The epidemiology of sepsis in Brazilian intensive care units (the Sepsis PREvalence Assessment Database, SPREAD): an observational study

*Flavia R Machado, Alexandre Biasi Cavalcanti, Fernando Augusto Bozza, Elaine M Ferreira, Fernanda Sousa Angotti Carrara, Juliana Lubarino Sousa, Noemi Caixeta, Reinaldo Salomao, Derek C Angus, Luciano Cesar Pontes Azevedo, on behalf of the SPREAD Investigators and the Latin American Sepsis Institute Network**

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*A complete list of the investigators of the trial is included at the end of the Article

Anesthesiology, Pain, and Intensive Care Department (Prof F R Machado PhD) **and Infectious Disease Department** (Prof R Salomao PhD), **Universidade Federal de São Paulo, São Paulo, Brazil; Latin America Sepsis Institute, São Paulo, Brazil** (Prof F R Machado, A B Cavalcanti PhD, F A Bozza PhD, E M Ferreira MsH, F S Angotti Carrara MsH, J L Sousa RN, N Caixeta, Prof R Salomao, Prof L C Pontes Azevedo PhD); **Brazilian Research in Intensive Care Network (BRICNet), São Paulo, Brazil** (Prof F R Machado, A B Cavalcanti, F A Bozza, Prof L C Pontes Azevedo); **Research Institute, Hospital do Coração (HCor), São Paulo, Brazil** (A B Cavalcanti); **Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, Brazil** (F A Bozza); **Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, USA** (Prof D C Angus MD); **and Hospital Sírio Libanes, São Paulo, Brazil** (Prof L C Pontes Azevedo)

Correspondence to: Prof Flavia R Machado, Latin America Sepsis Institute, Universidade Federal de São Paulo, 04039-002 São Paulo, Brazil **frmachado@unifesp.br**

Summary

Background The sepsis burden on acute care services in middle-income countries is a cause for concern. We estimated incidence, prevalence, and mortality of sepsis in adult Brazilian intensive care units (ICUs) and association of ICU organisational factors with outcome.

Methods We did a 1-day point prevalence study with follow-up of patients in ICU with sepsis in a nationally representative pseudo-random sample. We produced a sampling frame initially stratified by geographical region. Each stratum was then stratified by hospitals' main source of income (serving general public *vs* privately insured individuals) and ICU size (ten or fewer beds *vs* more than ten beds), finally generating 40 strata. In each stratum we selected a random sample of ICUs so as to enrol the total required beds in 1690 Brazilian adult ICUs. We followed up patients until hospital discharge censored at 60 days, estimated incidence from prevalence and length of stay, and generated national estimates. We assessed mortality prognostic factors using random-effects logistic regression models.

Findings On Feb 27, 2014, 227 (72%) of 317 ICUs that were randomly selected provided data on 2632 patients, of whom 794 had sepsis (30·2 septic patients per 100 ICU beds, 95% CI 28·4–31·9). The ICU sepsis incidence was 36·3 per 1000 patient-days (95% CI 29·8–44·0) and mortality was observed in 439 (55·7%) of 788 patients (95% CI 52·2–59·2). Low availability of resources (odds ratio [OR] 1·67, 95% CI 1·02–2·75, p=0·045) and adequacy of treatment (OR 0·56, 0·37–0·84, p=0·006) were independently associated with mortality. The projected incidence rate is 290 per 100 000 population (95% CI 237·9–351·2) of adult cases of ICU-treated sepsis per year, which yields about 420 000 cases annually, of whom 230 000 die in hospital.

Interpretation The incidence, prevalence, and mortality of ICU-treated sepsis is high in Brazil. Outcome varies considerably, and is associated with access to adequate resources and treatment. Our results show the burden of sepsis in resource-limited settings, highlighting the need to establish programmes aiming for sepsis prevention, early diagnosis, and adequate treatment.

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Introduction

Middle-income countries have better basic health care and socioeconomic conditions than do low-income countries and have been able to invest in considerably better hospital care. In particular, the number of intensive-care units (ICUs) in middle-income countries are growing.[1] However, concerns persist regarding both the adequacy of ICU resources and the quality of ICU care delivery in these settings.[2] Sepsis is one of the most frequent conditions worldwide for which ICU care is required.[3] Although there is no estimate of sepsis incidence from low-income and middle-income countries,[3] extrapolation based on results from studies in high-income countries suggest that low-income and middle-income countries comprise 85% of the global burden of sepsis.[4] Outcomes of sepsis, such as mortality, have improved in high-income countries,[5] with a case-fatality rate of hospital-treated cases of 26% in the past decade.[3] However, the scarce data suggest higher case-fatality in low-income and middle-income countries than in high-income countries.[6,7] Most observational studies of sepsis in low-income and middle-income countries, including previous studies in Brazil,[8–10] have enrolled small convenience cohorts that neither allowed robust inference of national or regional burden nor interrogation of the associations between resource availability, quality of treatment, and outcome.[11–13]

Thus, we have completed a nationwide, 1-day, point-prevalence study with follow-up to assess the national incidence, prevalence, and in-hospital mortality of sepsis in a stratified pseudo-random sample of Brazilian adult ICUs. We also assessed the association of select hospital and ICU organisational factors (eg, hospital ownership and public or private missions), availability of ICU resources for sepsis management, and compliance with international treatment guidelines with outcome.[14]

Research in context

Evidence before this study

Sepsis is one of the most frequent conditions worldwide for which care in an intensive-care unit (ICU) is required. However, there is no estimate of sepsis incidence from low-income and middle-income countries. A 2016 systematic review searched 15 regional and international databases, including PubMed and Embase, for studies on sepsis incidence from January, 1979, through May, 2015, without any language or publication restrictions using the terms "(sepsis OR septic*) AND (epidemiolog*, incidence, burden, OR prevalence)". The systematic review found a wide variability across countries and no epidemiological studies from low-income or middle-income countries. Extrapolation of data based on results from high-income countries is prone to bias. Outcomes of sepsis have improved in high-income countries. Conversely, the few available data suggest that there is higher case-fatality in low-income and middle-income countries than in high-income countries. Most observational studies of sepsis in low-income and middle-income countries settings, including previous Brazilian studies, enrolled small convenience samples that neither allowed robust inference of national or regional burden nor interrogation of the associations between resource availability, quality of treatment, and outcome.

Added value of this study

This is the first national study of patients cared for in a middle-income country showing a high incidence and prevalence of sepsis and associated mortality in a random and well sized weighted sample of ICUs. We showed that sepsis represents a high burden for our health-care systems both in terms of incidence and number of deaths. Additionally, we showed that, in a middle-income country, patients in hospitals with less availability of resources seemed to have higher mortality.

Implications of all the available evidence

Data from middle-income countries are few and it is of upmost importance to identify the effect of sepsis in those settings. We have unequivocally shown that sepsis represents a huge burden to our health-care system. Attention is needed in resource-constrained settings to establish preventive measures for reducing this burden and settling quality improvement initiatives that aim to recognise sepsis earlier and suggest adequate treatment. These results might increase awareness of sepsis burden by policy makers and stakeholders who set the priorities in institutions and government budgets.

Methods

Study design

The Sepsis PREvalence Assessment Database (SPREAD) study was a nationwide 1-day, prospective, point prevalence study with follow-up designed to assess the national incidence, prevalence, and in-hospital mortality of sepsis, with a stratified pseudo-random sample of adult ICUs in all Brazilian regions. We also used the prevalence measurement to estimate the ICU incidence of sepsis and to estimate the number of adult cases of sepsis treated in ICUs per year in Brazil. A cohort of all identified cases was followed up until hospital discharge or death to identify mortality and prognostic factors (appendix). All participating ICUs completed a web survey about organisational factors.

The study was approved by the research ethics committee (ERB) at the coordinating centre (Federal University of São Paulo, Brazil) under the number CAAE: 04719512.0.1001.5505. Informed consent was waived because of its observational nature and no direct patient contact.

Setting

Adopting the methods of a previous study of national critical care services in the USA,[15] we generated a stratified pseudo-random sample of all Brazilian adult ICUs as listed under the Brazilian Association of Intensive Care (Associação de Medicina Intensiva Brasileira, AMIB) 2010 ICU Census,[16] which was the last version available and comprised 2623 ICUs with 28 849 beds. We excluded neonatal and paediatric ICUs, cardiac care units, and burn units, leaving 1690 ICUs and 19 316 eligible beds. Our sampling strategy was primarily based on the objective of creating similarly sized strata, each of them made up of 100–500 ICU beds to enhance the representativeness of our random selection of ICUs. Based on the AMIB list we produced a sampling frame that was initially stratified by geographical region and size of the cities, considering also the location, whether in capital cities or the countryside. Each stratum was then stratified by hospitals' main source of income (serving general public or privately-insured individuals) and ICU size (ten or fewer beds *vs* more than ten beds) finally generating 40 strata. We used the randomise (RAND) function in Excel 2010, which generates pseudo-random numbers for ICUs within each stratum and sequentially contacted their medical directors by telephone and email, inviting them to participate in the study until the total number of beds in each stratum was reached (appendix).

See Online for appendix

Participants

We planned to enrol 784 patients with sepsis. With this sample size, we anticipated we could estimate both prevalence and in-hospital mortality with a 95% confidence interval of 7% or less. In a previous study done in Brazil,[8] the prevalence of sepsis was 32 patients per 100 occupied ICU beds. Thus, we estimated that we would need to screen 2450 ICU beds to enrol 784 septic patients. This number was adjusted to 2940 ICU beds to allow a dropout of 20%.

We asked all ICUs to enrol patients on Feb 27, 2014. The ICUs could optionally choose to enrol patients on Feb 26 or 28. On the day of data collection, all patients

who were previously admitted or admitted during the study day to the participating ICUs were included if they fulfilled the inclusion criteria. The inclusion criteria were age 18 years or older, presence of sepsis or septic shock, and current organ dysfunction secondary to sepsis, regardless of the day of dysfunction onset. We defined sepsis as the presence of infection complicated by acute organ dysfunction (previously called severe sepsis)[17] and septic shock as the presence of hypotension not responsive to fluids with need for vasopressors in the first 24 h of the sepsis diagnosis (appendix). There were no exclusion criteria.

Procedures

All institutions that agreed to participate in the 1-day prevalence assessment were invited to answer a structured web-survey constructed to analyse the institution infrastructure and availability of resources, as well as ICU organisational aspects such as staffing and use of protocols of care as proxy indicators of the quality of care (appendix). To assess the availability of resources, the steering committee selected eight items using an informal Delphi process, under the premise to measure the institution capacity to comply with the Surviving Sepsis Campaign 6-h bundles. We categorised this variable as follows: the ICUs that reported always having the eight items were considered as a high availability facility, seven items as an intermediate availability facility, and six or fewer items as a low availability facility (appendix). We identified the ICU availability rate as the number of ICU beds per 100 000 population according to the state in which the institution was located. Considering that there is an imbalance in the availability of beds between public and private institutions, we calculated for each state both rates and used the appropriate one according to the main source of income of the patient's institution (appendix).

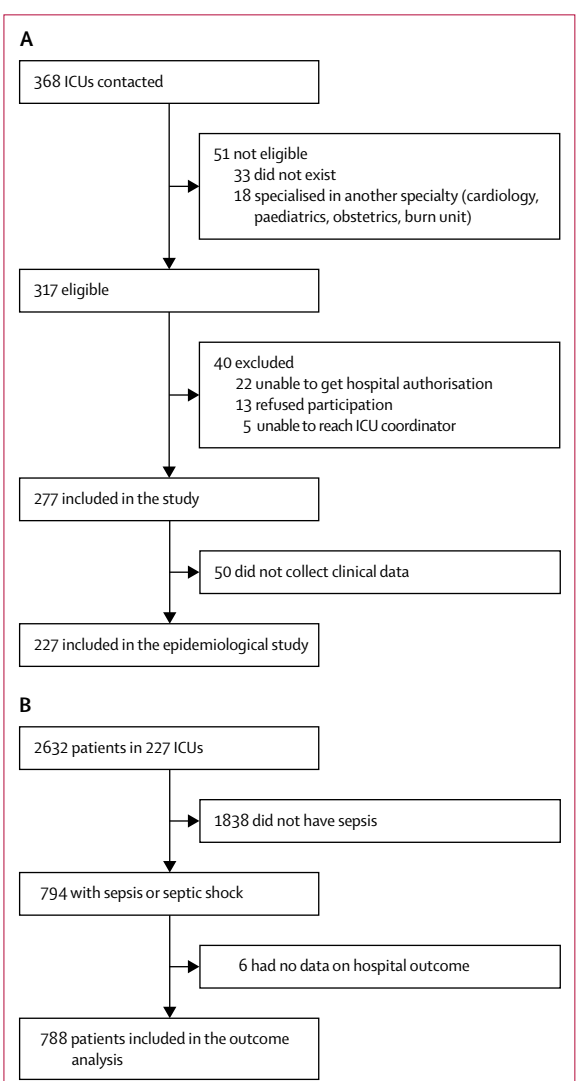

Figure 1: **Study flowchart**
(A) Flowchart of participating ICUs. (B) Flowchart of participants. ICU=intensive care unit.

On the study day, we obtained all data using an electronic case report form. We obtained demographic data, comorbidities, characteristics of the infection, and data on the sepsis management within the first 24 h of diagnosis, including compliance with all items of the Surviving Sepsis Campaign 6-h bundle (appendix)[14] and time to sepsis diagnosis. This timeframe was defined as the number of hours between the onset of the first dysfunction and its recognition by the health-care provider (appendix). We also obtained data to calculate the Simplified Acute Physiology Score 3 (SAPS 3) for the day of admission to the ICU and to calculate the Sequential Organ Failure Assessment (SOFA) for the day of sepsis diagnosis. We followed up the patients for 60 days or until hospital discharge to identify in-hospital mortality.

Statistical analysis

We calculated sepsis prevalence considering all patients with ongoing sepsis in patients who were previously admitted or who were admitted during the study day in the participating ICUs and reported the results as absolute numbers, percentages, and respective 95% CIs. We assessed whether prevalence varied according to geographical regions and availability of ICU rate using χ^2 and Spearman's test. We used the prevalence and duration of disease to estimate the incidence of sepsis in ICU.[18] We also generated national estimates of the incidence of ICU-treated sepsis in the adult population and in-hospital mortality based on our incidence of sepsis in ICU (appendix).

We assessed in-hospital mortality considering all cases and reported the results as absolute numbers, percentages, and respective 95% CI. However, because the patient cohort in this study was composed of prevalent cases of sepsis, there is a risk that mortality estimates might not hold for incidental cases. Therefore,

we did a sensitivity analysis to assess mortality in the group of patients that developed organ dysfunction during the study day.

In the univariate analysis to assess the prognostic factors, we tested categorical data by Fisher's exact test or χ^2 test, and continuous data without normal distribution by Mann-Whitney tests. We ran a multivariate analysis to identify if availability of resources, hospital profile, and adequacy of treatment were associated with an increased risk of death after controlling for severity of illness and other known predictors of mortality. Since we sampled ICUs and analysed outcomes at the patient level, we used logistic linear mixed models with random effects at the ICU level to account for any clustering effect. We included all variables with a p value of less than 0·05 in the univariate analysis for the model. To access adequacy of treatment, we used the compliance with the Surviving Sepsis Campaign 6-h bundles, analysing separately those patients non-compliant with antibiotics, those compliant at least with antibiotics but not with all items, and those compliant with the whole bundle. Age was not included with SAPS 3 in the final model because age is one of the variables considered in the SAPS 3 score. We assessed co-linearity first by examining scatter plot matrix and Pearson's correlation coefficient for continuous variables, or cross-tabulation for categorical variables. We further assessed co-linearity with variance inflation factor (VIF) analysis. Variables with substantial co-linearity (location at sepsis diagnosis and SOFA score) were excluded. The results of the multivariate analysis were expressed as odds ratios and the corresponding 95% CIs. We also developed a logistical linear mixed model with random effects at ICU level considering separately patients with community-acquired and health-care-associated infections (HAIs).

All tests were two-sided and a p value lower than 0·05 denoted significance. We completed all analyses using R 3.2.2 software (R Core Team, 2014).

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 368 contacted ICUs, 317 were eligible and 13 (4%) ICUs refused to participate. 277 (87%) of 317 units answered the resources survey, as it was a requirement to participate in the study, and 227 (72%) of 317 included patients in the study (figure 1). The percentage of ICUs included in each stratum was similar to the planned enrolment (appendix) and these ICUs were well distributed in all Brazilian regions (figure 2). The main characteristics of the participating ICUs are available in the appendix.

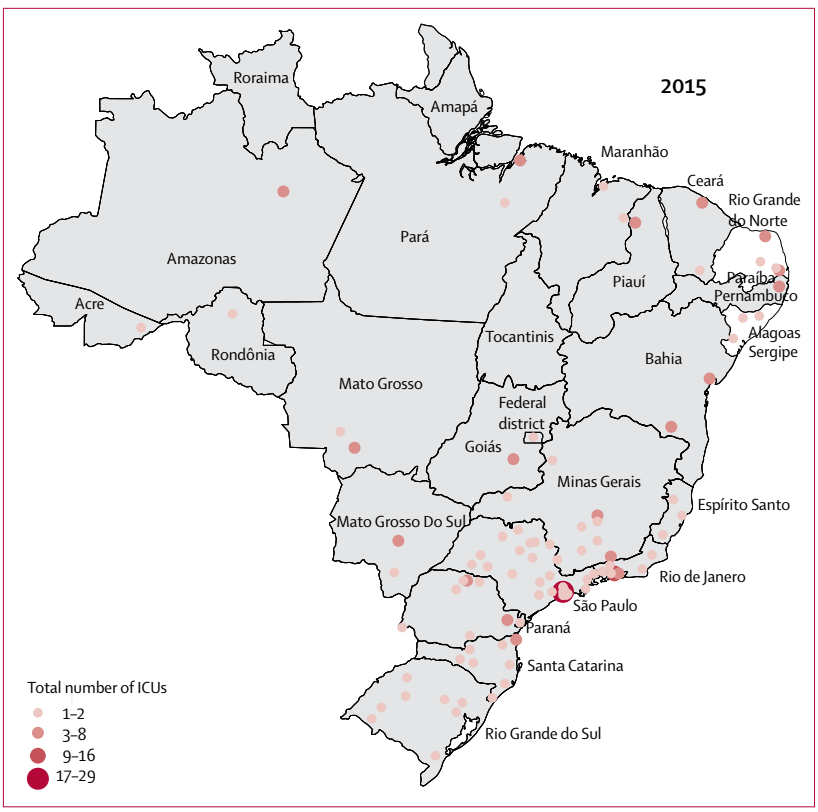

Figure 2: **Participating intensive care units by location in Brazilian states**

	All patients*	Survivors*	Non-survivors*	p value
Institution characteristics				
Main source of income	..	..	..	0·863
Private health system	337/794 (42%)	150/336 (45%)	186/336 (55%)	..
Public health system	457/794 (58%)	199/452 (44%)	253/452 (56%)	..
Resources availability†	..	..	..	0·014
High	522/794 (66%)	246/520 (47%)	274/520 (53%)	..
Intermediate	129/794 (16%)	55/125 (44%)	70/125 (56%)	..
Low	143/794 (18%)	48/143 (34%)	95/143 (66%)	..
Median ICU beds per 100 000 population‡	17·6 (11·6–27·0)	17·6 (11·5–26·9)	17·6 (11·6–27·0)	0·684
Patient characteristics				
Age, years	65·5 (49·0–79·0)	61·0 (43·0–75·0)	68·0 (54·5–80·0)	<0·0001
SAPS 3 score	70 (59–82)	65 (54–76)	74 (64–86)	<0·0001
SOFA score	8 (5–10)	7 (4–10)	8 (6–11)	<0·0001
Severity of illness	..	..	..	0·0033
Sepsis	328/792 (41%)	165/327 (50%)	162/327 (50%)	..
Septic shock	464/792 (59%)	184/461 (40%)	277/461 (60%)	..
Type of infection¶	..	..	..	<0·0001
Community	314/792 (40%)	162/311 (52%)	149/311 (48%)	..
Health-care-associated infections	478/792 (60%)	187/477 (39%)	290/477 (61%)	..

(Table 1 continues on next page)

	All patients*	Survivors*	Non-survivors*	p value
(Continued from previous page)				
Location at sepsis presentation	..	..	..	0·0009
Emergency department	270/792 (34%)	142/268 (53%)	126/268 (47%)	..
Wards	227/792 (29%)	83/226 (37%)	143/226 (63%)	..
ICU	295/792 (37%)	124/294 (42%)	170/294 (58%)	..
Source of infection	..	..	..	0·680
Lung	480/784 (61%)	211/476 (44%)	265/476 (56%)	..
Intra-abdominal	112/784(14%)	47/111 (42%)	64/111 (58%)	..
Urinary tract	71/784 (9%)	27/71 (38%)	44/71 (62%)	..
Other	121/784 (15%)	56/120 (47%)	64/120 (53%)	..
Time to sepsis diagnosis, h§	6·0 (1·5–23·9)	5·3 (2·0–22·5)	6·0 (1·4–24·0)	0·983
Time from diagnosis to ICU‖	..	..	..	0·043
≤6 h	269/441 (61%)	130/269 (48%)	139/269 (52%)	..
>6 h	172/441 (39%)	65/169 (38%)	104/169 (62%)	..
Adequate source control	..	..	..	0·005
Yes	171/227 (75%)	86/171 (50%)	85/171 (50%)	..
No	56/227 (25%)	16/56 (29%)	40/56 (71%)	..
Lactate sampling	..	..	..	0·835
Yes	543/789 (69%)	242/542 (45%)	300/542 (55%)	..
No	246/789 (31%)	107/244 (44%)	137/244 (56%)	..
Blood cultures sampling	..	..	..	0·161
Yes	591/789 (75%)	270/589 (46%)	319/589 (54%)	..
No	198/789 (25%)	79/197 (40%)	118/197 (60%)	..
Antibiotics in the first hour	..	..	..	0·0006
Yes	421/789 (53%)	210/419 (50%)	209/419 (50%)	..
No	368/789 (47%)	139/367 (37·9)	228/367 (62·1)	..
Fluids and vasopressors	..	..	..	0·218
Yes	312/457 (68%)	137/311 (44%)	174/311 (56%)	..
No	145/457 (32%)	55/145 (38%)	90/145 (62%)	..
CVP optimisation	..	..	..	0·932
Yes	168/409 (41%)	70/167 (42%)	97/167 (58%)	..
No	241/409 (59%)	100/241 (41%)	141/241 (59%)	..
$ScvO_2$ optimisation	..	..	..	0·521
Yes	151/409 (37%)	66/151 (44%)	85/151 (56%)	..
No	258/409 (63%)	104/257 (40%)	153/257 (60%)	..
Compliance with 6-h bundle	..	..	..	<0·0001
Non-compliance with antibiotics	368/789 (47%)	139/367 (38%)	228/367 (62%)	..
Compliance at least with antibiotics	260/789 (33%)	117/259 (45%)	142/259 (55%)	..
Complete compliance with 6-h bundle	161/789 (20%)	93/160 (58%)	67/160 (42%)	..

Data are n (%) or median (IQR). Missing data not provided by the sites are indicated by the denominators in each variable. ICU=intensive care unit. SAPS=simplified acute physiology score. SOFA=sequential organ failure assessment. CVP=central venous pressure. $ScvO_2$=central venous oxygen saturation. *For the whole population, the 100% refers to the columns and for the survival status it refers to the line. †In the resources availability assessment we assigned one point for availability of each of eight items relevant to the care of patients with sepsis and septic shock, and further classified ICUs as low (six items or fewer), intermediate (seven items) or high availability (all eight items). ‡According to the state in which the institution is located and its main source of income (public or private). ¶Health-care-associated infections include those infections acquired by out-clinic, hospice and homecare patients as well as those not present at hospital admission and started after 48 h of hospital stay. §Data available only for 425 patients. Patients with time to diagnosis equal to zero (n=366) were not considered. ‖Includes only 441 patients in whom sepsis was diagnosed outside the ICU. In 56 other patients, sepsis was only diagnosed after ICU admission.

Table 1: **Main characteristics of the 794 patients with ongoing sepsis on the study day according to survival status**

On the day of the survey, there were 2632 patients in the study ICUs. Of these, 132 (16·7%; 95% CI 14·2–19·5) had developed sepsis on the study day, and an additional 662 had an existing diagnosis of sepsis, resulting in a total of 794 patients with ongoing sepsis. Their main characteristics are available in table 1 (more detail provided in the appendix). HAIs formed 478 (60%) of 792 cases (two patients had missing data). From all sepsis cases, the proportion of ICU beds occupied by patients with sepsis was 30·2% (95% CI 28·4–31·9). This proportion was different among the Brazilian regions (p<0·0001, appendix) although it was not correlated with the availability of ICU beds (r=–0·053, p=0·427). Based on this occupation rate, we estimated an incidence of sepsis in the ICU of 36·3 (95% CI 29·8–44.0) cases per 1000 patient-days.

Vital status at hospital discharge was available for 788 (99%) of the 794 patients with sepsis. 439 of 788 patients with sepsis died in the hospital (56%, 95% CI 52–59). Of the 132 incident cases who developed sepsis on the study day there were 72 deaths (55%).

According to our analysis, 51 (23%) of 227 institutions had low availability of resources (appendix). Compliance with the 6-h bundle was low (161 [20%] of 789). Institutions with high availability of resources had a higher compliance rate with the 6-h bundle (122 [23%] of 520 patients) than those with low availability (19 [13%] of 142 patients, p=0·011; appendix).

Variables associated with mortality in univariate analyses are shown in table 1 and the appendix. In our assessment of resources, the only single individual item associated with mortality was the low availability of adequate cultures (appendix). In the final logistic linear mixed model with random effects at ICU level and adjustment for covariates (SAPS 3 score, location at sepsis onset, presence of shock), the low availability of resources was associated with higher mortality (table 2). Conversely, compliance at least with antibiotics within 1 h (OR 0·63, 95% CI 0·44–0·89, p=0·0090) and compliance with the entire 6-h bundle (0·56, 0·37–0·84, p=0·0059; table 2) were associated with lower mortality. However, in a direct comparison between the effect of compliance with antibiotics and compliance with the entire bundle there was no additional effect on mortality (p=0·168). The hospital main source of income was not associated with an increased risk of death (186 deaths [55%] in 336 patients with sepsis in the public health system *vs* 253 deaths [56%] in 452 patients with sepsis in the private health system, p=0·863; table 1).

In our post-hoc assessment according to the type of infection (appendix), the variables that remained associated with mortality both for community-acquired infection and HAI in the final multivariate model were SAPS 3 and presence of shock. The compliance with antibiotics seemed to be more important as a protective factor in patients with community-acquired infections than for patients with HAI (appendix). The low

availability of resources was no longer a significant risk factor, though the direction of effect estimates was similar to those observed in the main model (appendix).

Based on our estimate of the incidence of sepsis in the ICU, the adult population incidence of ICU-treated sepsis was 290·0 (95% CI 237·9–351·2) cases per 100 000 adult population (appendix), which translates to 419 047 (95% CI 343 722–507 498) adult patients with ICU-treated sepsis per year in Brazil, of whom 233 409 (95% CI 191 453–282 676) die in hospital.

Discussion

In this first national study of patients with sepsis cared for in Brazilian ICUs, we found high incidence, prevalence, and mortality rates of sepsis, resulting in an estimate of more than 200 000 deaths in adult patients with ICU-treated sepsis per year in Brazil. Additionally, there was substantial variability in the availability of basic resources for sepsis treatment, and fewer available resources were associated with worse outcomes.

There is substantial variation in sepsis prevalence, even between high-income countries.[11,12] In low-income and middle-income countries, high rates of sepsis have been reported.[19,20] There are many potential reasons for the high prevalence in these countries. The low awareness of sepsis among health-care professionals could lead to late recognition and treatment. As a consequence, infected patients would be more prone to become septic and require ICU care. High rates of HAI due to low adherence to preventive measures[21] can also contribute as we have shown in our study in which most patients who developed sepsis had HAI. Shortage of ICU beds might lead to an increase in the severity of illness of patients admitted to the ICU but not necessarily to an increase in sepsis prevalence unless sepsis cases outside the ICU have more severe symptoms than patients with other diseases. Although we were unable to show a correlation between the availability of ICU beds and prevalence, this finding has already been shown in another study.[22] Another potential explanation for this high prevalence is the absence of intermediate-care units in most Brazilian hospitals,[2] which might have contributed to a longer ICU stay and consequently to a higher prevalence of sepsis. Step-down units could decrease the ICU length of stay since patients who no longer need full critical-care support can be discharged.[23] Additionally, the low quality of care in the wards would limit discharge polices as well as the provision of basic support and monitoring to mild to moderate severity patients. Another potential cause of this high prevalence is differences in end-of-life care. A high variability in end-of-life practices has already been reported between countries.[24] In Brazil, end-of-life decisions are infrequent and gaps in communication, scarcity of legal regulation, absence of advanced directives, and cultural and religious beliefs might result in unnecessary efforts to sustain life.[25]

Our estimated incidence-rate of ICU-treated sepsis in the population studied was similar to the reported incidence in a meta-analysis based only on data from high-income countries (270 cases per 100 000 person-years).[3] Incidence estimates from low-income and middle-income countries are important since data are scarce and extrapolating estimates of sepsis from high-income countries might underestimate the true incidence in low-income and middle-income countries. Some characteristics (eg, deficiencies in primary health care) of low-income and middle-income countries might lead to higher sepsis incidence. As already mentioned, an increased incidence of HAI[21] and antibiotic resistance[26] might contribute to an increase in complicated infections due to inadequate treatment. Conversely, other characteristics might contribute to a decreased incidence of sepsis, such as a decreased life expectancy. High-income countries also deliver better care to patients with cancer, trauma, or those who have received a transplant, which increases the population at high risk of sepsis.

There are few studies from low-income and middle-income countries with nationally representative mortality data on sepsis. Some series have reported very high mortality rates,[6,7] although in other settings a lower mortality was reported.[19] In a 2014 study from China,[20] the authors reported an overall hospital mortality of 33·5% in patients admitted to the ICU. However, their patients had a lower Acute Physiology and Chronic Health Evaluation (APACHE) II score and less septic shock than did the patients in our cohort. Since Zhou and colleagues[20] used a convenient sample of ICUs that had a research background, their results might have been biased towards ICUs with a better quality of care.

	OR (95% CI)	p value
SAPS 3	1·03 (1·02–1·04)	<0·0001
Resource availability*	..	..
High	1·00	..
Intermediate	1·20 (0·72–1·98)	0·484
Low	1·67 (1·02–2·75)	0·045
Health-care-associated infection	1·55 (1·13–2·12)	0·0069
Septic shock	1·71 (1·24–2·37)	0·0013
Compliance with bundles	..	..
Non-compliance with antibiotics	1·00	..
Compliance at least with antibiotics	0·63 (0·44–0·89)	0·0090
Compliance with 6-h bundle	0·56 (0·37–0·84)	0·0059

SAPS=simplified acute physiology score. ICU=intensive care unit. *In the resources availability assessment we assigned one point for availability of each of eight items relevant to the care of patients with sepsis and septic shock, and further classified ICUs as having low (six or items or fewer), intermediate (seven items), or high (all eight items) availability of resources. We included in the multivariate analysis resource availability, SAPS score, severity of illness, location at sepsis diagnosis, ICU bed availability, geographical region, hospital profile, and compliance with 6-h bundles at cluster level. Location at sepsis diagnosis and SOFA score were not included because of co-linearity. Age was not included because it is already considered in the SAPS 3 score.

Table 2: **Multivariate analysis of factor associated with mortality**

Quality of care can widely vary in Brazil[2] and our large stratified pseudo-random sample of ICUs was essential to select an unbiased group of both private and public institutions. We were able to show that there is no difference in the mortality of patients with sepsis between private and public ICUs. Sepsis is a severe disease and the quality of care required to improve patients' survival is high. Although most of the best Brazilian health-care institutions are in the private system, the quality of care and adherence to guidelines in Brazilian private institutions can be variable. Our pseudo-random sample might have selected both high-quality and low-quality private hospitals, which might better represent our private health system. This finding is in contrast with previous studies that have suggested high mortality rates in public Brazilian ICUs in a convenient sample of institutions,[8,27] which probably led to a selection bias. This result is also in contrast with the quality improvement results from the Latin America Sepsis Institution (LASI) network[28] in which only private institutions had a sustained decrease in sepsis mortality throughout the years. However, this finding probably reflects the capacity of these institutions to implement and sustain a quality improvement initiative rather than the natural history of sepsis in the ICU. It is possible that some private institutions have better chances in having success than some public ones. There are many potential explanations for this difference, such as differences in the patients' awareness and consequent delayed arrival at the emergency department, inadequate resources, shortage of beds, higher risk of adverse events, and shortage of the number of health-care professionals as well as the lower qualification and inadequate training of health-care professionals in public than in private institutions. The overcrowding of emergency departments and unfavourable nurse-to-bed ratios were already associated with lower compliance with sepsis bundles,[29] which might also compromise training. Additionally, staff turnover, which is common in both health-care settings in Brazil, can result in a loss of productivity, increased costs, and organisational inefficiency.

There are several potential explanations for our high mortality rates. Low resource availability was associated with higher risk of death. Even though previous studies have shown that there are insufficient critical care resources to treat sepsis in low-income and middle-income countries,[30] to our knowledge this is the first report clearly showing that the constraint of basic resources is an independent risk factor for unfavourable outcomes. Our assessment of resources included only low-cost interventions and none represent highly technological advances. By contrast with some low-income countries where antibiotics and other low-cost resources are almost never available, some Brazilian institutions frequently receive an intermittent supply, which could represent a low awareness of sepsis burden by policy makers, and funding agencies. Delayed sepsis recognition[27] and late transfer to the ICU[31] are common occurrences in Brazil. We have also shown that compliance with an antibiotic regimen was associated with survival, reinforcing previous evidence that suggests this is a key step in sepsis care.[32] We were also able to show a clear association between mortality and HAI. Compliance with antibiotics might be less relevant among patients with HAI than those with community-acquired infection, suggesting that other factors might also contribute to survival.

Our study had some strengths. The selection of a large pseudo-random stratified sample of ICUs, with a final distribution matching the distribution in each predefined stratum, allowed us to have a representative sampling of Brazilian ICUs. Our design is not only robust to make data representative in a national level but also is a model that can be used in future studies aiming to assess sepsis burden in a national level. The low rate of refusal to participate also improves our internal and external validity. We had a broad capture of all relevant data, including time to sepsis diagnosis, compliance with bundles, and severity scores. We also assessed the ICU bed availability and other quality indicators of the participating units. Finally, this study is one of the first of this scale to be done in a middle-income country intensive-care setting.

Our study also has some limitations. First, our assessment of incidence was not a direct estimate, but it was derived from our estimates of prevalence and duration of disease in the ICU. ICU discharge was used as a proxy for the end of sepsis. Besides that, incidental cases were reported according to the total number of patients but not according to the total number of admissions. Second, we generated the data from a single day, which has limitations, such as seasonal variability. Third, our stratification process was based on the Brazilian geographical regions and not on smaller units such as the microregions, which would have generated a better representative sample. However, the use of microregions as strata would have required a higher number of ICUs, which would have made the study unfeasible. Fourth, we analysed ICU access on the basis of the number of beds in a given state when the availability was different in each city. This strategy might have compromised our ability to assess the association between access to ICU and mortality. However, analysing access by use of data from each city would have resulted in an overestimation of the numbers of ICU beds since many cities serve as reference for the surrounding region. A proper assessment would have required knowing the catchment area of each unit, which is currently unfeasible. Fifth, we did not use a score to assess the resources availability that considered all potential variables associated with mortality but rather we based our assessment on core elements of the first 6 h of care as recommended in the Surviving Sepsis Campaign Guidelines. Sixth, we did not monitor the quality of data collection with onsite verification of

source documents, although we implemented central monitoring of data for completeness and consistency. We also did not measure other quality processes such as the use of protocol-driven care, checklists, or multidisciplinary rounds. Our assessment of time to sepsis diagnosis was not accurate since there was little availability of data before admission to hospital or to the ICU. Finally, we did not assess end-of-life care and this approach might have influenced the prevalence data.

In conclusion, we have shown in a representative sample of ICUs of an emerging country, that sepsis prevalence, population-based incidence of ICU-treated-sepsis, and in-hospital mortality were high. The low availability of resources was one of the major factors associated with higher hospital mortality. Our results show that sepsis represents a huge burden in resource-limited settings. National polices that aim to reduce this burden are urgently needed and should be based on preventive measures, including health-care associated infection prevention and quality improvement initiatives aiming to improve early recognition and adequate treatment of sepsis.

Contributors

FRM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. FRM assumes full responsibility for the integrity of the submission as a whole, from inception to the published article. FRM, ABC, FAB, EMF, FSAC, JLS, NC, RS, DCA, and LCPA contributed substantially to the study design. FRM, ABC, EMF, FSAC, JLS, NC, and LCPA collected data. FRM, ABC, FAB, DCA, and LCPA analysed and interpreted the data, and contributed to the writing of the manuscript. All authors read and approved this manuscript before submission.

Participant sites

Albert Sabin Hospital e Maternidade S R Zajac; *AMECOR—UTI I* M V Bley; *AMECOR—UTI II* M V Bley; *Casa de Saúde de Santos* A Scazufca, P Rosateli; *Casa de Saúde Maria Lucinda* T Reis; *Casa de Saúde Nossa Senhora do Carmo* A Nogueira Junior, P A Nunes Neto; *Casa de Saúde Santa Maria* I L S Filho; *Casa de Saúde Santa Rosa* H Lima; *Casa de Saúde São Sebastião* M Vieira, M Zanchet; *Casa de Saúde Stella Maris* I Ferreira; *CEGEN* R Miguita; *Centro de Referencia da Mulher* G M Petisco; *Centro Hospitalar Unimed* G A Westphal; *Centro Medico Hospitalar de Vila Velha* J R P Santos; *Clinica Campo Grande* V Damasceno, J T dos Santos; *Clinica Dom Rodrigo LTDA* F Fernandes; *Clinica Masterplastica Monte Sinai* Almeida E P; *Complexo de Saúde do Município de Guarabira* M Lemos; *Complexo Hospital Esperança* M F A Lima; *Complexo Hospitalar Padre Bento* R Camacho; *EMCOR* A Ribeiro; *Complexo Hospitalar São Bernardo do Campo* M O G Douglas, G A Mattei; *Hospital Abreu Sodré AACD* E A Junior; *Hospital Adventista de Manaus* P Ferreira; H R M P Rabelo; *Hospital Albert Sabin* S P S Pinto; *Hospital Alcides Carneiro* L E Fontes, D Machado; *Hospital Ana Nery* M Guitzel; *Hospital Hospital Bandeirantes* M Lucio, C N P Conceição; *Hospital Barão de Lucena* A Barros; *Hospital Barra D'Or* D Salgado; *Hospital Beneficência Portuguesa—UTI neurológica* V C Veiga, S S O Rojas; *Hospital Beneficência Portuguesa—UTI 3ª andar* V C Veiga, S S O Rojas; *Hospital Bruno Born* KM de Paula; *Hospital Totalcor* R Hatum; *Hospital Central Coronel Pedro Germano* L Fraenkel; *Hospital Copa D'Or—Cirúrgica Mista* W N Viana, A P G Santos; *Hospital Copa D'Or—Geral* L Rabello, L Tanaka; *Hospital da Divina Providencia* M Uchoa; *Hospital da Providencia de Apucarana* M D Moura, H Gneco; *Hospital da Restauração* M F Buarque, K Monteiro; *Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo—UTI Cirúrgica* A P Nassar Jr; *Hospital das Clinicas da Faculdade Medicina Universidade São Paulo—UTI Neuro* E Koterba, M J Teixeira; *Hospital das Clinicas da UNICAMP* A L E Falcão, V G S Pinto; *Hospital das Clinicas de Ananindeua* J M M Junior; *Hospital das Clinicas de Botucatu* A L Gut, L M Stefano; *Hospital das Clinicas de Niterói* M Damasceno, M V Lontra; *Hospital das Clinicas de Tangara da Serra* C Cozzani; *Hospital de Clinicas Gaspas Vianna* E B Sobrinho; *Hospital das Clinicas—Incor-FMUSP* S G Lage, L Kopel; *Hospital das Nações* N C M Youssef; *Hospital de Câncer de Barretos* L C Sanches, C P Amendola; *Hospital de Caridade Astrogildo de Azevedo—UTI Geral* C Kmohan, C B Silva; *Hospital de Caridade Astrogildo de Azevedo—UTI Neuro* L Schifelbain; *Hospital de Caridade São Braz* E Bellotto; *Hospital de Caridade São Vicente de Paulo* P Viecili; *Hospital de Clinicas da Faculdade Medicina da Universidade de São Paulo—Emergências Clínicas* L Azevedo, L Monteiro; *Hospital de Clinicas Integrada Bangu* S Vieira; *Hospital de Emergência Henrique Sergio Gregori* A M Abrão, A P Moraes; *Hospital de Fornecedores de Cana de Piracicaba* H Insaurrale; *Hospital de Messejana Dr Carlos Alberto S Gomes* M Gadelha; *Hospital de Urgência de Teresina* D Marisa; *Hospital do Coração Anis Rassi* R N Diniz; *Hospital do Coração de São Paulo* E R Romano; *Hospital do Servidor Publico de São Paulo* S Luzzi, E Rezende; *Hospital Dona Helena* M C Filho; *Hospital Pronto Socorro Dr Aristoteles Platão Bezerra de Araújo* R H F C Martins; *Hospital Eduardo de Menezes* F B Carvalho, G C Moreira; *Hospital e Maternidade de Assis* J Paula; *Hospital e Maternidade Flavio Ribeiro Coutinho* F Fernandes; *Hospital e Maternidade Santa Maria Cruz Azul* F Haag Jr; *Hospital e Maternidade Santo Antônio* FS Lucena; *Hospital e Maternidade Vital Brasil* R S Machado; *Hospital e Pronto Socorro 28 de Agosto* W O Filho, L O Cavalcante; *Hospital Municipal Gentil Filho* H Carvalho Filho, G S Lima; *Hospital de Pronto Socorro de Porto Alegre* J N Trombka; *Hospital Escola da Universidade Federal de Pelotas* E C Machado, M P Bainy; *Hospital Municipal Rocha Faria* C H Ramos; *Hospital Estrela* C Hoppe, G D Luckmeyer; *Hospital Eufrasia Teixeira Leite* C Vogas; *Hospital Evangélico de Cachoeiro de Itapemirim—UTI Geral* M M Thompson; *Hospital Evangélico de Londrina* R K Sousa; *Hospital Femina SA* R Fernandes; *Hospital Geral de Itaquaquecetuba* E Lourenço, G L Peixoto; *Hospital Geral de Pedreira* A Mocelin; *Hospital Geral de Vitoria da Conquista* M M L Silva, J S A Neto; *Hospital Geral do Ingá Instituto de Urologia e Nefrologia* C Villela, S L Mendonça; *Hospital Geral Teixeira da Costa* S C Prado; *Hospital Geral Vila Nova Cachoeirinha* R Goulart; *Hospital Getúlio Vargas* J J L Duarte; *Hospital Helio Anjos Ortiz* H A O Junior; *Hospital IBR* J N Andrade, L F Souza; *Hospital IGESP* L Fernandes; *Hospital Ipiranga Mogi das Cruzes* M L Neto; *Hospital Ipiranga (Gestão Assistencial II)* S S Fernandes; *Hospital João XXIII* F Amâncio; *Hospital Madre Teresa* J C Versiani; *Hospital Maicé* F Pitanga, M B Alcantara; *Hospital Maria José Baeta Reis Ascomcer* C C Reiff; *Hospital Maternidade Interlagos* R Rosenblat; *Hospital Materno Infantil* M S Nobrega, M L F S Nobrega; *Hospital Memorial São José* G Costa; *Hospital Metropolitano de Urgência e Emergência* N Assunção; *Hospital Monte Sinai* E P Almeida; *Hospital Municipal Carlos Tortelly* L Neder; *Hospital Municipal de Foz do Iguaçu* R Almeida, J Fuck; *Hospital Municipal de Paracatu* R M Souza, A G Ribeiro; *Hospital Municipal Djalma Marques* A A G Alves, S H C Carvalho; *Hospital Municipal Dr Munnir Rafful* M Arbex; *Hospital Municipal Lourenço Jorge* E C Oliveira; *Hospital Municipal Odilon Behrens* F B Carvalho, R S Melo; *Hospital Municipal Pirituba Jose Soares Hungria* K Conde, N Q Abreu; *Hospital Municipal Santa Isabel* C L T Melo, A A Carvalho; *Hospital Municipal São José* M C Filho; *Hospital Municipal Souza Aguiar* R Lannes, H Missaka; *Hospital Municipal Walter Cantídio UFC* A H Furtado Jr, A A Peixoto Jr; *Hospital Nereu Ramos* I Maia, M P Pincelli; *Hospital Nossa Senhora Auxiliadora* R Camacho; *Hospital Nossa Senhora da Abadia* M P Yunes; *Hospital Nossa Senhora das Merces* A N Pessoa; *Hospital Nossa Senhora de Fatima* S Figueiredo; *Hospital Nossa Senhora de Lourdes* F A Botoni, C T Cunha; *Hospital Nossa Senhora dos Navegantes* F A Olson; *Hospital Novo Atibaia* R Franco, A F Bemfica; *Hospital Ortopédico de Goiânia Geraldo Pedra* M S Nobrega, A D F Junior; *Hospital Paulo Sacramento* E L A Ferreira; *Hospital Português* O Messeder, R Passos; *Hospital Primavera* J A Lira; *Hospital Proncor* C A Vilela; *Hospital Regional da Asa Norte* S M D Junior, C S Ferreira; *Regional Hospital Nossa Senhora Aparecida* P J A Muller; *Hospital Regional de Franca* R Perreira dos Santos; *Hospital Regional de Mato Grosso do Sul* P Rubini; *Hospital Regional de Tucuruí* D Monteiro; *Hospital Regional do Litoral* L E Rodrigues; *Hospital Regional do Vale do Paraíba* G F Ruivo, M C Gomes; *Hospital Regional Dr Vivaldo Simões* E Egito; *Hospital Regional Hans Dieter Schmidt* M G Assef; *Hospital Regional João Penido—Rede Fundação Hospitalar do Estado de Minas Gerais (FHEMIG)*

M A M Lima, A F Borges; *Hospital Regional Unimed Ceará* M Gadelha; *Hospital Salvador* S Jezler; *Hospital Samaritano PB* C Mendes, P C Gottardo; *Hospital Samaritano RJ* R Lima, C M F Filho; *Hospital Samaritano SP* V P Campagnucci; *Hospital Dr José Pedro Bezerra* I Solino; *Hospital Santa Cruz—UTI I* A P Lorca; *Hospital Santa Cruz—UTI II* A P Lorca; *Hospital Santa Helena* G M Rodrigues; *Hospital Santa Isabel* K B Gerent; *Hospital Santa Joana Recife* O Barbosa, G T Henriques Filho; *Hospital Santa Juliana* E Troncoso; *Hospital Santa Lucia de Divinópolis* A Ventura, M A Silva; *Hospital Santa Paula* J G Houly; *Hospital São Bernardo SA* J P M Pimentel, R A Ramos; *Hospital São Camilo Ipiranga* F Gianini; *Hospital São Francisco* B Casemiro; *Hospital São Francisco de Americana* E M Pinto; *Hospital São Francisco de Assis* G A Silva, M Sebold; *Hospital São Jorge*—E Vieira; *Hospital São José (Sociedade São Vicente de Paula)* R Ferreira, L A Gomes; *Hospital São Lucas* W J Lovato, *CMP Liberal; Hospital São Marcos—UTI I* W Dantas, L Ishy; *Hospital São Marcos—UTI II* W Dantas, L Ishy; *Hospital São Mateus* J Moreira; *Hospital São Paulo PR* I Gagliardi; *Hospital São Paulo* L O Goes; *Hospital São Paulo de Ensino da UNIFESP—UTI Clinica* L S Vendrame, H P Guimarães; *Hospital São Paulo de Ensino da UNIFESP—UTI PS* A Gois; *Hospital São Paulo de Ensino da UNIFESP—UTI Anestesiologia* F R Machado; *Hospital São Paulo de Ensino da UNIFESP—UTI Pneumologia* M Rodrigues Jr, P C B Vieira; *Hospital São Sebastião* W Bittencourt; *Hospital Sapiranga* E Melnick, M Schneider; *Hospital Saúde da Mulher* L Rezegue, N J M Nogueira; *Hospital Sírio Libanês* L Azevedo; *Hospital SOCIMED* E P Godinho; *Hospital Stela Maris* B F Mazza; *Hospital Unimed de Limeira* L E Paciencia; *Hospital Unimed de Sorocaba* S Ferraz, C R A Imamura; *Hospital Unimed Macaé* J Tavares; *Hospital Unimed Rio* J C Santos; *Hospital Unimed Natal* E Vale; *Hospital Universitário Antônio Pedro* J Mugait Filho; *Hospital Universitário Cajuru* L A Tannous, P G D João; *Hospital Universitário Clementino Fraga Filho* C T I Geral, D Salgado, A P Matera; *Hospital Universitário da Universidade Federal da Grande Dourados* M Matsui, E Eberhart Neto; *Hospital Universitário da Universidade Federal de Juiz de Fora* B V Pinheiro, E V Carvalho; *Hospital Universitário Getúlio Vargas* H Matos, M Lippi; *Associação Beneficente Hospital Universitário* A L Campos, D C Albuquerque; *Hospital Universitário João de Barros Barreto* D Monteiro; *Hospital Universitário Júlio Muller* D Castiglioni, G S Silva; *Hospital Universitário Maria Aparecida Pedrossian* S F Pinto; *Hospital Universitário Pedro Ernesto* S Cunha, E Novello; *Hospital Universitário Professor Alberto Antunes* M E B Silva; *Hospital Universitário Regional do Norte do Paraná—UTI I* C Grion, J Festti; *Hospital Universitário Regional do Norte do Paraná—UTI II* C Grion, J Festti; *Hospital Universitário Santa Terezinha* C R A Souza; *Hospital Universitário São Francisco na Providência de Deus* G C Mecatti, E B Junqueira; *Hospital Universitário Ciências Médicas* R S Dutra, G B Mirachi; *Hospital Vera Cruz* D A Mendes, E M F Moura; *Hospital Santa Mônica* I F Silva, M G P Mota; *Instituto de Doenças Tropicais Natan Portella* T Carneiro; *Instituto de Medicina Nuclear e Endocrinologia—UTI I* A Celso; *Instituto de Neurologia de Curitiba* A Réa-Neto, M C Oliveira; *Instituto Nacional de Infectologia—Fundação Oswaldo Cruz* A Japiassú, P P Castro; *Instituto do Câncer do Ceará* H J M Costa; *Instituto Dr Jose Frota Central* A V Rolim, D Rocha; *Instituto Nacional de Câncer Inca I—UTI I* C Righy; *Instituto Nacional de Câncer Inca I—UTI II* C Righy; *Instituto Nacional de Câncer II* R Espinoza; *Intensicare* V Santos; *Medimig* B Fernandino, A L Pereira; *Natal Hospital Center* V L D Rego; *Samur* M M L Silva, L A Melo; *Santa Casa de Araraquara* M Amaral; *Santa Casa de Lorena* L Guilherme; *Santa Casa de Maceió* H Chagas Ferro, F J L Silva; *Santa Casa de Misericórdia de Marilia* H V C J Carrasco, S El-Fakouri; *Santa Casa de Misericórdia Sant'ana do Livramento* J Alvarez, D de Castro; *Santa Casa de Misericórdia* P M Shiavetto; *Santa Casa de Misericórdia de Guaxupé* S R Gallate; *Santa Casa de Misericórdia de São José do Rio Preto* E Thomé Filho*, S G Veneziano; *Santa Casa de Monte Alto—Campos* W O Filho; *Santa Casa de Ribeirão Preto* P Antoniazzi; *Santa Casa de Santa Cruz do Rio Pardo* W H Filho; *Santa Casa de Sertãozinho* P Sadala, C Balbino; *Santa Casa de Vitoria da Conquista* G Moreno, M S F Dias; *São Bernardo Apart Hospital* R P Lopez, M L Rodrigues; *União de Clinicas do Ceará* J Terceiro, M F Serpa; *Unidade de Emergência Dr Daniel Hoully* L Santos; *Hospital Unimed Manaus* W O Filho, M M Lippi.
*This author died since completion of the study.

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We declare no competing interests.

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