Countries/Regions (*n* = 1,561)	Upper Middle-Income Countries/ Regions (*n* = 1,890)	High-Income Countries/Regions (*n* = 1,529)	*P* Value
Demographics					
Age, yr, median (IQR)	64 (51–76)	60 (47–72)	63 (49–74)	70 (58–79)	<0.001
Male sex, *n* (%)	3,059 (61.4)	953 (61.1)	1,156 (61.2)	950 (62.1)	0.792
Admission type, *n* (%)					
Medical	4,071 (81.7)	1,354 (86.7)	1,391 (73.0)	1,326 (86.7)	<0.001
Unscheduled surgical	653 (13.1)	138 (8.8)	340 (18.0)	175 (11.5)	
Scheduled surgical	256 (5.1)	69 (4.4)	159 (8.4)	28 (1.8)	
Admission source, *n* (%)					
Emergency department	2,477 (49.7)	946 (60.6)	733 (38.8)	798 (52.2)	<0.001
General ward	1,416 (28.4)	265 (17.0)	658 (34.8)	493 (32.2)	
Operating room	375 (7.5)	77 (4.9)	216 (11.4)	82 (5.4)	
Interhospital transfer	333 (6.7)	121 (7.8)	153 (8.1)	59 (3.9)	
Other ICU or HDU	319 (6.4)	112 (7.2)	115 (6.1)	92 (6.0)	
Others	60 (1.2)	40 (2.6)	15 (0.8)	5 (0.3)	
Comorbidities, *n* (%)					
Diabetes mellitus	1,669 (33.5)	569 (36.5)	566 (30.0)	534 (34.9)	<0.001
Cardiovascular disease	1,353 (27.2)	432 (27.7)	510 (27.0)	411 (26.9)	0.863
Chronic lung disease	950 (19.1)	354 (22.7)	341 (18.0)	255 (16.9)	<0.001
Chronic kidney disease	904 (18.2)	291 (18.6)	279 (14.8)	334 (21.8)	<0.001
Chronic neurological disease	769 (15.4)	173 (11.1)	283 (15.0)	313 (20.5)	<0.001
Solid malignant tumor	588 (11.8)	151 (9.7)	192 (10.2)	245 (16.0)	<0.001
Chronic liver disease	250 (5.0)	80 (5.1)	79 (4.2)	91 (6.0)	0.060
Immunosuppression	230 (4.6)	74 (4.7)	70 (3.7)	86 (5.6)	0.027
Hematological malignancy	185 (3.7)	52 (3.3)	49 (2.6)	84 (5.5)	<0.001
Peptic ulcer disease	163 (3.3)	45 (2.9)	76 (4.0)	42 (2.8)	0.074
Connective tissue disease	162 (3.3)	36 (2.3)	84 (4.4)	42 (2.8)	0.001
HIV infection	28 (0.6)	11 (0.7)	9 (0.5)	8 (0.5)	0.682
No comorbidities	923 (18.5)	284 (18.2)	405 (21.4)	234 (15.3)	<0.001
Duration in hospital before ICU admission, d	0 (0–3)	0 (0–1)	1 (0–4)	1 (0–6)	<0.001
Severity, median (IQR)					
APACHE II score	20 (14–26)	17 (12–23)	20 (15–26)	21 (16–28)	<0.001
SIRS criteria	2 (2–3)	3 (2–3)	2 (2–3)	2 (2–3)	<0.001
SOFA score	7 (4–10)	6 (4–9)	8 (5–11)	8 (5–11)	<0.001

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; HDU = high-dependency unit; IQR = interquartile range; SIRS = systemic inflammatory response syndrome; SOFA = Sequential Organ Failure Assessment.

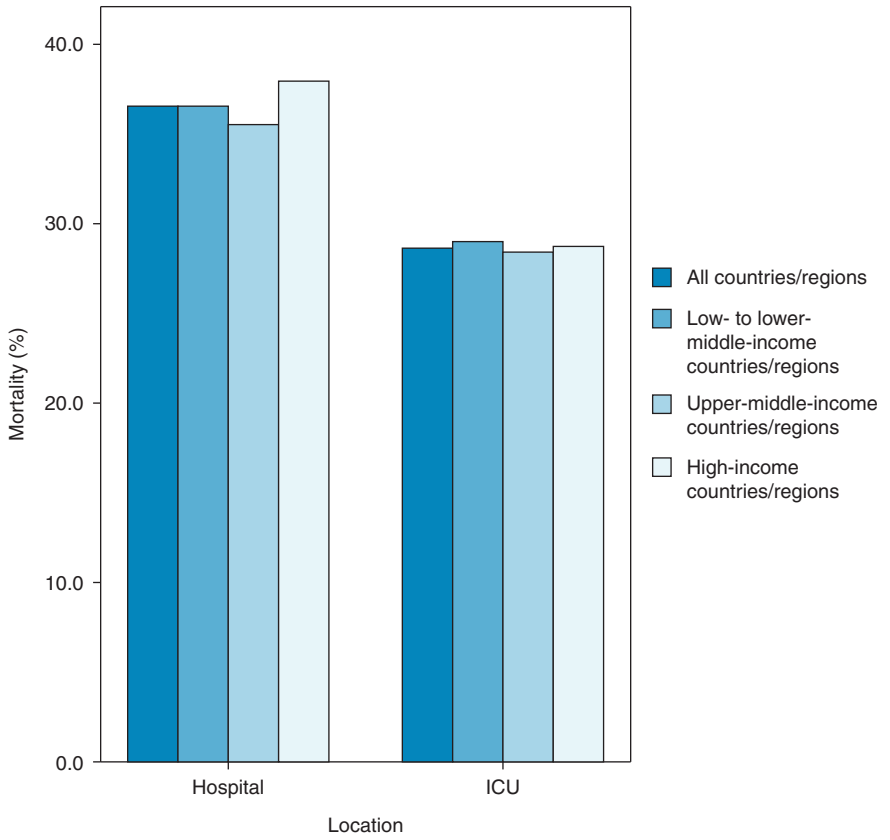

Figure 1. Hospital and ICU mortality stratified by World Bank income classification. ICU = intensive care unit.

April (22.5% [1,147 of 5,091]), July (21.4% [1,228 of 5,739]), and October (21.0% [1,032 of 4,924]).

Causes of Sepsis

Respiratory, intraabdominal, and urinary sepsis were most common in countries/regions of all three income classifications (*see* Table E6). No pathogens were detected in 28.3% of patients. Gram-negative bacteria were isolated in 51.8% of patients (with *Klebsiella pneumonia*, *Acinetobacter baumannii*, and *Escherichia coli* predominating), gram-positive bacteria in 20.2% (with *Enterococcus* species and *Staphylococcus aureus* predominating), fungi in 13.3% (with *Candida* species predominating), and viruses in 7.2% (with influenza predominating, especially during winter) (*see* Table E7). Tuberculosis (1.7%), dengue (1.1%), and malaria (0.2%) were not common.

Outcomes

Overall 90-day hospital mortality was 36.6%, with no difference among LICs/LMICs, UMICs, and HICs on univariable analysis (36.6% vs. 35.5% vs. 37.9%; $P = 0.361$) (Figure 1; *see* Table E8) but higher 90-day hospital mortality in LICs/LMICs compared with HICs on multivariable analysis (adjusted odds ratio [AOR], 1.84; 95% confidence interval [CI], 1.00–3.37; $P = 0.049$) (Table 2). Crude 90-day ICU mortality was also similar across income categories. The median ICU and hospital LOSs were 12 (IQR, 6–23) and 21 (IQR, 11–38) days, respectively, with HICs having the longest LOSs. Among patients with septic shock, 90-day ICU and hospital mortality rates were 32.7% and 41.7% respectively (*see* Table E9).

Sepsis Bundle Compliance and Association with 90-Day Hospital Mortality

Compliance with the 1-hour bundle and 3-hour bundle was 21.5% and 36.6%, respectively (Table 3; *see* Figure E4). After excluding patients who did not complete the bundle elements within 24 hours from Time 0, the median times of antibiotic administration, blood cultures, and lactate measurement were 60 (IQR, 30–150), 43 (IQR, 15–148), and 32 (IQR, 11–120) minutes, respectively. Compliance with the 1-hour (26.0% vs. 22.1% vs. 16.2%; $P < 0.001$) and 3-hour (39.3% vs. 32.8% vs. 38.5%; $P = 0.001$) bundles was highest in LICs/LMICs compared with UMICs and HICs. Only 56.3% (398 of 707) of patients who required surgical source control received it within 12 hours (*see* Table E10).

On multivariable generalized linear mixed model analysis, delay in antibiotic administration after 3 hours (AOR, 2.55; 95% CI, 2.09–3.11; $P < 0.001$) and absence of antibiotic administration within 24 hours from Time 0 (AOR, 5.09; 95% CI, 4.03–6.44; $P < 0.001$) were significantly associated with increased 90-day hospital mortality compared with antibiotic administration within 1 hour (Table 4; *see* Table E11). Across the various permutations of completion of individual bundle elements, compared with patients for whom no bundle element was completed, lower 90-day hospital mortality was seen only in subgroups in which antibiotics were administered within 1 and 3 hours (Table 4). There were similar associations between the timing of antibiotics and 90-day ICU mortality (*see* Tables E12 and E13). There was no interaction between antibiotic administration compliance and the country/region's economic status. As such, the association of increased mortality with late administration of antibiotics is not secondary to an interaction with economic status of the participating countries. Findings were similar when the study population was stratified according to the presence/absence of septic shock (*see* Tables E14 and E15). In particular, among patients with septic shock, the volume of fluids administered within 3 hours (AOR, 1.00; 95% CI, 1.00–1.00; $P = 0.289$) and the timing of vasopressors had no significant associations with 90-day hospital mortality (*see* Tables E15 and E16).

Other Life-Sustaining Treatments and Missing Data

Invasive mechanical ventilation was provided to 73.0% of patients, noninvasive ventilation to 16.7% (832 of 4,980), high-flow nasal oxygen to 11.5%, vasopressors to 69.0%, and kidney replacement therapy to 31.0% (*see* Table E17). Missing data (comprising <3% of all data) are described in Table E18.

Table 2. Multivariable Analysis with Variables Identified for Adjustment with Hospital Mortality as the Dependent Variable against World Bank Income Classification

Variable*	AOR (95% CI)†	*P* Value
Age	1.01 (1.01–1.01)	<0.001
Male sex	1.20 (1.05–1.37)	0.007
Comorbidities		
Diabetes mellitus	1.03 (0.89–1.19)	0.691
Solid malignant tumor	1.95 (1.60–2.37)	<0.001
Immunosuppression	1.51 (1.12–2.04)	0.006
Hematological malignancy	1.99 (1.42–2.78)	<0.001
HIV infection	1.62 (0.70–3.76)	0.262
APACHE II score	1.06 (1.05–1.07)	<0.001
Admission from emergency department	0.74 (0.64–0.85)	<0.001
Respiratory source of sepsis	1.09 (0.95–1.26)	0.230
Admission type		
Medical	Reference	
Elective surgical	0.73 (0.53–1.01)	0.058
Unscheduled surgical	0.74 (0.60–0.92)	0.007
World Bank income classification of countries/regions		
High income	Reference	
Upper middle income	1.50 (0.76–2.94)	0.240
Low to lower middle income	1.84 (1.00–3.37)	0.049

Definition of abbreviations: AOR = adjusted odds ratio; APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval.
*Variables that could themselves have associations with hospital mortality were inserted into multivariable generalized mixed models, together with the countries'/regions' World Bank income classifications. Country and intensive care unit center were incorporated as random effects.
†Association with hospital mortality on multivariable analysis.

Discussion

In this four-day point prevalence study, 22.4% of patients in Asian ICUs were admitted for sepsis. Respiratory, intraabdominal, and urinary sepsis predominated, and gram-negative bacteria were detected in more than half of patients. One in three patients admitted to ICUs for sepsis died in the hospital, with higher 90-day hospital mortality rates in LICs/LMICs compared with HICs on multivariable analysis. Although compliance with the 1-hour and 3-hour sepsis bundles was 21.5% and 36.6%, respectively, antibiotic administration within 3 hours of diagnosis was the only bundle element associated with decreased 90-day hospital mortality.

The strengths of our study include its being the largest of its kind in Asia, its inclusion of multiple centers from different countries/regions of different income categories, its conduct over four seasons, and its prospective nature with little missing data, all of which increase its representativeness. Our study also considered endemic diseases, including malaria, dengue, and tuberculosis, in contrast to previous studies, which tended to focus on more commonly seen bacteria (5, 6).

Our study also has several limitations. First, despite our best efforts to reach out widely, participation was voluntary, and this likely resulted in a disproportionate number of participating ICUs with university affiliations and accredited training programs. Although we lacked access to national ICU registries, survey data suggest that the participating ICUs in this study were representative of all ICUs in these countries/regions (18). Second, given the large sample size, we relied on ICU representatives to accurately interpret case report forms using a data dictionary, and data verification was difficult. Third, because of the study's real-world nature, we did not protocolize microbiological investigations. Fourth, to improve the feasibility of conducting the study in busy ICUs, we opted not to collect

Table 3. Completion of Sepsis Bundle Elements

	All (*n* = *4,980*)	Low- to Lower-Middle-Income Countries/Regions (*n* = *1,561*)	Upper-Middle-Income Countries/Regions (*n* = *1,890*)	High-Income Countries/Regions (*n* = *1,529*)	*P* Value
Completion of elements within 1 h, *n* (%)*					
Antibiotics	2,343 (47.0)	883 (56.6)	911 (48.2)	549 (35.9)	<0.001
Blood cultures	2,244 (45.1)	789 (50.5)	784 (41.5)	671 (43.9)	<0.001
Lactate measurement	2,455 (49.3)	734 (47.0)	950 (50.3)	771 (50.4)	0.094
Full bundle	1,072 (21.5)	406 (26.0)	418 (22.1)	248 (16.2)	<0.001
Completion of elements within 3 h, *n* (%)*					
Antibiotics	3,562 (71.5)	1,220 (78.2)	1,313 (69.5)	1,029 (67.3)	<0.001
Blood cultures	2,876 (57.8)	947 (60.7)	972 (51.4)	957 (62.6)	<0.001
Lactate measurement	2,994 (60.1)	863 (55.3)	1,162 (61.5)	969 (63.4)	<0.001
Full bundle	1,822 (36.6)	613 (39.3)	620 (32.8)	589 (38.5)	0.001
Time to completion, min, median (IQR)†					
Antibiotics	60 (30–150)	49 (25–110)	60 (25–158)	90 (37–180)	<0.001
Blood cultures	43 (15–148)	34 (15–104)	44 (15–203)	54 (19–152)	<0.001
Lactate measurement	32 (11–120)	30 (11–75)	36 (10–148)	33 (12–133)	0.008

Definition of abbreviation: IQR = interquartile range.
*We used Bonferroni correction for pairwise comparisons.
†Median timings on the basis of element completion within 24 hours from Time 0.

Table 4. Association of Completion of Sepsis Bundle Elements with Hospital Mortality

All (*n* = *4,980*)	Dead (*n* = *1,822*) [*n* (%)]	Alive (*n* = *3,158*) [*n* (%)]	AOR (95% CI)*	*P* Value
Association of timing of antibiotic administration with hospital mortality†				
Performed within 24 h (*n* = 4,432)	1,469 (33.1)	2,963 (66.9)	Not applicable	
0–60 min (*n* = 2,343)	690 (29.4)	1,653 (70.6)	Reference	
61–120 min (*n* = 747)	217 (29.0)	530 (71.0)	1.04 (0.85–1.28)	0.696
121–180 min (*n* = 472)	140 (29.7)	332 (70.3)	1.04 (0.81–1.34)	0.748
>180 min to ⩽24 h (*n* = 870)	422 (48.5)	448 (51.5)	2.55 (2.09–3.11)	<0.001
Not performed within 24 h (*n* = 535)	353 (66.0)	182 (34.0)	5.09 (4.03–6.44)	<0.001
Association of timing of obtaining blood cultures with hospital mortality‡				
Performed within 24 h (*n* = 3,680)	1,321 (35.9)	2,359 (64.1)	Not applicable	
0–60 min (*n* = 2,244)	760 (33.9)	1,484 (66.1)	Reference	
61–120 min (*n* = 413)	149 (36.1)	264 (63.9)	0.95 (0.73–1.23)	0.701
121–180 min (*n* = 219)	90 (41.1)	129 (58.9)	1.11 (0.79–1.56)	0.534
>180 min to ⩽24 h (*n* = 804)	322 (40.0)	482 (60.0)	0.90 (0.72–1.11)	0.330
Not performed within 24 h (*n* = 1,281)	500 (39.0)	781 (71.0)	0.89 (0.74–1.07)	0.225
Association of timing of obtaining lactate measurement with hospital mortality§				
Performed within 24 h (*n* = 3,716)	1,316 (35.4)	2,400 (64.6)	Not applicable	
0–60 min (*n* = 2,455)	830 (33.8)	1,625 (66.2)	Reference	
61–120 min (*n* = 334)	132 (39.5)	202 (60.5)	1.16 (0.88–1.52)	0.295
121–180 min (*n* = 205)	73 (35.6)	132 (64.4)	0.95 (0.67–1.34)	0.764
>180 min to ⩽24 h (*n* = 722)	281 (38.9)	441 (61.1)	0.94 (0.76–1.17)	0.597
Not performed within 24 h (*n* = 1,256)	505 (40.2)	751 (59.8)	0.88 (0.73–1.07)	0.209
Association of permutations of completed elements within 1 h with hospital mortality				
No elements completed (*n* = 1,285)	582 (45.3)	703 (54.7)	Reference	
Antibiotics only (*n* = 546)	164 (30.0)	382 (70.0)	0.44 (0.35–0.56)	<0.001
Blood cultures only (*n* = 318)	128 (40.3)	190 (59.7)	0.85 (0.64–1.12)	0.250
Lactate only (*n* = 556)	229 (41.2)	327 (58.8)	0.92 (0.73–1.16)	0.493
Antibiotics and lactate (*n* = 349)	87 (24.9)	262 (75.1)	0.43 (0.32–0.57)	<0.001
Antibiotics and blood cultures (*n* = 376)	118 (31.4)	258 (68.6)	0.48 (0.37–0.64)	<0.001
Blood cultures and lactate (*n* = 478)	193 (40.4)	285 (59.6)	0.89 (0.70–1.14)	0.352
Antibiotics, blood cultures, and lactate (*n* = 1,072)	321 (29.9)	751 (70.1)	0.55 (0.45–0.68)	<0.001
Association of permutation of completed elements within 3 h with hospital mortality				
No elements completed (*n* = 611)	339 (55.5)	272 (44.5)	Reference	
Antibiotics only (*n* = 641)	176 (27.5)	465 (72.5)	0.28 (0.21–0.36)	<0.001
Blood cultures only (*n* = 187)	107 (57.2)	80 (42.8)	1.21 (0.84–1.76)	0.310
Lactate only (*n* = 300)	163 (54.3)	137 (45.7)	1.12 (0.82–1.53)	0.481
Antibiotics and lactate (*n* = 552)	145 (26.3)	407 (73.7)	0.31 (0.23–0.41)	<0.001
Antibiotics and blood cultures (*n* = 547)	165 (30.2)	382 (69.8)	0.31 (0.23–0.41)	<0.001
Blood cultures and lactate (*n* = 320)	166 (51.9)	154 (48.1)	0.93 (0.68–1.27)	0.641
Antibiotics, blood cultures, and lactate (*n* = 1,882)	561 (29.8)	1,261 (67.0)	0.38 (0.30–0.47)	<0.001

Definition of abbreviations: AOR = adjusted odds ratio; CI = confidence intervals; ICU = intensive care unit.
*Generated using multivariable generalized linear mixed models, adjusted for age, sex, comorbidities (diabetes mellitus, solid malignant tumors, immunosuppression, hematological malignancies, HIV infection), admission from emergency department, Acute Physiology and Chronic Health Evaluation II score, respiratory site of infection, ICU characteristics (university affiliation, accredited training program, mixed vs. medical vs. surgical vs. others, closed vs. open model), country, and World Bank income classification. Country and ICU center were incorporated into the model as random effects.
†Missing 13 values.
‡Missing 19 values.
§Missing eight values.

data on antibiotic resistance and appropriateness. Fifth, patients were not followed up after discharge, some of whom might have been discharged against medical advice and were at higher risk of death (19).

Our study complements but differs from the 2017 EPIC III study (5). Because of the distinct inclusion criteria, we found a sepsis prevalence rate of 22.4%, while EPIC III had a prevalence of infection (including ICU-acquired infection and not specifically sepsis) of 60.1% in Asian ICUs. Like EPIC III, the most common pathogens in our study in all countries/regions were consistently gram-negative bacteria, followed by gram-positive bacteria, fungi, and viruses. Nosocomial pathogens were more commonly isolated in UMICs and HICs, possibly because of more ICU admissions from non-ED sources. This highlights the importance of considering empirical

antibiotics on the basis of patterns of antibiotic resistance (20).

Of note, diseases such as tuberculosis, dengue, and malaria account for only 3% of ICU admissions in our study. This stands in contrast to smaller studies, which suggested that tropical diseases might cause 20–30% of ICU admissions in LICs/LMICs (21, 22). Three factors may explain our findings. First, seasonal variation in prevalence might have contributed, even though we did attempt to mitigate this by conducting our study across the year. Second, a lack of adequate microbiological support might have led to an underdetection of various tropical diseases (21), even though we note that 95.1% (4,737 of 4,980), 72.8% (3,623 of 4,980), and 88.1% (4,389 of 4,980) of the included patients were admitted to ICUs with supporting laboratories capable of diagnosing tuberculosis, dengue, and malaria, respectively. Third, the vast majority (97.0%) of our participating ICUs were from urban areas, a mix that is broadly representative of the situation in Asia, including LICs/LMICs, as demonstrated in a recent multinational survey by Phua and colleagues (18). Thus, patients with tropical diseases in rural areas might have had limited access to any ICUs. Regardless, and in sum, our findings suggest that although tropical diseases are prevalent in Asia and may preferentially affect selected areas (23–25), they do not appear to substantially burden ICUs in general.

Benefits of early antibiotics stand out among the sepsis bundle elements evaluated in our study. However, the optimal timing for antibiotics remains controversial (11–13). Although it has been shown that antibiotic initiation within 3 hours of arrival at the ED may reduce sepsis mortality (26), other studies suggest that even earlier administration may further improve survival (27–30). Yet other investigators have not found an association of antibiotics in or before arrival at the ED with outcomes (31–34). The 2021 Surviving Sepsis Campaign guidelines eventually adopted a tiered approach on the basis of the likelihood of sepsis and the presence of shock. When further evaluation is still required for patients without shock, antibiotic administration within 3 hours after the encounter was recommended if concern for infection persisted (16). Our findings, suggesting a 90-day hospital mortality increase only when antibiotics were delayed beyond 3 hours (not 1 hour) from sepsis recognition, provide additional support for this particular recommendation. Of note, however, although our findings applied to both patients with sepsis and those with septic shock, immediate antibiotic administration within the hour among patients with shock remained a strong recommendation in the latest 2021 Surviving Sepsis Campaign update, on the basis of prior evidence of increasing mortality with each hour of delay (16, 26–28). Although ideal, practical issues on the ground, including the time needed for clinical assessment, antibiotic prescription, blood cultures, and drug delivery, may pose challenges in fulfilling this recommendation, especially in resource-limited settings (35).

Certain features of our study population are worth noting compared with earlier studies. First, our cohort comprised only patients requiring ICU admission for sepsis, compared with studies focusing on any patients with sepsis in the ED, of whom only a portion required intensive care (34, 36). Second, 38.5% of our cohort had septic shock, compared with a smaller proportion in other studies (33, 36). The effect size of antibiotics as a time-sensitive intervention may increase as illness severity increases. Perhaps unsurprisingly, the timing of blood cultures and lactate measurement was not associated with 90-day hospital mortality, as these are processes of care rather than lifesaving treatments. Similarly, fluid administration and vasopressor initiation within 1 hour did not appear to confer any survival benefit for septic shock. Theoretically, earlier norepinephrine initiation allows the rapid achievement of blood pressure targets with less fluid (37, 38), but side effects including immunoparalysis remain a concern (39).

There have been few patient-level data on sepsis mortality from LICs/LMICs since the MOSAICS I study in 2009 (6). Although direct comparison is not possible given the different study populations, crude 90-day hospital mortality appears to have improved over time among ICUs in LICs/LMICs and UMICs that participated in both MOSAICS I and MOSAICS II (*see* Table E19) (7). We postulate that this could be attributed to earlier sepsis recognition, leading to improved bundle compliance and specifically more timely antibiotics. Interestingly, bundle compliance was higher in LICs/LMICs than in UMICs and HICs. Two factors may account for this. First more patients from LICs/LMICs were admitted from EDs, where prompt detection of severe illness on presentation was more likely than in general wards, where the risk of occult deterioration might have been higher. Second, patients from LICs/LMICs were younger and less sick, thus potentially rendering clinical care less complex and allowing a more targeted focus on sepsis bundle compliance. Yet, although crude 90-day mortality appears similar across countries/regions of the three income groups in our present study, and despite earlier antibiotic administration among LICs/LMICs, adjusted 90-day hospital mortality was in fact higher among LICs/LMICs on multivariable analysis. Notwithstanding the fact that 8.2% of patients from HICs were still in the hospital 90 days after enrollment (*see* Table E8), thus potentially leading to underreporting of hospital mortality rate, sepsis mortality is generally recognized as being substantially higher in LICs/LMICs than in HICs (2). This difference is also reflected in many other conditions, such as stroke (40) and ischemic heart disease (41). Our results are likely further confirmation of existing trends and could be related to unaccounted confounders and processes of care, such as nurse-to-patient ratio, patients' functional status and frailty states, quality of intensive care beyond the sepsis bundles, and availability of advanced technology.

Taken together, our findings suggest the need for a nuanced application of the sepsis bundles. Especially in the most resource limited settings, where complex work flows may not be feasible (42), early antibiotic administration must be emphasized. Administration within 3 hours of sepsis recognition, as opposed to 1 hour, is more achievable, allowing clinicians time for further evaluation and consideration of alternative diagnoses and thus reducing overuse of antibiotics for patients without sepsis.

Conclusions

Sepsis accounts for 22.4% of admissions to participating Asian ICUs, half of which are associated with gram-negative bacteria. Ninety-day hospital mortality is high, while compliance with the sepsis bundles remains low. Delay in antibiotic administration beyond 3 hours of sepsis diagnosis is associated with increased mortality. After controlling for confounding, 90-day hospital mortality is higher in LICs/LMICs compared with HICs. ■

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