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Primary bacteremia is associated with a higher mortality risk in patients with sepsis: a prospective observational cohort study

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ABSTRACT

Objective: to investigate whether common infection foci (pulmonary, intra-abdominal and primary bacteremia) are associated with variations in the mortality risk in sepsis patients.

Design: Prospective, observational, blinded cohort study.

Setting: Three intensive care units (ICU) of a university medical center Methods

Participants: 327 adult Caucasian patients with sepsis of pulmonary, intra-abdominal and primary bacteremia origins participated in this study.

primary and secondary outcome measures: The patients were followed up for 90 days, and mortality was recorded as the primary outcome variable. Sepsis-related organ failure assessment (SOFA) scores were evaluated at the onset of sepsis and throughout the observational period as secondary outcome variables to monitor organ failure.

Results: A total of 327 critically ill patients with sepsis were enrolled in this study. The 90-day mortality risk was significantly higher among patients with primary bacteremia than among those with pulmonary and intra-abdominal foci (p=0.0208). To exclude the effects of several baseline variables, we performed a multivariate Cox regression analysis. Primary bacteremia remained a significant co-variate for mortality in the multivariate analysis (hazard ratio, 2.20 [95% CI, 1.2-4.0]; p=0.0098). During their stay in the ICU, the patients with primary bacteremia presented significantly higher SOFA scores than those of the patients with other infection foci (p=0.0002). An analysis of organ-specific SOFA sub-scores revealed a significantly higher SOFA-renal score among the patients with primary bacteremia compared with other infection foci (p=0.0028); the primary bacteremia patients required significantly more renal replacement therapy (p<0.0001).

Conclusions: These results indicate that sepsis patients with primary bacteremia present a higher mortality risk compared with that of sepsis patients of pulmonary or intra-abdominal origins. These results should be assessed in sepsis patients from larger, independent cohorts.

Strengths and limitations of this study

- This is the first study to evaluate mortality risk among sepsis patients with primary bloodstream infections compared with those with respiratory or intra-abdominal infections over an observational period of 90 days.
- The strengths of our study include that it is the first to investigate organ-specific manifestations associated with common sepsis infection sites (respiratory, intra-abdominal and bloodstream) by quantifying SOFA scores and evaluating the requirements for organ support in the ICU.
- The limitation of this study is the relative small number of patients.

NTRODUCTION

Sepsis is defined as a systemic inflammatory response that occurs during severe infection[1-3]. Sepsis affects more than 750,000 patients in the United States each year and remains one of the leading causes of death worldwide[4]. Respiratory, intra-abdominal, urinary and primary bloodstream infections make up 80% of all infection sites[5]. According to epidemiological data, the lung is the most common site of infection, followed by the abdomen and the blood[2].

Pneumonia, hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP) and subsequent sepsis remain important causes of morbidity and mortality in critically ill patients despite advances in antimicrobial therapy, better supportive care modalities, and a wide range of preventive measures[6-8]. Hospital-acquired pneumonia (HAP) is the most frequent infection in surgical intensive care units (ICUs) and is defined as a pulmonary infection that was not incubating at the time of admission and occurred at least 48 h after hospital admission. Ventilator-associated pneumonia (VAP) is defined as either a pulmonary infection arising more than 48 h after tracheal intubation with no evidence of pneumonia at the time of intubation or the diagnosis of a new pulmonary infection if the initial ICU admission was due to pneumonia[9].

Intra-abdominal infections are a common cause of sepsis. They comprise a markedly heterogeneous group of infectious processes that share an anatomical site of origin between the diaphragm and the pelvis[10]. Their clinical course is dictated by a number of infection-related factors, including the microbiology of the infection, the anatomical location, the degree of localization, and the presence of correctable anatomical derangements involving intra-abdominal viscera. Intra-abdominal infections may progress to sepsis[11 12]. Typically, patients with intra-abdominal infections in the surgical ICU develop secondary peritonitis as a

result of the microbial infection of the peritoneal space following perforation, abscess formation, ischemic necrosis, or a penetrating injury of the intra-abdominal contents[10].

Bloodstream infections (BSIs) are one of the leading causes of death due to nosocomial events in the ICU. Immune depression and invasive health care procedures act together to create a high risk of nosocomial BSIs in critically ill patients[13]. The outcomes of BSIs have been the focus of many case-control and cohort studies[13-15]. BSIs lead to poor patient outcomes[14 16], prolonged patient stays in ICU and in the hospital[14 17 18], and substantial extra costs for the medical system[19 20].

Whether the characteristics of the infection, infection site and pathogenic organism independently affect the outcome in patients with sepsis remains debated. Whereas previous studies have shown an independent significant contribution of the infection site and the pathogenic organism to the survival of sepsis patients[21], recent observations were unable to detect any significant impact of the infection site on mortality among patients with sepsis[22].

This study aimed to explore whether common sepsis infection sites: respiratory, intra-abdominal and bloodstream infections are associated with changes in the survival rate (90-day) among patients with sepsis in a representative university medical center, where patients are treated according to the most recent sepsis guidelines.

MATERIALS AND METHODS

Patients

Adult Caucasian patients admitted to the University Medical Center Goettingen (UMG) ICUs between April 2012 and May 2013 were screened daily according to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) criteria for sepsis, severe sepsis, or septic shock[23 24]. Patients were enrolled if they presented sepsis of a respiratory, intra-abdominal or primary bloodstream origin. Caucasian origin was assessed by questioning the patients, their next of kin or their legal representatives. The patient exclusion criteria were described previously[25 26]. The study was approved by the University of Goettingen ethics committee, Goettingen, Germany (15/1/12) and conformed to the Declaration of Helsinki ethical principles (Seoul, 2008). For each patient, written informed consent was obtained from either the patient or his/her legal representative.

Data collection

Patients were followed up for 90 days, and mortality risk was recorded as the primary outcome variable. Sequential Organ Failure Assessment (SOFA)[27] and Acute Physiology and Chronic Health Evaluation (APACHE) II[28] scores were evaluated at the onset of sepsis. Organ function was reassessed over the 28 days on the ICU monitor morbidity as previously described[25]. Organ failure, organ support requirement and length of ICU-stay were recorded as secondary outcome variables.

Statistical analyses

Statistical analyses were performed using the Statistica (StatSoft, Tulsa, Oklahoma, USA, version 10) software program. Based on contingency tables, significance was calculated using two-sided Fisher's exact or chi-square tests, as appropriate. Two continuous variables were compared using the Mann-Whitney test. Time-to-event data were compared using the log-rank test from the Statistica package survival analysis. For variables identified as significant in the univariate survival analysis (respiratory, intra-abdominal and primary bacteremia infections), potential confounders (age, gender and BMI) and covariates that varied at baseline (diabetes mellitus (IDDM) and history of cancer), we performed multivariate cox regression models against survival. A p-value less than 0.05 was considered significant.

RESULTS

Study population

A total of 327 adult Caucasian patients with sepsis were enrolled in this study. At enrollment, 61% of the patients had a pulmonary infection; 32% uffered from an intra-abdominal infection; and 7% presented a primary bloodstream infection (Table 1). The age of the patients ranged from 19 to 91 years (median, 65 years). At baseline, the patient disease severity SOFA and APACHE II scores were 9.3±4.0 and 21.5±7.3, respectively (Table 1). Comorbidities included hypertension, myocardial infarction history, chronic obstructive pulmonary disease (COPD), renal dysfunction, non-insulin-dependent diabetes mellitus, insulin-dependent diabetes mellitus, chronic liver diseases, history of cancer, and history of stroke (Table 1).

Table 1. Patient baseline characteristics with regard to the infection site

	All n=327	Pulmonary n=198	Intra-abdominal n=105	Bloodstream n=24	p-value
Age, mean ± SD	62±15	61±15	65±13	60±16	0.2426
Male, %	67%	70	61	62	0.2614
Body-mass index, mean ± SD	27±6	27±7	27±5	29±5	0.0885
SOFA score, mean ± SD	9.3±4.0	9.4±3.6	8.9±4.7	10.5±5.1	0.3099
APACHE II score, mean ± SD	21.5±7.3	21.8±6.8	20.6±8.1	22.8±7.6	0.3538
Organ support, %					
Mechanical ventilation	85	90	74	87	0.0008
Use of vasopressor	64	62	65	70	0.6778
Renal-replacement therapy	8	7	9	20	0.0781
Comorbidities, %					
Hypertension	57	55	59	66	0.5395
History of myocardial infarction	8	9	7	8	0.9087
COPD	17	17	17	16	0.9880
Renal dysfunction	11	10	9	25	0.0857
Diabetes mellitus (NIDDM)	9	10	8	8	0.8928
Diabetes mellitus (IDDM)	11	8	11	33	0.0015)
Chronic liver diseases	5	3	8	8	0.1538
History of cancer	18	15	30	0	0.0003
History of stroke	6	8	4	0	0.2192

The data are presented as the mean±SD or percentages.

Disease severity at the onset of sepsis

There were no differences regarding age, gender, or body mass index among the three groups. Moreover, no differences were found in the SOFA and APACHE II scores with regard to the infection sites at the onset of sepsis. The patients in the intra-abdominal infections group required significantly less mechanical ventilation compared with the other groups (p=0.0008). The patients in the bloodstream infection group suffered significantly more from insulin-dependent diabetes mellitus (p=0.0015) compared with the other groups, whereas the patients in the bloodstream infection group were significantly less likely to report a history of cancer (p=0.0003) (Table 1).

Mortality analysis

According to Kaplan-Meier survival analysis, the mortality risk increased during the 90-day observation period among bloodstream infection patients (p=0.0208). Analysis of the 28-day mortality revealed that the patients in the bloodstream infection group were at a significantly increased risk of death compared with that of the other groups (p=0.0012) (Table 2). Furthermore, 90-day mortality analysis indicated a higher incidence of death among the patients in the bloodstream infection group, although this finding was not significant (p=0.0544).

Table 2. Disease progression with regard to infection site

	All n=327	Pulmonary n=198	Intra-abdominal n=105	Bloodstream n=24	p-value
SOFA	6.9±3.6	7.3±3.4	5.8±3.5	8.5±4.7	0.0002
SOFA-Subscores					
SOFA-Respiratory	1.9±0.7	2.2±0.6	1.5±0.7	1.9±0.9	<0.0001
SOFA-Cardiovascular	1.5±0.9	1.5±0.9	1.3±0.9	1.7±1.2	0.4567
SOFA-Central nervous system	1.8±1.1	2.1±1.0	1.4±1.0	2.0±1.2	<0.0001
SOFA-Renal	0.8±1.1	0.8±1.1	0.7±1.0	1.6±1.4	0.0028
SOFA-Coagulation	0.3±0.5	0.3±0.6	0.2±0.5	0.6±0.8	0.4662
SOFA-Hepatic	0.4±0.7	0.3±0.6	0.5±0.8	0.5±0.6	0.0030
Organ support*, %					
Mechanical ventilation		85	62	76	<0.0001
Use of vasopressor		54	45	49	0.8355
Renal replacement therapy		11	12	29	0.0069
Length of stay in ICU (days)	18±15	17±14	20±16	16±13	0.5061
Mortality analysis, %:					
Death by day 28	94 (28)	64 (32)	18 (17)	12 (50)	0.0012
Death by day 90	118 (36)	70 (35)	34 (32)	14 (58)	0.0544

The data are presented as the mean±SD or percentages.
*Based on the total number of observations during the follow-up period.

Multivariate analysis

To exclude the effects of various baseline variables on survival among the three investigated groups, we performed a multivariate Cox regression analysis. Bacteremia remained a

significant co-variate for mortality in the multivariate analysis (hazard ratio, 2.20 [95% CI, 1.2-4.0]; p=0.0098) (Table 3).

Table 3. Cox regression analysis

Infection site	Variable	Hazard ratio	95% CI	p-value
Pulmonary:				
	Age	1.02	1.00-1.03	0.0011
	Gender	0.84	0.57-1.25	0.4003
	BMI	1.00	0.98-1.03	0.5038
	Diabetes mellitus (IDDM)	1.28	0.75-2.17	0.3548
	History of cancer	1.24	0.80-1.92	0.3227
	Pulmonary infection	1.11	0.76-1.62	0.5554
Intra-abdominal:				
	Age	1.02	1.00-1.03	0.0008
	Gender	0.85	0.58-1.27	0.4511
	BMI	1.00	0.98-1.03	0.5020
	Diabetes mellitus (IDDM)	1.26	0.75-2.13	0.3737
	History of cancer	1.32	0.85-2.05	0.2090
	Intra-abdominal infection	0.67	0.45-1.01	0.0589
Bloodstream:				
	Age	1.02	1.00-1.03	0.0008
	Gender	0.84	0.57-1.25	0.4018
	BMI	1.00	0.97-1.03	0.6464
	Diabetes mellitus (IDDM)	1.06	0.61-1.85	0.8173
	History of cancer	1.34	0.86-2.09	0.1910
	Bloodstream infection	2.20	1.21-4.02	0.0098

Disease severity

During the observational period, the bloodstream infection patients presented significantly higher SOFA scores compared with those of patients in the other groups (p=0.0002) (Table 2). Four of the six organ-specific SOFA scores varied significantly among the study groups (respiratory, central nervous system (CNS), renal and hepatic). The patients in the pulmonary infection group presented higher SOFA-respiratory scores compared with those of the other groups (p<0.0001), and together with the patients in the bloodstream infection group, required more mechanical ventilation (p<0.0001). The patients in the pulmonary and bloodstream groups presented higher SOFA-CNS scores compared with those of patients in the intra-abdominal infection group (p<0.0001). Analysis of the SOFA-renal scores indicated that the patients in the bloodstream infection group presented higher SOFA-renal scores over the

study period in the ICU (p=0.0028). They also required significantly more renal replacement therapy (p<0.0069). The SOFA-hepatic score was significantly higher in the intra-abdominal and infection groups compared with the pulmonary infection group (p=0.0030).

Additionally, the gram-negative infection rate was significantly higher in the patients from the pulmonary infection group (75%) compared with those whose sepsis had intra-abdominal and bloodstream infection origins (57% and 54%, respectively; p=0.0026) (Table 4).

Table 4. Infection types over the observational period

Infection site	Respiratory	Abdominal	Bloodstream	p-value
Infection type				
Gram-negative	75%	57%	54%	0.0026
Gram-positive	78%	84%	79%	0.5142
Fungal	52%	76%	42%	<0.0001
Virus	0.08%	0.06%	0.13%	0.4941

Furthermore, septic patients with intra-abdominal infections presented a higher incidence of fungal infections (76%) compared with those of patients in the pulmonary and bloodstream infection groups (52% and 42%, respectively; p<0.0001) (Table 4).

DISCUSSION

The present study addressed whether common infection sites among patients with sepsis are associated with the survival rate.

The primary endpoint, the mortality risk within 90 days of the onset of sepsis, was significantly higher in patients with primary bloodstream infections compared with those with respiratory or intra-abdominal infections (Fig. 1). Primary bacteremia remained a significant co-variate for mortality in the multivariate analysis (Table 3).

According to the SOFA and APACHE II scores, infection site was not associated with the acute-illness severity at the onset of sepsis (Table 1). We believe that the similarity in SOFA and APACHE II scores at sepsis onset among the three groups can be attributed to the phenotypic heterogeneity of sepsis. This heterogeneity is influenced by many factors, including the pathogenic organism responsible for the infection and the amount of time elapsed since the onset of infection, as well as other individual parameters, such as co-morbidities and genetic makeup.

The significant result of this study with respect to mortality risk within 90 days was that the rate of mortality (58%) was higher among patients with primary bloodstream infections, and this result is in line with the results of several investigations showing similar mortality rates among patients with nosocomial bloodstream infections[13 29]. Moreover, our study supplements the work of previous investigations by evaluating a longer-term end point (90 days) because sepsis patients continue to be at an increased risk of mortality, even after ICU/hospital discharge[30].

The strengths of our study include that it is the first to investigate organ-specific manifestations associated with common sepsis infection sites (respiratory, intra-abdominal and bloodstream) by quantifying SOFA scores and evaluating the requirements for organ support in the ICU (Table 2). The more pronounced types of respiratory failure, which are quantified by the SOFA-respiratory score and the need for mechanical ventilation (Table 2),

among patients with pulmonary infections is plausible because these patients frequently present comprised pulmonary function. Patients with primary bacteremia are also at a high risk of respiratory failure due to systemic inflammatory response syndrome, release of pro-inflammatory cytokines (such as tumor necrosis factor (TNF), IL-1 and IL-6,[31]) and recruitment of neutrophils to the lungs, which induces the release of toxic mediators, such as reactive oxygen species and proteases, thus contributing to lung damage and respiratory failure[32].

The observed severe morbidity, quantified by the SOFA mean score in patients with primary bloodstream infections, resulted in an increased 28-day mortality rate.

We believe that the significant difference in the SOFA-CNS score between the genotypes (with higher scores in the respiratory and the bloodstream groups) occurred because patients in these groups required much more mechanical ventilation, causing them to be treated more frequently with sedating medication, which impacts the CNS and thus affects the SOFA-CNS score.

The observed distinct renal failure among bloodstream infection patients indicated by the SOFA-renal score, which was accompanied by frequent renal replacement therapy (Table 2), was in accordance with former observations indicating that bloodstream infections are associated with a higher incidence of renal failure[33]. The frequent utilization of renal replacement therapy suggests persistent organ dysfunction, which is a well-known contributor to sepsis-related mortality and may explain the higher mortality among bloodstream infection patients observed in our study (Table 2, Fig. 1)[34].

The SOFA-hepatic score was higher among patients with intra-abdominal and primary bloodstream infections compared with patients with pulmonary infections (Table 2). This result can be attributed to the fact that kupffer cells release several cytokines able to induce hepatocellular dysfunction in response to endotoxemia in patients with bloodstream infections[35]. Patients with intra-abdominal infections are also predisposed to develop

hepatic imbalances because they are at increased risk of developing secondary bloodstream infections.

To the best of our knowledge, this is the first investigation to evaluate 90-day survival in common sepsis infection sites (respiratory, intra-abdominal and primary bloodstream). This study revealed a significantly higher mortality rate among patients with primary bloodstream infections (58%) compared with patients with respiratory and intra-abdominal infections, although all patients were treated according to current guidelines for the treatment of sepsis (Surviving Sepsis Campaign)[36]. Because of this dramatically higher mortality rate among patients with primary bloodstream sepsis, we believe that future sepsis trials should focus on this vulnerable group of high-risk patients. Clearly, more appropriate interventions and further improvements in prevention and care are urgently needed.

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Contributors All authors have contributed to study design, data acquisition (clinical and experimental), or the analysis and interpretation of data. Specifically, YK performed clinical data collection and participated in the statistical analysis and interpretation of the data. AP, JE, MG and MB participated in study design, supervised patient enrollment and clinical data monitoring and interpreted data. TB contributed to study design and conception and performed and approved the statistical analyses. AM and JH designed the study, supervised the sample and data collection, performed analyses, interpreted data and drafted the manuscript. All authors were involved either in manuscript drafting or revision. All authors have approved the final version of the manuscript.

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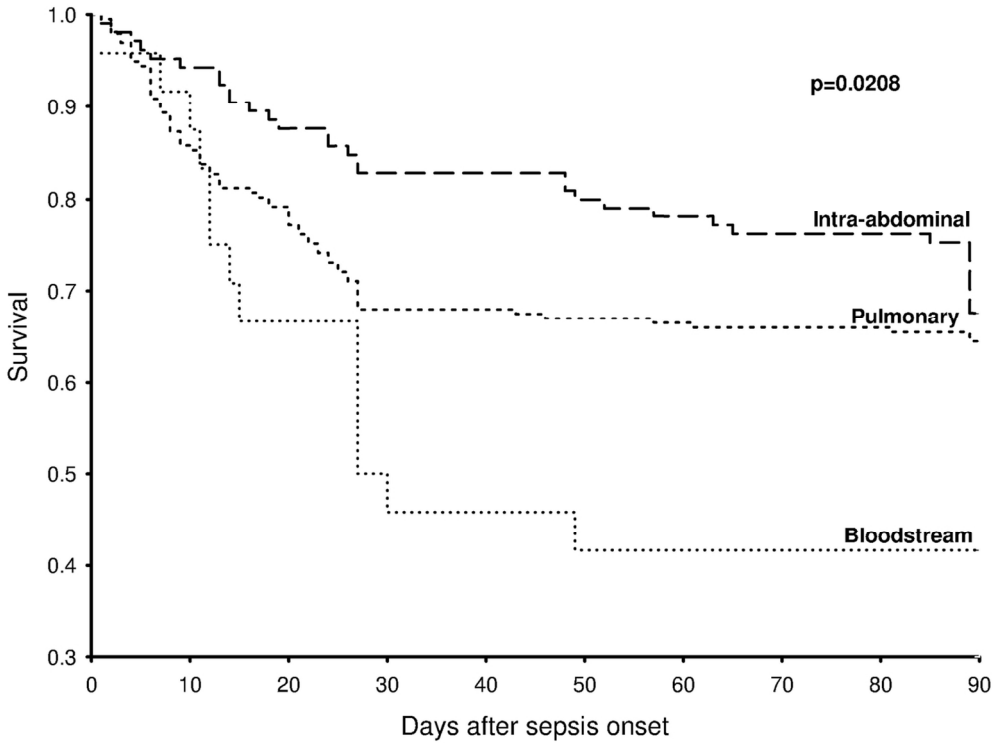

Figure 1. Kaplan-Meier survival analysis

The Kaplan-Meier curve shows the survival curves until day 90 for the three infection site groups. The mortality risk among the patients under study was higher among the patients with bloodstream infections compared with those in the pulmonary and intra-abdominal infection groups (p=0.0208, log-rank test).

124x93mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(*b*) Report category boundaries when continuous variables were categorized	12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-17
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Primary bacteremia is associated with a higher mortality risk compared with pulmonary and intra-abdominal infections in patients with sepsis: a prospective observational cohort study

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Primary bacteremia is associated with a higher mortality risk compared with pulmonary and intra-abdominal infections in patients with sepsis: a prospective observational cohort study

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ABSTRACT

Objective: To investigate whether common infection foci (pulmonary, intra-abdominal and primary bacteremia) are associated with variations in mortality risk in sepsis patients.

Design: Prospective, observational cohort study.

Setting: Three surgical intensive care units (ICU) at a university medical center.

Participants: A total of 327 adult Caucasian patients with sepsis originating from pulmonary, intra-abdominal and primary bacteremia participated in this study.

Primary and secondary outcome measures: The patients were followed for 90 days, and mortality risk was recorded as the primary outcome variable. To monitor organ failure, sepsis-related organ failure assessment (SOFA) scores were evaluated at the onset of sepsis and throughout the observational period as secondary outcome variables.

Results: A total of 327 critically ill patients with sepsis were enrolled in this study. Kaplan-Meier survival analysis showed that the 90-day mortality risk was significantly higher among patients with primary bacteremia than among those with pulmonary and intra-abdominal foci (58%, 35% and 32%, respectively; p=0.0208). To exclude the effects of several baseline variables, we performed multivariate Cox regression analysis. Primary bacteremia remained a significant covariate for mortality in the multivariate analysis (hazard ratio, 2.10; 95% CI, 1.14-3.86; p=0.0166). During their stay in the ICU, the patients with primary bacteremia presented significantly higher SOFA scores than those of the patients with pulmonary and intra-abdominal infection foci (8.5±4.7, 7.3±3.4 and 5.8±3.5, respectively). Patients with primary bacteremia presented higher SOFA-renal score compared with the patients with other infection foci (1.6±1.4, 0.8±1.1 and 0.7±1.0, respectively); the primary bacteremia patients required significantly more renal replacement therapy than the patients in the other groups (29%, 11% and 12%, respectively).

Conclusions: These results indicate that sepsis patients with primary bacteremia present a higher mortality risk compared with patients with sepsis of pulmonary or intra-abdominal origins. These results should be assessed in sepsis patients in larger, independent cohorts.

Strengths and limitations of this study

- This is the first study to evaluate mortality risk among sepsis patients with primary bloodstream infections compared with those with respiratory or intra-abdominal infections over an observational period of 90 days.
- The strengths of our study include that it is the first to investigate organ-specific manifestations associated with common sepsis infection sites (respiratory, intra-abdominal and bloodstream) by quantifying SOFA scores and evaluating the requirements for organ support in the ICU.
- One potentially uncontrolled confounder that was not adjusted for is appropriate antibiotic therapy.

INTRODUCTION

Sepsis is defined as a systemic inflammatory response that occurs during severe infection[1-3]. Sepsis affects more than 750,000 patients in the United States each year and remains one of the leading causes of death worldwide[4]. Although the incidence of this major health care problem has been increasing, the implementation of early goal-directed therapy in patients with severe sepsis and septic shock has in part successfully reduced mortality[5]. Guidelines for disease control have been written by the Surviving Sepsis Campaign (SSC), a joint collaboration between the Society of Critical Care Medicine and the European Society of Intensive Care Medicine committed to reducing mortality from severe sepsis and septic shock worldwide[6]. These guidelines contain clear recommendations for improving disease outcomes (e.g., guidelines for resuscitation and recommendations pertaining to infections, including for the use of diagnostics, hemodynamic support and adjunctive therapy and for supportive therapy for severe sepsis)[6].

Respiratory, intra-abdominal, urinary and primary bloodstream infections make up 80% of all infection sites[7]. According to epidemiological data, the lung is the most common site of infection, followed by the abdomen and the blood[2].

Pneumonia, hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP) and subsequent sepsis remain important causes of morbidity and mortality in critically ill patients despite advances in antimicrobial therapy, better supportive care modalities, and a wide range of preventive measures[8-10].

Intra-abdominal infections are a common cause of sepsis. These infections comprise a markedly heterogeneous group of infectious processes that share an anatomical site of origin between the diaphragm and the pelvis[11]. Their clinical course is dictated by a number of infection-related factors, including the microbiology of the infection, the anatomical location,

the degree of localization, and the presence of correctable anatomical derangements involving intra-abdominal viscera[12 13].

Bloodstream infections (BSIs) are a major cause of death due to nosocomial events in intensive care units (ICUs)[14]. Immunosuppression and invasive health care procedures act together to create a high risk of nosocomial BSIs in critically ill patients[15]. The outcomes of BSIs have been the focus of many case-control and cohort studies[15-17]. BSIs lead to poor patient outcomes[16 18], prolonged patient stays in the ICU and in the hospital[16 19 20], and substantial extra medical costs[21 22].

Whether the characteristics of the infection, infection site and pathogenic organism independently affect the outcome in patients with sepsis remains a subject of debate. Whereas previous studies have shown an independent, significant contribution of the infection site and the pathogenic organism to the survival of sepsis patients[23], recent investigations have not found any significant impact of the infection site on mortality among patients with sepsis[24].

This study aimed to explore whether common origins of sepsis infections, in particular respiratory, intra-abdominal and bloodstream infection sites, are associated with changes in the 90-day survival rate among patients with sepsis in a representative university medical center, where patients are treated according to the most recent sepsis guidelines.

MATERIALS AND METHODS

Patients

Adult Caucasian patients admitted to ICUs at the University Medical Center-Goettingen (UMG) between April 2012 and May 2013 were screened daily according to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) criteria for sepsis, severe sepsis, or septic shock[25 26]. This study was approved by the University of Goettingen ethics committee in Goettingen, Germany (1/15/12) and conformed to the ethical principles of the Declaration of Helsinki (Seoul, 2008). For each patient, written, informed consent was obtained from either the patient or his or her legal representative. Patients were enrolled if they presented sepsis of a respiratory, intra-abdominal or primary bloodstream origin. Caucasian origin was assessed by questioning the patients, their next of kin or their legal representatives.

Definitions

In this study, patients with sepsis of respiratory origin had hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP). HAP is the most frequent infection in surgical intensive care units and is defined as a pulmonary infection that was not incubating at the time of admission and that occurred at least 48 h after hospital admission[27]. Ventilator-associated pneumonia (VAP) is defined as either a pulmonary infection arising more than 48 h after tracheal intubation with no evidence of pneumonia at the time of intubation or the diagnosis of a new pulmonary infection if the initial ICU admission was due to pneumonia[27].

Typically, patients with intra-abdominal infections in the surgical ICU develop secondary peritonitis as a result of microbial infection of the peritoneal space following perforation, abscess formation, ischemic necrosis, or a penetrating injury of the intra-abdominal contents[11].

Primary BSI comprises BSI of unknown origin in patients without an identifiable focus of infection and intravascular BSI (related to the presence of a catheter, implantable cardioverter-defibrillator or pacemaker)[11].

Exclusion criteria

As described previously[28 29], the patient exclusion criteria were the following: (1) age less than 18 years; (2) being pregnant or nursing an infant; (3) immunosuppressive therapy (e.g., cyclosporine or azathioprine) or cancer-related chemotherapy; (4) documented or suspected acute myocardial infarction within the previous 6 weeks; (5) a history of New York Heart Association functional class IV chronic heart failure; (6) human immunodeficiency virus infection; (7) a do not resuscitate or do not treat order or the patient and/or his or her legal representative not being committed to aggressive management; (8) not being expected to survive the 28-day observation period or not being likely to be placed on life support because of an uncorrectable medical condition, including a poorly controlled neoplasm or end-stage lung disease; (9) a chronic vegetative state or a similar long-term neurological condition; (10) current participation in any interventional study (of a drug or device); (11) inability to be fully evaluated during the study period; and (12) being a study-site employee or a family member of a study-site employee involved in conducting this study.

Data collection

Patients were followed up for 90 days, and mortality risk was recorded as the primary outcome variable. Sequential Organ Failure Assessment (SOFA)[30] and Acute Physiology and Chronic Health Evaluation (APACHE) II[31] scores were evaluated at the onset of sepsis. Organ function was reassessed over 28 days in the ICU to monitor morbidity as previously described[28]. Organ failure, organ support requirements and the length of ICU stay were recorded as secondary outcome variables. All relevant clinical data were extracted from the electronic patient record system (IntelliSpace Critical Care and Anesthesia (ICCA); Philips Healthcare, USA); all medical records, including microbiology reports, can be found in this system. We sought to determine whether patients suffered from preexisting conditions, for example, comorbidities, by examining physicians' notes, administering an anamnestic questionnaire to the patients or their legal representatives and consulting each patient's family doctor.

Statistical analyses

Statistical analyses were performed using Statistica software (version 10; StatSoft, Tulsa, Oklahoma, USA). Based on contingency tables, significance was calculated using two-sided Fisher's exact or chi-square tests, as appropriate. Two continuous variables were compared using the Mann-Whitney test. Time-to-event data were compared using the log-rank test from the Statistica package for Kaplan-Meier survival analysis. For variables identified as significant in univariate survival analyses (respiratory infections, intra-abdominal infections and primary bacteremia), potential confounders (age, gender and BMI) and covariates that varied at baseline (diabetes mellitus (IDDM), history of cancer and "No history of surgery"), we performed multivariate Cox regression analysis to examine survival times. A value of $p<0.05$ was considered statistically significant.

RESULTS

Study population

A total of 327 adult Caucasian patients with sepsis were enrolled in this study. At enrollment, 61% of the patients had a pulmonary infection; 32% suffered from an intra-abdominal infection; and 7% presented with a primary bloodstream infection (Table 1). Patients' ages ranged from 19 to 91 years (median, 65 years). At baseline, patients' SOFA and APACHE II scores, which measure disease severity, were 9.3±4.0 and 21.5±7.3, respectively (Table 1). Comorbidities included hypertension, myocardial infarction history, chronic obstructive pulmonary disease (COPD), renal dysfunction, non-insulin-dependent diabetes mellitus, insulin-dependent diabetes mellitus, chronic liver diseases, history of cancer, and a history of stroke (Table 1).

Table 1. Patient baseline characteristics with regard to the infection site

	All n=327	Pulmonary n=198	Intra-abdominal n=105	Bloodstream n=24	p-value
Age, mean ± SD	62±15	61±15	65±13	60±16	0.2426
Male, %	67%	70	61	62	0.2614
Body mass index, mean ± SD	27±6	27±7	27±5	29±5	0.0885
SOFA score, mean ± SD	9.3±4.0	9.4±3.6	8.9±4.7	10.5±5.1	0.3099
APACHE II score, mean ± SD	21.5±7.3	21.8±6.8	20.6±8.1	22.8±7.6	0.3538
Organ support, %					
Mechanical ventilation	85	90	74	87	0.0008
Use of vasopressor	64	62	65	70	0.6778
Renal replacement therapy	8	7	9	20	0.0781
Comorbidities, %					
Hypertension	57	55	59	66	0.5395
History of myocardial infarction	8	9	7	8	0.9087
COPD	17	17	17	16	0.9880
Renal dysfunction	11	10	9	25	0.0857
Diabetes mellitus (NIDDM)	9	10	8	8	0.8928
Diabetes mellitus (IDDM)	11	8	11	33	0.0015
Chronic liver diseases	5	3	8	8	0.1538
History of cancer	18	15	30	0	0.0003
History of stroke	6	8	4	0	0.2192
Recent surgical history, %					
Elective surgery	30	27	37	25	0.1730
Emergency surgery	48	45	56	42	0.1401

No history of surgery	21	28	7	33	<0.0001

The data are presented as the means±SDs or percentages.

Disease severity at the onset of sepsis

No differences in age, gender, or body mass index were found among the three groups of study subjects. Moreover, no differences were found in the SOFA and APACHE II scores with respect to the infection sites at the onset of sepsis. The patients in the group with intra-abdominal infections required significantly less mechanical ventilation compared with the other groups with pulmonary and bloodstream infections (74%, 90% and 87%, respectively). The patients with bloodstream infections suffered significantly more from insulin-dependent diabetes mellitus compared with patients with pulmonary or intra-abdominal infections (33%, 8%, 11%, respectively). In contrast, none of the patients with bloodstream infections had a history of cancer, unlike the patients with pulmonary and intra-abdominal infections (15% and 30%, respectively; Table 1).

Mortality analysis

Kaplan-Meier survival analysis showed that the 90-day mortality risk was significantly higher among patients with primary bacteremia than among those with pulmonary and intra-abdominal foci (58%, 35% and 32%, respectively; Figure 1). Analysis of the 28-day mortality data similarly revealed that the patients with bloodstream infections had a significantly increased risk of death compared with the patients with pulmonary and intra-abdominal infections (50%, 32% and 17%, respectively; Table 2). Moreover, 90-day mortality analysis suggested a higher incidence of death among the patients with bloodstream infections, although this finding was not significant (p=0.0544; Table 2).

Table 2. Disease severity with regard to infection site

	All n=327	Pulmonary n=198	Intra-abdominal n=105	Bloodstream n=24	p-value
SOFA	6.9±3.6	7.3±3.4	5.8±3.5	8.5±4.7	0.0002
SOFA Subscores					
SOFA-Respiratory	1.9±0.7	2.2±0.6	1.5±0.7	1.9±0.9	<0.0001
SOFA-Cardiovascular	1.5±0.9	1.5±0.9	1.3±0.9	1.7±1.2	0.4567
SOFA-Central nervous system	1.8±1.1	2.1±1.0	1.4±1.0	2.0±1.2	<0.0001
SOFA-Renal	0.8±1.1	0.8±1.1	0.7±1.0	1.6±1.4	0.0028
SOFA-Coagulation	0.3±0.5	0.3±0.6	0.2±0.5	0.6±0.8	0.4662
SOFA-Hepatic	0.4±0.7	0.3±0.6	0.5±0.8	0.5±0.6	0.0030
Organ support*, %					
Mechanical ventilation		85	62	76	<0.0001
Use of vasopressor		54	45	49	0.8355
Renal replacement therapy		11	12	29	0.0069
Length of stay in ICU (days)	18±15	17±14	20±16	16±13	0.5061
Mortality analysis, %:					
Death by day 28	94 (28)	64 (32)	18 (17)	12 (50)	0.0012
Death by day 90	118 (36)	70 (35)	34 (32)	14 (58)	0.0544

The data are presented as means±SDs or percentages.
*Based on the total number of observations during the follow-up period.

Multivariate analysis

To exclude the effects of several baseline variables on survival among the three groups being investigated, we performed multivariate Cox regression analysis. Bloodstream infection remained a significant covariate for mortality in the multivariate analysis (hazard ratio, 2.10; 95% CI, 1.14-3.86; p=0.0166; Table 3). This finding indicates that, despite baseline differences in some variables (i.e., IDDM, Cancer and "No history of surgery"), the presence of a primary bloodstream infection remains a prognostic variable with a significant effect on the outcome (90-day survival; Table 3).

Table 3. Cox regression analysis

Infection site	Variable	Hazard ratio	95% CI	p-value
Pulmonary:				
	Age	1.02	1.00-1.03	0.0009
	Gender	1.19	0.80-1.76	0.3803
	BMI	1.00	0.97-1.03	0.7058
	Diabetes mellitus (IDDM)	1.29	0.75-2.19	0.3450
	History of cancer	1.26	0.81-1.95	0.2921
	No history of surgery	1.37	0.87-2.14	0.1634
	Pulmonary infection	1.05	0.72-1.55	0.7675
Intra-abdominal:				
	Age	1.02	1.00-1.03	0.0007
	Gender	1.17	0.79-1.73	0.4302
	BMI	1.00	0.97-1.03	0.6497
	Diabetes mellitus (IDDM)	1.28	0.75-2.16	0.3534
	History of cancer	1.33	0.85-2.06	0.2036
	No history of surgery	1.25	0.80-1.97	0.3209
	Intra-abdominal infection	0.71	0.46-1.08	0.1142
Bloodstream:				
	Age	1.02	1.01-1.03	0.0007
	Gender	1.18	0.80-1.75	0.3956
	BMI	1.00	0.97-1.03	0.7930
	Diabetes mellitus (IDDM)	1.07	0.61-1.88	0.7877
	History of cancer	1.36	0.87-2.12	0.1719
	No history of surgery	1.30	0.84-2.02	0.2290
	Bloodstream infection	2.10	1.14-3.86	0.0166

Disease severity

During the observational period, patients with bloodstream infections presented significantly higher mean SOFA scores compared with patients in the other groups (8.5±4.7, 7.3±3.4 and 5.8±3.5, respectively; Table 2). Four of the six organ-specific SOFA scores (respiratory,

central nervous system (CNS), renal and hepatic) varied significantly among the study groups. The patients with pulmonary infections presented higher SOFA-respiratory scores than did patients with intra-abdominal and bloodstream infections (2.2±0.6, 1.5±0.7 and 1.9±0.9, respectively; Table 2), and together with the patients with bloodstream infections, required more mechanical ventilation than patients with intra-abdominal infections (85%, 76% and 62%, respectively; Table 2). The patients with pulmonary and bloodstream infections presented higher SOFA-CNS scores than those of the patients with intra-abdominal infections (2.1±1.0, 2.0±1.2 and 1.4±1.0, respectively; Table 2). Analysis of the SOFA-renal scores indicated that the patients with bloodstream infections presented higher SOFA-renal scores over the study period in the ICU compared with the patients with pulmonary and intra-abdominal infections (1.6±1.4, 0.8±1.1 and 0.7±1.0, respectively; Table 2). These patients also required significantly more renal replacement therapy (29%, 11% and 12%, respectively; Table 2). The SOFA-hepatic score was significantly higher in the patients with intra-abdominal and bloodstream infections compared with the patients with pulmonary infections (0.5±0.8, 0.5±0.6 and 0.3±0.6, respectively; Table 2). Additional results regarding disease severity were added to the supplemental data (see online supplementary data, Table1).

In addition, the gram-negative infection rate was significantly higher among the patients with pulmonary infections (75%) compared with those whose sepsis had intra-abdominal and bloodstream infection origins (57% and 54%, respectively; Table 4). Additional results regarding microbiological findings and anti-infective therapy were added to the supplemental data (see online supplementary data, Table 2 and Table 3; respectively).

Table 4. Infection types over the observational period

Infection site	Pulmonary	Intra-abdominal	Bloodstream	p-value
Infection type				
Gram-negative bacteria	75%	57%	54%	0.0026
Gram-positive bacteria	78%	84%	79%	0.5142
Fungus	52%	76%	42%	<0.0001
Virus	0.08%	0.06%	0.13%	0.4941

Furthermore, septic patients with intra-abdominal infections presented a higher incidence of fungal infections (76%) compared with the patients with pulmonary and bloodstream infections (52% and 42%, respectively; Table 4).

DISCUSSION

The present study addressed whether common infection sites among patients with sepsis are associated with the survival rate.

The primary endpoint, the mortality risk within 90 days of the onset of sepsis, was higher in patients with primary bloodstream infections compared with those with respiratory or intra-abdominal infections (58%, 35% and 32%, respectively; Fig. 1). Primary bacteremia remained a significant covariate for mortality in the multivariate analysis (Table 3).

According to the SOFA and APACHE II scores, the infection site was not associated with the acute-illness severity at the onset of sepsis (Table 1). We believe that the similarity in SOFA and APACHE II scores at sepsis onset among the three groups can be attributed to the phenotypic heterogeneity of sepsis. This heterogeneity is affected by several factors, including the causative organism of the infection and the amount of time elapsed since the infection began, as well as by individual patient characteristics, such as comorbidities and genetic makeup[28].

The most significant result of this study with respect to 90-day mortality risk was that the mortality rate (58%) was higher among patients with primary bloodstream infections; this result is in agreement with the results of several previous investigations that found similar mortality rates in patients with nosocomial bloodstream infections; e.g., Garrouste-Orgeas et al. found that patients with nosocomial BSI had a mortality rate of 61.5%[14 15]. Our study also goes beyond previous investigations by evaluating a longer-term end point (90 days); this end point was investigated because sepsis patients continue to face an increased risk of mortality, even after ICU and hospital discharge[32].

Severe morbidity, quantified by the SOFA mean score in patients with primary bloodstream infections, resulted in an increased 28-day mortality rate compared with the patients with pulmonary and intra-abdominal infections (50%, 32% and 17%, respectively; Table 2).

The strengths of our study include that it is the first to investigate organ-specific manifestations associated with common sepsis infection sites (respiratory, intra-abdominal and bloodstream) by quantifying SOFA scores and evaluating the requirements for organ support in the ICU (Table 2). The more pronounced types of respiratory failure, which are quantified by the SOFA-respiratory score and the need for mechanical ventilation (Table 2), among patients with pulmonary infections are plausible because these patients frequently present comprised pulmonary function. Patients with primary bacteremia are also at a high risk of respiratory failure due to systemic inflammatory response syndrome, release of pro-inflammatory cytokines (such as tumor necrosis factor (TNF), IL-1 and IL-6,[33]) and recruitment of neutrophils to the lungs, which induces the release of toxic mediators, such as reactive oxygen species and proteases, thus contributing to lung damage and respiratory failure[34].

We believe that the difference in the SOFA-CNS score between the genotypes (with higher scores in the respiratory and the bloodstream groups) occurred because patients in these groups required much more mechanical ventilation, causing them to be treated more frequently with sedating medication, which impacts the CNS and thus affects the SOFA-CNS score.

The observed distinct renal failure among bloodstream infection patients indicated by the SOFA-renal score, which was accompanied by frequent renal replacement therapy (Table 2), was in accordance with former observations indicating that bloodstream infections are associated with a higher incidence of renal failure[35]. The frequent utilization of renal replacement therapy suggests persistent organ dysfunction, which is a well-known contributor to sepsis-related mortality and may explain the higher mortality among bloodstream infection patients observed in our study (Table 2, Figure 1)[36].

The SOFA-hepatic score was higher among patients with intra-abdominal and primary bloodstream infections compared with patients with pulmonary infections (Table 2). This

result can be attributed to the fact that Kupffer cells release several cytokines able to induce hepatocellular dysfunction in response to endotoxemia in patients with bloodstream infections[37].

There are some limitations to this study, along with potential confounding. One limitation to this study is the possibility of selection bias; for example, the patients in this study may have had a higher mortality rate in general than septic patients in other ICUs (e.g., in secondary medical care centers) because patients admitted to our surgical ICUs frequently had more severe coexisting diseases than did patients in other ICUs (non-tertiary care center ICUs). A second potential limitation to this study is measurement bias. For example, many clinical parameters (e.g., blood pressure, heart rate, and respiratory frequency) were registered automatically in the electronic patient record system, and we cannot guarantee that all registered clinical parameters were always correct because of potential measurement errors. However, we did check all clinical records for plausibility before conducting our statistical analysis. Finally, one uncontrolled confounder that was not adjusted for is appropriate antibiotic therapy; although patients with clinical signs of infection were routinely promptly given antibiotic therapy, data regarding the exact times at which patients received antibiotic doses after sepsis onset are unavailable.

To the best of our knowledge, this investigation is the first to evaluate 90-day survival rates with respect to common sepsis infection sites (respiratory, intra-abdominal and primary bloodstream). This study revealed a significantly higher mortality rate among patients with primary bloodstream infections (58%) compared with patients with respiratory and intra-abdominal infections, although all patients were treated according to current guidelines for the treatment of sepsis (Surviving Sepsis Campaign)[6]. Because of this dramatically higher mortality rate among patients with primary bloodstream sepsis, we believe that future sepsis trials should focus on this vulnerable group of high-risk patients. More appropriate interventions and further improvements in prevention and care are urgently needed.

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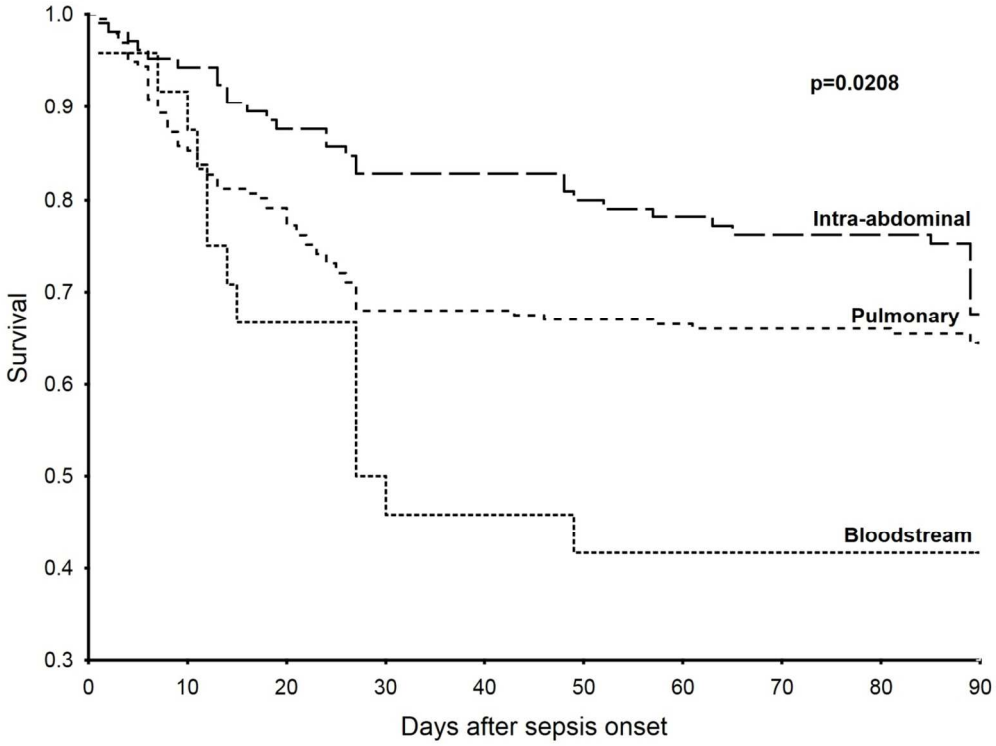

Figure 1. Kaplan-Meier survival:
The Kaplan-Meier curve shows the survival curves until day 90 for the three infection site groups. The mortality risk among the patients under study was higher among the patients with bloodstream infections compared with those in the pulmonary and intra-abdominal infection groups (p=0.0208, log-rank test).
119x90mm (300 x 300 DPI)

Supplementary Data; Table 1: Vital parameters, laboratory parameters, kidney parameters and inflammation values

	Alle n=327	Fokus Lunge n=198	Fokus Abdomen n=105	Fokus Bakteriämie n=24	P value
vital parameters, mean ± SD					
Temperature (°C), max	37.9±0.5	38.0±0.5	37.7±0.4	37.8±0.6	0.0032
Temperature (°C), min	36.8±0.5	36.9±0.4	36.7±0.5	36.6±0.6	0.0054
Heart rate (bpm), max	103±12	103±12	103±11	102±15	0.5067
Heart rate (bpm), min	72±11	72±11	74±11	73±12	0.4774
MAP (mmHg), max	100±11	101±12	99±10	94±15	0.0781
MAP (mmHg), min	66±9	66±9	67±8	62±9	0.0243
Vasopressor (µg/kg/min) (n)	10±9 (247)	10±9 (147)	10±7 (83)	10±9 (17)	0.2268
laboratory parameters, mean ± SD					
Lactate (mmol/l)	1.7±1.1	1.6±1.0	1.7±1.1	2.0±1.2	0.1278
Thrombocytes (1000/µl)	295±148	281±133	329±168	257±154	0.0344
Quick (%) (n)	83±16 (325)	83±16 (196)	84±17 (105)	77±16 (24)	0.1528
kidney values					
Urine output (ml/day)	3055±1406	2900±1281	3555±1443	2144±1535	<0.0001
Urine output (ml/kg/h)	1.6±0.8	1.5±0.8	1.8±0.8	0.9±0.6	<0.0001
Creatinine (mg/dl)	1.3±0.9	1.3±0.9	1.2±1.0	1.6±1.0	0.0148
inflammatory values					
Leukocytes (1000/µl)	13±5	12±4	15±5	14±5	0.0001
CRP (mg/l) (n)	150±85 (175)	141±97 (70)	154±69 (90)	168±107 (15)	0.2159
Procalcitonin (ng/dl) (n)	4.8±12.0 (280)	3.3±9.7 (176)	7.4±15.6 (81)	7.1±11.3 (23)	<0.0001

CRP=C-reactive protein; MAP=Mean arterial pressure; The data are presented as the mean±SD or percentages. Min and Max indicate the lowest/highest value that has been recorded daily within the observation period.

Supplementary Data; Table 2. Recorded microbiological findings

	All n=327	Pulmonary n=198	Intra-abdominal n=105	Bloodstream n=24
Bacteria				
Gram-negative, n (%)				
Acinetobacter genomospecies 3	2 (0.6)	2 (1.0)	0 (0.0)	0 (0.0)
Bacteroides fragilis	11 (3.4)	0 (0.0)	11 (10.5)	0 (0.0)
Bacteroides ovaters	2 (0.6)	1 (0.5)	1 (1.0)	0 (0.0)
Bacteroides species	3 (0.9)	0 (0.0)	3 (2.9)	0 (0.0)
Bacteroides thetaiotaomicron	4 (1.2)	1 (0.5)	3 (2.9)	0 (0.0)
Bacteroides uniformis	4 (1.2)	0 (0.0)	4 (3.8)	0 (0.0)
Chlamydia pneumoniae IgA	6 (1.8)	6 (3.0)	0 (0.0)	0 (0.0)
Chlamydia pneumoniae lgG	2 (0.6)	1 (0.5)	0 (0.0)	1 (4.2)
Chlamydophila pneumoniae	2 (0.6)	2 (1.0)	0 (0.0)	0 (0.0)
Citobacter braakii	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
Citrobacter freundii	3 (0.9)	2 (1.0)	1 (1.0)	0 (0.0)
Citrobacter koseri	2 (0.6)	1 (0.5)	1 (1.0)	0 (0.0)
Enterobacter aerogenes	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Enterobacter asburiae	2 (0.6)	1 (0.5)	1 (1.0)	0 (0.0)
Enterobacter cloacae	22 (6.7)	14 (7.0)	5 (4.8)	3 (12.5)
ESBL E.coli	5 (1.5)	2 (1.0)	2 (1.9)	1 (4.2)
Escherichia coli	53 (16.2)	35 (17.7)	15 (14.3)	3 (12.5)
Haemophilus influenza	12 (3.7)	12 (6.1)	0 (0.0)	0 (0.0)
Haemophilus parainfluenzae	3 (0.9)	2 (1.0)	1 (1.0)	0 (0.0)
Hafnia alvei	2 (0.6)	2 (1.0)	0 (0.0)	0 (0.0)
Klebsiella oxytoca	8 (2.5)	8 (4.0)	0 (0.0)	0 (0.0)
Klebsiella pneumoniae	13 (4.0)	10 (5.1)	3 (2.9)	0 (0.0)
Morgonella morganii	3 (0.9)	3 (1.5)	0 (0.0)	0 (0.0)
Pantoea agglomerans	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Proteus mirabilis	9 (2.8)	8 (4.0)	1 (1.0)	0 (0.0)
Proteus species	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Proteus vulgaris	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
Pseudomonas aeruginosa	26 (8.0)	20 (10.1)	5 (4.8)	1 (4.2)
Pseudomonas korrensis	1 (0.3)	0 (0.0)	0 (0.0)	1 (4.2)
Serratia marcescens	8 (2.5)	7 (3.5)	0 (0.0)	1 (4.2)
Serratia ureilytica	1 (0.3)	0 (0.0)	0 (0.0)	1 (4.2)
Stenotrophomonas maltophila	5 (1.5)	3 (1.5)	1 (1.0)	1 (4.2)
Gram-positive, n (%)				
Aerococcus urinae	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Clostridium difficile	5 (1.5)	1 (0.5)	3 (2.9)	1 (4.2)
Clostridium innocuum	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
Clostridium perfringens	3 (0.9)	0 (0.0)	3 (2.9)	0 (0.0)
Enterococcus avium	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
Enterococcus casseliflavus	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
Enterococcus faecalis	33 (10.1)	10 (5.1)	23 (21.9)	0 (0.0)
Enterococcus faecium	35 (10.7)	4 (2.0)	27 (25.7)	4 (16.7)

Enterococcus mundtii	1 (0.3)	0 (0.0)	0 (0.0)	1 (4.2)
Enterococcus species	29 (8.9)	25 (12.6)	3 (2.9)	1 (4.2)
Coagulase negative Staphylococci	12 (3.7)	8 (4.0)	3 (2.9)	1 (4.2)
Lactobacillus paracasei	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
MRSA	6 (1.8)	5 (2.5)	0 (0.0)	1 (4.2)
Peptostreptococcus species	2 (0.6)	1 (0.5)	1 (1.0)	0 (0.0)
Rothia mucilaginosa	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Staphyloccocus aureus	52 (15.9)	47 (23.7)	1 (1.0)	4 (16.7)
Staphylococcus capitis	7 (2.1)	5 (2.5)	1 (1.0)	1 (4.2)
Staphylococcus epidermidis	36 (11.0)	24 (12.1)	9 (8.6)	3 (12.5)
Staphylococcus haemolyticus	2 (0.6)	2 (1.0)	0 (0.0)	0 (0.0)
Staphylococcus hominis	4 (1.2)	3 (1.5)	1 (1.0)	0 (0.0)
Staphylococcus wameri	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Streptococcus agalactiae	4 (1.2)	3 (1.5)	1 (1.0)	0 (0.0)
Streptococcus anginosus	3 (0.9)	0 (0.0)	2 (1.9)	1 (4.2)
Streptococcus constellatus	5 (1.5)	3 (1.5)	2 (1.9)	0 (0.0)
Streptococcus pneumonia	4 (1.2)	4 (2.0)	0 (0.0)	0 (0.0)
Streptococcus viridans	2 (0.6)	1 (0.5)	0 (0.0)	1 (4.2)
Fungi, n (%)				
Aspergillus flavus	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Aspergillus fumigatus	3 (0.9)	1 (0.5)	1 (1.0)	1 (4.2)
Candida albicans	110 (33.6)	67 (33.8)	38 (36.2)	5 (20.8)
Candida dubliniensis	3 (0.9)	2 (1.0)	1 (1.0)	0 (0.0)
Candida glabrata	25 (7.7)	16 (8.0)	6 (5.7)	3 (12.5)
Candida guilliermondii	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
Candida IgG	3 (0.9)	1 (0.5)	2 (1.9)	0 (0.0)
Candida krusei	5 (1.5)	2 (1.0)	2 (1.9)	1 (4.2)
Candida lusitaniae	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Candida palmioleophila	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
Candida parapsilosis	4 (1.2)	3 (1.5)	1 (1.0)	0 (0.0)
Candida tropicalis	14 (4.3)	6 (3.0)	8 (7.6)	0 (0.0)
Viruses, n (%)				
Adenovirus-Ag-IFT	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
CMV	5 (1.5)	3 (1.5)	1 (1.0)	1 (4.2)
H1N1 (2009 RNA)	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
H1N1 DNA	4 (1.2)	4 (2.0)	0 (0.0)	0 (0.0)
HSV	4 (1.2)	1 (0.5)	2 (1.9)	1 (4.2)
RS-Virusantigen IFT	2 (0.6)	2 (1.0)	0 (0.0)	0 (0.0)
Varizella zoster virus	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)

CMV: Cytomegalovirus; MRSA: Methicillin-resistant Staphylococcus aureus; RS-Virus: Respiratory Syncytial Virus.

Supplementary Data; Table 3. Anti-infective agents

	All n=327	Pulmonary n=198	Intra-abdominal n=105	Bloodstream n=24
Antibiotics, n (%)				
Penicillins	168 (51)	133 (67)	21 (20)	14 (58)
Aminopenicillins	43 (13)	30 (15)	11 (10)	2 (8)
2. generation cephalosporines	49 (15)	42 (21)	4 (3)	3 (12)
3. generation cephalosporines	87 (26)	60 (30)	23 (21)	4 (16)
Carbapenems	215 (65)	107 (54)	91 (86)	17 (70)
Macrolides	84 (25)	70 (35)	6 (5)	8 (33)
Aminoglycosides	15 (4)	7 (3)	6 (5)	2 (8)
Fluorchinolones	50 (15)	29 (14)	17 (16)	4 (16)
Imidazoles	38 (11)	14 (7)	22 (20)	2 (8)
Glycopeptides	125 (38)	44 (22)	63 (60)	18 (75)
Lipopeptides	2 (0.6)	1 (0.5)	1 (0.9)	0 (0)
Lincosamides	11 (3)	8 (4)	1 (0.9)	2 (8)
Oxazolidinones	106 (32)	60 (30)	39 (37)	7 (29)
Glycylcyclines	4 (1)	0 (0)	3 (2)	1 (4)
Rifampicin	4 (1)	3 (1)	0 (0)	1 (4)
Sulfamethoxazol/Trimethoprim	12 (3)	7 (3)	4 (3)	1 (4)
Antifungals, n (%)				
Echinocandin	60 (18)	25 (12)	25 (23)	10 (41)
Triazole derivatives	91 (27)	22 (11)	62 (59)	7 (29)
Polyene	5 (1)	5 (2)	0 (0)	0 (0)
Antivirals, n (%)				
Aciclovir	5 (1)	3 (1)	2 (1)	0 (0)
Ganciclovir/Valganciclovir	2 (0.6)	1 (0.5)	0 (0)	1 (4)
Oseltamivir	4 (1.2)	4 (2)	0 (0)	0 (0)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(*b*) Report category boundaries when continuous variables were categorized	12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-17
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Primary bacteremia is associated with a higher mortality risk compared with pulmonary and intra-abdominal infections in patients with sepsis: a prospective observational cohort study

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Keywords: Apache II; Pulmonary infection; intra-abdominal infection; intensive care unit; organ failure marker; SOFA scores

Word count 3058

ABSTRACT

Objective: To investigate whether common infection foci (pulmonary, intra-abdominal and primary bacteremia) are associated with variations in mortality risk in sepsis patients.

Design: Prospective, observational cohort study.

Setting: Three surgical intensive care units (ICU) at a university medical center.

Participants: A total of 327 adult Caucasian patients with sepsis originating from pulmonary, intra-abdominal and primary bacteremia participated in this study.

Primary and secondary outcome measures: The patients were followed for 90 days, and mortality risk was recorded as the primary outcome variable. To monitor organ failure, sepsis-related organ failure assessment (SOFA) scores were evaluated at the onset of sepsis and throughout the observational period as secondary outcome variables.

Results: A total of 327 critically ill patients with sepsis were enrolled in this study. Kaplan-Meier survival analysis showed that the 90-day mortality risk was significantly higher among patients with primary bacteremia than among those with pulmonary and intra-abdominal foci (58%, 35% and 32%, respectively; p=0.0208). To exclude the effects of several baseline variables, we performed multivariate Cox regression analysis. Primary bacteremia remained a significant covariate for mortality in the multivariate analysis (hazard ratio, 2.10; 95% CI, 1.14-3.86; p=0.0166). During their stay in the ICU, the patients with primary bacteremia presented significantly higher SOFA scores than those of the patients with pulmonary and intra-abdominal infection foci (8.5±4.7, 7.3±3.4 and 5.8±3.5, respectively). Patients with primary bacteremia presented higher SOFA-renal score compared with the patients with other infection foci (1.6±1.4, 0.8±1.1 and 0.7±1.0, respectively); the primary bacteremia patients required significantly more renal replacement therapy than the patients in the other groups (29%, 11% and 12%, respectively).

Conclusions: These results indicate that sepsis patients with primary bacteremia present a higher mortality risk compared with patients with sepsis of pulmonary or intra-abdominal origins. These results should be assessed in sepsis patients in larger, independent cohorts.

Strengths and limitations of this study

- This is the first study to evaluate mortality risk among sepsis patients with primary bloodstream infections compared with those with respiratory or intra-abdominal infections over an observational period of 90 days.
- The strengths of our study include that it is the first to investigate organ-specific manifestations associated with common sepsis infection sites (respiratory, intra-abdominal and bloodstream) by quantifying SOFA scores and evaluating the requirements for organ support in the ICU.
- One potentially uncontrolled confounder that was not adjusted for is appropriate antibiotic therapy.

INTRODUCTION

Sepsis is defined as a systemic inflammatory response that occurs during severe infection[1-3]. Sepsis affects more than 750,000 patients in the United States each year and remains one of the leading causes of death worldwide[4]. Although the incidence of this major health care problem has been increasing, the implementation of early goal-directed therapy in patients with severe sepsis and septic shock has in part successfully reduced mortality[5]. Guidelines for disease control have been written by the Surviving Sepsis Campaign (SSC), a joint collaboration between the Society of Critical Care Medicine and the European Society of Intensive Care Medicine committed to reducing mortality from severe sepsis and septic shock worldwide[6]. These guidelines contain clear recommendations for improving disease outcomes (e.g., guidelines for resuscitation and recommendations pertaining to infections, including for the use of diagnostics, hemodynamic support and adjunctive therapy and for supportive therapy for severe sepsis)[6].

Respiratory, intra-abdominal, urinary and primary bloodstream infections make up 80% of all infection sites[7]. According to epidemiological data, the lung is the most common site of infection, followed by the abdomen and the blood[2].

Pneumonia, hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP) and subsequent sepsis remain important causes of morbidity and mortality in critically ill patients despite advances in antimicrobial therapy, better supportive care modalities, and a wide range of preventive measures[8-10].

Intra-abdominal infections are a common cause of sepsis. These infections comprise a markedly heterogeneous group of infectious processes that share an anatomical site of origin between the diaphragm and the pelvis[11]. Their clinical course is dictated by a number of infection-related factors, including the microbiology of the infection, the anatomical location,

the degree of localization, and the presence of correctable anatomical derangements involving intra-abdominal viscera[12 13].

Bloodstream infections (BSIs) are a major cause of death due to nosocomial events in intensive care units (ICUs)[14]. Immunosuppression and invasive health care procedures act together to create a high risk of nosocomial BSIs in critically ill patients[15]. The outcomes of BSIs have been the focus of many case-control and cohort studies[15-17]. BSIs lead to poor patient outcomes[16 18], prolonged patient stays in the ICU and in the hospital[16 19 20], and substantial extra medical costs[21 22].

Whether the characteristics of the infection, infection site and pathogenic organism independently affect the outcome in patients with sepsis remains a subject of debate. Whereas previous studies have shown an independent, significant contribution of the infection site and the pathogenic organism to the survival of sepsis patients[23], recent investigations have not found any significant impact of the infection site on mortality among patients with sepsis[24].

This study aimed to explore whether common origins of sepsis infections, in particular respiratory, intra-abdominal and bloodstream infection sites, are associated with changes in the 90-day survival rate among patients with sepsis in a representative university medical center, where patients are treated according to the most recent sepsis guidelines.

MATERIALS AND METHODS

Patients

Adult Caucasian patients admitted to ICUs at the University Medical Center-Goettingen (UMG) between April 2012 and May 2013 were screened daily according to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) criteria for sepsis, severe sepsis, or septic shock[25 26]. This study was approved by the University of Goettingen ethics committee in Goettingen, Germany (1/15/12) and conformed to the ethical principles of the Declaration of Helsinki (Seoul, 2008). For each patient, written, informed consent was obtained from either the patient or his or her legal representative. Patients were enrolled if they presented sepsis of a respiratory, intra-abdominal or primary bloodstream origin. Caucasian origin was assessed by questioning the patients, their next of kin or their legal representatives.

Definitions

In this study, patients with sepsis of respiratory origin had hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP). HAP is the most frequent infection in surgical intensive care units and is defined as a pulmonary infection that was not incubating at the time of admission and that occurred at least 48 h after hospital admission[27]. Ventilator-associated pneumonia (VAP) is defined as either a pulmonary infection arising more than 48 h after tracheal intubation with no evidence of pneumonia at the time of intubation or the diagnosis of a new pulmonary infection if the initial ICU admission was due to pneumonia[27].

Typically, patients with intra-abdominal infections in the surgical ICU develop secondary peritonitis as a result of microbial infection of the peritoneal space following perforation, abscess formation, ischemic necrosis, or a penetrating injury of the intra-abdominal contents[11].

Primary BSI comprises BSI of unknown origin in patients without an identifiable focus of infection and intravascular BSI (related to the presence of a catheter, implantable cardioverter-defibrillator or pacemaker)[11].

Exclusion criteria

As described previously[28 29], the patient exclusion criteria were the following: (1) age less than 18 years; (2) being pregnant or nursing an infant; (3) immunosuppressive therapy (e.g., cyclosporine or azathioprine) or cancer-related chemotherapy; (4) documented or suspected acute myocardial infarction within the previous 6 weeks; (5) a history of New York Heart Association functional class IV chronic heart failure; (6) human immunodeficiency virus infection; (7) a do not resuscitate or do not treat order or the patient and/or his or her legal representative not being committed to aggressive management; (8) not being expected to survive the 28-day observation period or not being likely to be placed on life support because of an uncorrectable medical condition, including a poorly controlled neoplasm or end-stage lung disease; (9) a chronic vegetative state or a similar long-term neurological condition; (10) current participation in any interventional study (of a drug or device); (11) inability to be fully evaluated during the study period; and (12) being a study-site employee or a family member of a study-site employee involved in conducting this study.

Data collection

Patients were followed up for 90 days, and mortality risk was recorded as the primary outcome variable. Sequential Organ Failure Assessment (SOFA)[30] and Acute Physiology and Chronic Health Evaluation (APACHE) II[31] scores were evaluated at the onset of sepsis. Organ function was reassessed over 28 days in the ICU to monitor morbidity as previously described[28]. Organ failure, organ support requirements and the length of ICU stay were recorded as secondary outcome variables. All relevant clinical data were extracted from the electronic patient record system (IntelliSpace Critical Care and Anesthesia (ICCA); Philips Healthcare, USA); all medical records, including microbiology reports, can be found in this system. We sought to determine whether patients suffered from preexisting conditions, for example, comorbidities, by examining physicians' notes, administering an anamnestic questionnaire to the patients or their legal representatives and consulting each patient's family doctor.

Statistical analyses

Statistical analyses were performed using Statistica software (version 10; StatSoft, Tulsa, Oklahoma, USA). Based on contingency tables, significance was calculated using two-sided Fisher's exact or chi-square tests, as appropriate. Two continuous variables were compared using the Mann-Whitney test. Time-to-event data were compared using the log-rank test from the Statistica package for Kaplan-Meier survival analysis. For variables identified as significant in univariate survival analyses (respiratory infections, intra-abdominal infections and primary bacteremia), potential confounders (age, gender and BMI) and covariates that varied at baseline (diabetes mellitus (IDDM), history of cancer and "No history of surgery"), we performed multivariate Cox regression analysis to examine survival times. A value of $p<0.05$ was considered statistically significant.

RESULTS

Study population

A total of 327 adult Caucasian patients with sepsis were enrolled in this study. At enrollment, 61% of the patients had a pulmonary infection; 32% suffered from an intra-abdominal infection; and 7% presented with a primary bloodstream infection (Table 1). Patients' ages ranged from 19 to 91 years (median, 65 years). At baseline, patients' SOFA and APACHE II scores, which measure disease severity, were 9.3±4.0 and 21.5±7.3, respectively (Table 1). Comorbidities included hypertension, myocardial infarction history, chronic obstructive pulmonary disease (COPD), renal dysfunction, non-insulin-dependent diabetes mellitus, insulin-dependent diabetes mellitus, chronic liver diseases, history of cancer, and a history of stroke (Table 1).

Table 1. Patient baseline characteristics with regard to the infection site

	All n=327	Pulmonary n=198	Intra-abdominal n=105	Bloodstream n=24	p-value
Age, mean ± SD	62±15	61±15	65±13	60±16	0.2426
Male, %	67%	70	61	62	0.2614
Body mass index, mean ± SD	27±6	27±7	27±5	29±5	0.0885
SOFA score, mean ± SD	9.3±4.0	9.4±3.6	8.9±4.7	10.5±5.1	0.3099
APACHE II score, mean ± SD	21.5±7.3	21.8±6.8	20.6±8.1	22.8±7.6	0.3538
Organ support, %					
Mechanical ventilation	85	90	74	87	0.0008
Use of vasopressor	64	62	65	70	0.6778
Renal replacement therapy	8	7	9	20	0.0781
Comorbidities, %					
Hypertension	57	55	59	66	0.5395
History of myocardial infarction	8	9	7	8	0.9087
COPD	17	17	17	16	0.9880
Renal dysfunction	11	10	9	25	0.0857
Diabetes mellitus (NIDDM)	9	10	8	8	0.8928
Diabetes mellitus (IDDM)	11	8	11	33	0.0015
Chronic liver diseases	5	3	8	8	0.1538
History of cancer	18	15	30	0	0.0003
History of stroke	6	8	4	0	0.2192
Recent surgical history, %					
Elective surgery	30	27	37	25	0.1730
Emergency surgery	48	45	56	42	0.1401

No history of surgery	21	28	7	33	<0.0001

The data are presented as the means±SDs or percentages.

Disease severity at the onset of sepsis

No differences in age, gender, or body mass index were found among the three groups of study subjects. Moreover, no differences were found in the SOFA and APACHE II scores with respect to the infection sites at the onset of sepsis. The patients in the group with intra-abdominal infections required significantly less mechanical ventilation compared with the other groups with pulmonary and bloodstream infections (74%, 90% and 87%, respectively). The patients with bloodstream infections suffered significantly more from insulin-dependent diabetes mellitus compared with patients with pulmonary or intra-abdominal infections (33%, 8%, 11%, respectively). In contrast, none of the patients with bloodstream infections had a history of cancer, unlike the patients with pulmonary and intra-abdominal infections (15% and 30%, respectively; Table 1).

Mortality analysis

Kaplan-Meier survival analysis showed that the 90-day mortality risk was significantly higher among patients with primary bacteremia than among those with pulmonary and intra-abdominal foci (58%, 35% and 32%, respectively; Figure 1). Analysis of the 28-day mortality data similarly revealed that the patients with bloodstream infections had a significantly increased risk of death compared with the patients with pulmonary and intra-abdominal infections (50%, 32% and 17%, respectively; Table 2). Moreover, 90-day mortality analysis suggested a higher incidence of death among the patients with bloodstream infections, although this finding was not significant (p=0.0544; Table 2).

Table 2. Disease severity with regard to infection site

	All n=327	Pulmonary n=198	Intra-abdominal n=105	Bloodstream n=24	p-value
SOFA	6.9±3.6	7.3±3.4	5.8±3.5	8.5±4.7	0.0002
SOFA Subscores					
SOFA-Respiratory	1.9±0.7	2.2±0.6	1.5±0.7	1.9±0.9	<0.0001
SOFA-Cardiovascular	1.5±0.9	1.5±0.9	1.3±0.9	1.7±1.2	0.4567
SOFA-Central nervous system	1.8±1.1	2.1±1.0	1.4±1.0	2.0±1.2	<0.0001
SOFA-Renal	0.8±1.1	0.8±1.1	0.7±1.0	1.6±1.4	0.0028
SOFA-Coagulation	0.3±0.5	0.3±0.6	0.2±0.5	0.6±0.8	0.4662
SOFA-Hepatic	0.4±0.7	0.3±0.6	0.5±0.8	0.5±0.6	0.0030
Organ support*, %					
Mechanical ventilation		85	62	76	<0.0001
Use of vasopressor		54	45	49	0.8355
Renal replacement therapy		11	12	29	0.0069
Length of stay in ICU (days)	18±15	17±14	20±16	16±13	0.5061
Mortality analysis, %:					
Death by day 28	94 (28)	64 (32)	18 (17)	12 (50)	0.0012
Death by day 90	118 (36)	70 (35)	34 (32)	14 (58)	0.0544

The data are presented as means±SDs or percentages.
*Based on the total number of observations during the follow-up period.

Multivariate analysis

To exclude the effects of several baseline variables on survival among the three groups being investigated, we performed multivariate Cox regression analysis. Bloodstream infection remained a significant covariate for mortality in the multivariate analysis (hazard ratio, 2.10; 95% CI, 1.14-3.86; p=0.0166; Table 3). This finding indicates that, despite baseline differences in some variables (i.e., IDDM, Cancer and "No history of surgery"), the presence of a primary bloodstream infection remains a prognostic variable with a significant effect on the outcome (90-day survival; Table 3).

Table 3. Cox regression analysis

Infection site	Variable	Hazard ratio	95% CI	p-value
Pulmonary:				
	Age	1.02	1.00-1.03	0.0009
	Gender	1.19	0.80-1.76	0.3803
	BMI	1.00	0.97-1.03	0.7058
	Diabetes mellitus (IDDM)	1.29	0.75-2.19	0.3450
	History of cancer	1.26	0.81-1.95	0.2921
	No history of surgery	1.37	0.87-2.14	0.1634
	Pulmonary infection	1.05	0.72-1.55	0.7675
Intra-abdominal:				
	Age	1.02	1.00-1.03	0.0007
	Gender	1.17	0.79-1.73	0.4302
	BMI	1.00	0.97-1.03	0.6497
	Diabetes mellitus (IDDM)	1.28	0.75-2.16	0.3534
	History of cancer	1.33	0.85-2.06	0.2036
	No history of surgery	1.25	0.80-1.97	0.3209
	Intra-abdominal infection	0.71	0.46-1.08	0.1142
Bloodstream:				
	Age	1.02	1.01-1.03	0.0007
	Gender	1.18	0.80-1.75	0.3956
	BMI	1.00	0.97-1.03	0.7930
	Diabetes mellitus (IDDM)	1.07	0.61-1.88	0.7877
	History of cancer	1.36	0.87-2.12	0.1719
	No history of surgery	1.30	0.84-2.02	0.2290
	Bloodstream infection	2.10	1.14-3.86	0.0166

Disease severity

During the observational period, patients with bloodstream infections presented significantly higher mean SOFA scores compared with patients in the other groups (8.5±4.7, 7.3±3.4 and 5.8±3.5, respectively; Table 2). Four of the six organ-specific SOFA scores (respiratory,

central nervous system (CNS), renal and hepatic) varied significantly among the study groups. The patients with pulmonary infections presented higher SOFA-respiratory scores than did patients with intra-abdominal and bloodstream infections (2.2±0.6, 1.5±0.7 and 1.9±0.9, respectively; Table 2), and together with the patients with bloodstream infections, required more mechanical ventilation than patients with intra-abdominal infections (85%, 76% and 62%, respectively; Table 2). The patients with pulmonary and bloodstream infections presented higher SOFA-CNS scores than those of the patients with intra-abdominal infections (2.1±1.0, 2.0±1.2 and 1.4±1.0, respectively; Table 2). Analysis of the SOFA-renal scores indicated that the patients with bloodstream infections presented higher SOFA-renal scores over the study period in the ICU compared with the patients with pulmonary and intra-abdominal infections (1.6±1.4, 0.8±1.1 and 0.7±1.0, respectively; Table 2). These patients also required significantly more renal replacement therapy (29%, 11% and 12%, respectively; Table 2). The SOFA-hepatic score was significantly higher in the patients with intra-abdominal and bloodstream infections compared with the patients with pulmonary infections (0.5±0.8, 0.5±0.6 and 0.3±0.6, respectively; Table 2).

In addition, the gram-negative infection rate was significantly higher among the patients with pulmonary infections (75%) compared with those whose sepsis had intra-abdominal and bloodstream infection origins (57% and 54%, respectively; Table 4).

Table 4. Infection types over the observational period

Infection site	Pulmonary	Intra-abdominal	Bloodstream	p-value
Infection type				
Gram-negative bacteria	75%	57%	54%	0.0026
Gram-positive bacteria	78%	84%	79%	0.5142
Fungus	52%	76%	42%	<0.0001
Virus	0.08%	0.06%	0.13%	0.4941

Furthermore, septic patients with intra-abdominal infections presented a higher incidence of fungal infections (76%) compared with the patients with pulmonary and bloodstream infections (52% and 42%, respectively; Table 4).

DISCUSSION

The present study addressed whether common infection sites among patients with sepsis are associated with the survival rate.

The primary endpoint, the mortality risk within 90 days of the onset of sepsis, was higher in patients with primary bloodstream infections compared with those with respiratory or intra-abdominal infections (58%, 35% and 32%, respectively; Fig. 1). Primary bacteremia remained a significant covariate for mortality in the multivariate analysis (Table 3).

According to the SOFA and APACHE II scores, the infection site was not associated with the acute-illness severity at the onset of sepsis (Table 1). We believe that the similarity in SOFA and APACHE II scores at sepsis onset among the three groups can be attributed to the phenotypic heterogeneity of sepsis. This heterogeneity is affected by several factors, including the causative organism of the infection and the amount of time elapsed since the infection began, as well as by individual patient characteristics, such as comorbidities and genetic makeup[28].

The most significant result of this study with respect to 90-day mortality risk was that the mortality rate (58%) was higher among patients with primary bloodstream infections; this result is in agreement with the results of several previous investigations that found similar mortality rates in patients with nosocomial bloodstream infections; e.g., Garrouste-Orgeas et al. found that patients with nosocomial BSI had a mortality rate of 61.5%[14 15]. Our study also goes beyond previous investigations by evaluating a longer-term end point (90 days); this end point was investigated because sepsis patients continue to face an increased risk of mortality, even after ICU and hospital discharge[32].

Severe morbidity, quantified by the SOFA mean score in patients with primary bloodstream infections, resulted in an increased 28-day mortality rate compared with the patients with pulmonary and intra-abdominal infections (50%, 32% and 17%, respectively; Table 2).

The strengths of our study include that it is the first to investigate organ-specific manifestations associated with common sepsis infection sites (respiratory, intra-abdominal and bloodstream) by quantifying SOFA scores and evaluating the requirements for organ support in the ICU (Table 2). The more pronounced types of respiratory failure, which are quantified by the SOFA-respiratory score and the need for mechanical ventilation (Table 2), among patients with pulmonary infections are plausible because these patients frequently present comprised pulmonary function. Patients with primary bacteremia are also at a high risk of respiratory failure due to systemic inflammatory response syndrome, release of pro-inflammatory cytokines (such as tumor necrosis factor (TNF), IL-1 and IL-6,[33]) and recruitment of neutrophils to the lungs, which induces the release of toxic mediators, such as reactive oxygen species and proteases, thus contributing to lung damage and respiratory failure[34].

We believe that the difference in the SOFA-CNS score between the genotypes (with higher scores in the respiratory and the bloodstream groups) occurred because patients in these groups required much more mechanical ventilation, causing them to be treated more frequently with sedating medication, which impacts the CNS and thus affects the SOFA-CNS score.

The observed distinct renal failure among bloodstream infection patients indicated by the SOFA-renal score, which was accompanied by frequent renal replacement therapy (Table 2), was in accordance with former observations indicating that bloodstream infections are associated with a higher incidence of renal failure[35]. The frequent utilization of renal replacement therapy suggests persistent organ dysfunction, which is a well-known contributor to sepsis-related mortality and may explain the higher mortality among bloodstream infection patients observed in our study (Table 2, Figure 1)[36].

The SOFA-hepatic score was higher among patients with intra-abdominal and primary bloodstream infections compared with patients with pulmonary infections (Table 2). This

result can be attributed to the fact that Kupffer cells release several cytokines able to induce hepatocellular dysfunction in response to endotoxemia in patients with bloodstream infections[37].

There are some limitations to this study, along with potential confounding. One limitation to this study is the possibility of selection bias; for example, the patients in this study may have had a higher mortality rate in general than septic patients in other ICUs (e.g., in secondary medical care centers) because patients admitted to our surgical ICUs frequently had more severe coexisting diseases than did patients in other ICUs (non-tertiary care center ICUs). A second potential limitation to this study is measurement bias. For example, many clinical parameters (e.g., blood pressure, heart rate, and respiratory frequency) were registered automatically in the electronic patient record system, and we cannot guarantee that all registered clinical parameters were always correct because of potential measurement errors. However, we did check all clinical records for plausibility before conducting our statistical analysis. Finally, one uncontrolled confounder that was not adjusted for is appropriate antibiotic therapy; although patients with clinical signs of infection were routinely promptly given antibiotic therapy, data regarding the exact times at which patients received antibiotic doses after sepsis onset are unavailable.

To the best of our knowledge, this investigation is the first to evaluate 90-day survival rates with respect to common sepsis infection sites (respiratory, intra-abdominal and primary bloodstream). This study revealed a significantly higher mortality rate among patients with primary bloodstream infections (58%) compared with patients with respiratory and intra-abdominal infections, although all patients were treated according to current guidelines for the treatment of sepsis (Surviving Sepsis Campaign)[6]. Because of this dramatically higher mortality rate among patients with primary bloodstream sepsis, we believe that future sepsis trials should focus on this vulnerable group of high-risk patients. More appropriate interventions and further improvements in prevention and care are urgently needed.

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Primary bacteremia is associated with a higher mortality risk compared with pulmonary and intra-abdominal infections in patients with sepsis: a prospective observational cohort study

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ABSTRACT

Objective: To investigate whether common infection foci (pulmonary, intra-abdominal and primary bacteremia) are associated with variations in mortality risk in sepsis patients.

Design: Prospective, observational cohort study.

Setting: Three surgical intensive care units (ICU) at a university medical center.

Participants: A total of 327 adult Caucasian patients with sepsis originating from pulmonary, intra-abdominal and primary bacteremia participated in this study.

Primary and secondary outcome measures: The patients were followed for 90 days, and mortality risk was recorded as the primary outcome variable. To monitor organ failure, sepsis-related organ failure assessment (SOFA) scores were evaluated at the onset of sepsis and throughout the observational period as secondary outcome variables.

Results: A total of 327 critically ill patients with sepsis were enrolled in this study. Kaplan-Meier survival analysis showed that the 90-day mortality risk was significantly higher among patients with primary bacteremia than among those with pulmonary and intra-abdominal foci (58%, 35% and 32%, respectively; p=0.0208). To exclude the effects of several baseline variables, we performed multivariate Cox regression analysis. Primary bacteremia remained a significant covariate for mortality in the multivariate analysis (hazard ratio, 2.10; 95% CI, 1.14-3.86; p=0.0166). During their stay in the ICU, the patients with primary bacteremia presented significantly higher SOFA scores than those of the patients with pulmonary and intra-abdominal infection foci (8.5±4.7, 7.3±3.4 and 5.8±3.5, respectively). Patients with primary bacteremia presented higher SOFA-renal score compared with the patients with other infection foci (1.6±1.4, 0.8±1.1 and 0.7±1.0, respectively); the primary bacteremia patients required significantly more renal replacement therapy than the patients in the other groups (29%, 11% and 12%, respectively).

Conclusions: These results indicate that sepsis patients with primary bacteremia present a higher mortality risk compared with patients with sepsis of pulmonary or intra-abdominal origins. These results should be assessed in sepsis patients in larger, independent cohorts.

Strengths and limitations of this study

- This is the first study to evaluate mortality risk among sepsis patients with primary bloodstream infections compared with those with respiratory or intra-abdominal infections over an observational period of 90 days.
- The strengths of our study include that it is the first to investigate organ-specific manifestations associated with common sepsis infection sites (respiratory, intra-abdominal and bloodstream) by quantifying SOFA scores and evaluating the requirements for organ support in the ICU.
- One potentially uncontrolled confounder that was not adjusted for is appropriate antibiotic therapy.

INTRODUCTION

Sepsis is defined as a systemic inflammatory response that occurs during severe infection[1-3]. Sepsis affects more than 750,000 patients in the United States each year and remains one of the leading causes of death worldwide[4]. Although the incidence of this major health care problem has been increasing, the implementation of early goal-directed therapy in patients with severe sepsis and septic shock has in part successfully reduced mortality[5]. Guidelines for disease control have been written by the Surviving Sepsis Campaign (SSC), a joint collaboration between the Society of Critical Care Medicine and the European Society of Intensive Care Medicine committed to reducing mortality from severe sepsis and septic shock worldwide[6]. These guidelines contain clear recommendations for improving disease outcomes (e.g., guidelines for resuscitation and recommendations pertaining to infections, including for the use of diagnostics, hemodynamic support and adjunctive therapy and for supportive therapy for severe sepsis)[6].

Respiratory, intra-abdominal, urinary and primary bloodstream infections make up 80% of all infection sites[7]. According to epidemiological data, the lung is the most common site of infection, followed by the abdomen and the blood[2].

Pneumonia, hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP) and subsequent sepsis remain important causes of morbidity and mortality in critically ill patients despite advances in antimicrobial therapy, better supportive care modalities, and a wide range of preventive measures[8-10].

Intra-abdominal infections are a common cause of sepsis. These infections comprise a markedly heterogeneous group of infectious processes that share an anatomical site of origin between the diaphragm and the pelvis[11]. Their clinical course is dictated by a number of infection-related factors, including the microbiology of the infection, the anatomical location,

the degree of localization, and the presence of correctable anatomical derangements involving intra-abdominal viscera[12 13].

Bloodstream infections (BSIs) are a major cause of death due to nosocomial events in intensive care units (ICUs)[14]. Immunosuppression and invasive health care procedures act together to create a high risk of nosocomial BSIs in critically ill patients[15]. The outcomes of BSIs have been the focus of many case-control and cohort studies[15-17]. BSIs lead to poor patient outcomes[16 18], prolonged patient stays in the ICU and in the hospital[16 19 20], and substantial extra medical costs[21 22].

Whether the characteristics of the infection, infection site and pathogenic organism independently affect the outcome in patients with sepsis remains a subject of debate. Whereas previous studies have shown an independent, significant contribution of the infection site and the pathogenic organism to the survival of sepsis patients[23], recent investigations have not found any significant impact of the infection site on mortality among patients with sepsis[24].

This study aimed to explore whether common origins of sepsis infections, in particular respiratory, intra-abdominal and bloodstream infection sites, are associated with changes in the 90-day survival rate among patients with sepsis in a representative university medical center, where patients are treated according to the most recent sepsis guidelines.

MATERIALS AND METHODS

Patients

Adult Caucasian patients admitted to ICUs at the University Medical Center-Goettingen (UMG) between April 2012 and May 2013 were screened daily according to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) criteria for sepsis, severe sepsis, or septic shock[25 26]. This study was approved by the University of Goettingen ethics committee in Goettingen, Germany (1/15/12) and conformed to the ethical principles of the Declaration of Helsinki (Seoul, 2008). For each patient, written, informed consent was obtained from either the patient or his or her legal representative. Patients were enrolled if they presented sepsis of a respiratory, intra-abdominal or primary bloodstream origin. Because interracial genetic differences may affect the clinical course of infectious diseases, we have exclusively recruited Caucasians, who form the majority of patients admitted to our surgical ICUs, into this clinical investigation. Caucasian origin was assessed by questioning the patients, their next of kin or their legal representatives.

Definitions

In this study, patients with sepsis of respiratory origin had hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP). HAP is the most frequent infection in surgical intensive care units and is defined as a pulmonary infection that was not incubating at the time of admission and that occurred at least 48 h after hospital admission[27]. Ventilator-associated pneumonia (VAP) is defined as either a pulmonary infection arising more than 48 h after tracheal intubation with no evidence of pneumonia at the time of intubation or the diagnosis of a new pulmonary infection if the initial ICU admission was due to pneumonia[27].

Typically, patients with intra-abdominal infections in the surgical ICU develop secondary peritonitis as a result of microbial infection of the peritoneal space following perforation,

abscess formation, ischemic necrosis, or a penetrating injury of the intra-abdominal contents[11].

Primary BSI comprises BSI of unknown origin in patients without an identifiable focus of infection, and intravascular catheter-related BSI (catheter, implantable cardioverter-defibrillator or pacemaker related); according to The International Sepsis Forum Consensus Conference on Definitions of Infection in the Intensive Care Unit[11].

Exclusion criteria

As described previously[28 29], the patient exclusion criteria were the following: (1) age less than 18 years; (2) being pregnant or nursing an infant; (3) immunosuppressive therapy (e.g., cyclosporine or azathioprine) or cancer-related chemotherapy; (4) documented or suspected acute myocardial infarction within the previous 6 weeks; (5) a history of New York Heart Association functional class IV chronic heart failure; (6) human immunodeficiency virus infection; (7) a do not resuscitate or do not treat order or the patient and/or his or her legal representative not being committed to aggressive management; (8) not being expected to survive the 28-day observation period or not being likely to be placed on life support because of an uncorrectable medical condition, including a poorly controlled neoplasm or end-stage lung disease; (9) a chronic vegetative state or a similar long-term neurological condition; (10) current participation in any interventional study (of a drug or device); (11) inability to be fully evaluated during the study period; and (12) being a study-site employee or a family member of a study-site employee involved in conducting this study.

Data collection

Patients were followed up for 90 days, and mortality risk was recorded as the primary outcome variable. Sequential Organ Failure Assessment (SOFA)[30] and Acute Physiology and Chronic Health Evaluation (APACHE) II[31] scores were evaluated at the onset of sepsis. Organ function was reassessed over 28 days in the ICU to monitor morbidity as previously described[28]. Organ failure, organ support requirements and the length of ICU stay were recorded as secondary outcome variables. All relevant clinical data were extracted from the electronic patient record system (IntelliSpace Critical Care and Anesthesia (ICCA); Philips Healthcare, Andover, Massachusetts, USA); all medical records, including microbiology reports, can be found in this system. We sought to determine whether patients suffered from preexisting conditions, for example, comorbidities, by examining physicians' notes, administering an anamnestic questionnaire to the patients or their legal representatives and consulting each patient's family doctor.

Statistical analyses

Statistical analyses were performed using Statistica software (version 10; StatSoft, Tulsa, Oklahoma, USA). Based on contingency tables, significance was calculated using two-sided Fisher's exact or chi-square tests, as appropriate. Two continuous variables were compared using the Mann-Whitney test. Time-to-event data were compared using the log-rank test from the Statistica package for Kaplan-Meier survival analysis. For variables identified as significant in univariate survival analyses (respiratory infections, intra-abdominal infections and primary bacteremia), potential confounders (age, gender and BMI) and covariates that varied at baseline (diabetes mellitus (IDDM), history of cancer and "No history of surgery"), we performed multivariate Cox regression analysis to examine survival times. A value of $p<0.05$ was considered statistically significant.

RESULTS

Study population

A total of 327 adult Caucasian patients with sepsis were enrolled in this study. At enrollment, 61% of the patients had a pulmonary infection; 32% suffered from an intra-abdominal infection; and 7% presented with a primary bloodstream infection (Table 1). Patients' ages ranged from 19 to 91 years (median, 65 years). At baseline, patients' SOFA and APACHE II scores, which measure disease severity, were 9.3±4.0 and 21.5±7.3, respectively (Table 1). Comorbidities included hypertension, myocardial infarction history, chronic obstructive pulmonary disease (COPD), renal dysfunction, non-insulin-dependent diabetes mellitus, insulin-dependent diabetes mellitus, chronic liver diseases, history of cancer, and a history of stroke (Table 1). Many patients were discharged before 90 days. We were able to follow all of these patients. If the patient or legal representative could not be reached by telephone or mail, we confidentially contacted the local registry office and inquired whether the patient was still alive (still registered).

Table 1. Patient baseline characteristics with regard to the infection site

	All n=327	Pulmonary n=198	Intra-abdominal n=105	Bloodstream n=24	p-value
Age, mean ± SD	62±15	61±15	65±13	60±16	0.2426
Male, %	67%	70	61	62	0.2614
Body mass index, mean ± SD	27±6	27±7	27±5	29±5	0.0885
SOFA score, mean ± SD	9.3±4.0	9.4±3.6	8.9±4.7	10.5±5.1	0.3099
APACHE II score, mean ± SD	21.5±7.3	21.8±6.8	20.6±8.1	22.8±7.6	0.3538
Organ support, %					
Mechanical ventilation	85	90	74	87	0.0008
Use of vasopressor	64	62	65	70	0.6778
Renal replacement therapy	8	7	9	20	0.0781
Comorbidities, %					
Hypertension	57	55	59	66	0.5395
History of myocardial infarction	8	9	7	8	0.9087
COPD	17	17	17	16	0.9880
Renal dysfunction	11	10	9	25	0.0857
Diabetes mellitus (NIDDM)	9	10	8	8	0.8928
Diabetes mellitus (IDDM)	11	8	11	33	0.0015

Chronic liver diseases	5	3	8	8	0.1538
History of cancer	18	15	30	0	0.0003
History of stroke	6	8	4	0	0.2192
Recent surgical history, %					
Elective surgery	30	27	37	25	0.1730
Emergency surgery	48	45	56	42	0.1401
No history of surgery	21	28	7	33	<0.0001

The data are presented as the means±SDs or percentages. NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus.

Disease severity at the onset of sepsis

No differences in age, gender, or body mass index were found among the three groups of study subjects. Moreover, no differences were found in the SOFA and APACHE II scores with respect to the infection sites at the onset of sepsis. The patients in the group with intra-abdominal infections required significantly less mechanical ventilation compared with the other groups with pulmonary and bloodstream infections (74%, 90% and 87%, respectively). The patients with bloodstream infections suffered significantly more from insulin-dependent diabetes mellitus compared with patients with pulmonary or intra-abdominal infections (33%, 8%, 11%, respectively). In contrast, none of the patients with bloodstream infections had a history of cancer, unlike the patients with pulmonary and intra-abdominal infections (15% and 30%, respectively; Table 1).

Mortality analysis

Kaplan-Meier survival analysis showed that the 90-day mortality risk was significantly higher among patients with primary bacteremia than among those with pulmonary and intra-abdominal foci (58%, 35% and 32%, respectively; Figure 1). Analysis of the 28-day mortality data similarly revealed that the patients with bloodstream infections had a significantly increased risk of death compared with the patients with pulmonary and intra-abdominal infections (50%, 32% and 17%, respectively; Table 2). Moreover, 90-day mortality analysis suggested a higher incidence of death among the patients with bloodstream infections, although this finding was not significant (p=0.0544; Table 2).

Table 2. Disease severity with regard to infection site

	All n=327	Pulmonary n=198	Intra-abdominal n=105	Bloodstream n=24	p-value
SOFA	6.9±3.6	7.3±3.4	5.8±3.5	8.5±4.7	0.0002
SOFA Subscores					
SOFA-Respiratory	1.9±0.7	2.2±0.6	1.5±0.7	1.9±0.9	<0.0001
SOFA-Cardiovascular	1.5±0.9	1.5±0.9	1.3±0.9	1.7±1.2	0.4567
SOFA-Central nervous system	1.8±1.1	2.1±1.0	1.4±1.0	2.0±1.2	<0.0001
SOFA-Renal	0.8±1.1	0.8±1.1	0.7±1.0	1.6±1.4	0.0028
SOFA-Coagulation	0.3±0.5	0.3±0.6	0.2±0.5	0.6±0.8	0.4662
SOFA-Hepatic	0.4±0.7	0.3±0.6	0.5±0.8	0.5±0.6	0.0030
Organ support*, (%):					
Mechanical ventilation		85	62	76	<0.0001
Use of vasopressor		54	45	49	0.8355
Renal replacement therapy		11	12	29	0.0069
Length of stay in ICU (days)	18±15	17±14	20±16	16±13	0.5061
Mortality analysis, (%):					
Death by day 28	94 (28)	64 (32)	18 (17)	12 (50)	0.0012
Death by day 90	118 (36)	70 (35)	34 (32)	14 (58)	0.0544

The data are presented as means±SDs or percentages.
*Based on the total number of observations during the follow-up period.

Multivariate analysis

To exclude the effects of several baseline variables on survival among the three groups being investigated, we performed multivariate Cox regression analysis. Bloodstream infection remained a significant covariate for mortality in the multivariate analysis (hazard ratio, 2.10; 95% CI, 1.14-3.86; p=0.0166; Table 3). This finding indicates that, despite baseline differences in some variables (i.e., IDDM, Cancer and "No history of surgery"), the presence of a primary bloodstream infection remains a prognostic variable with a significant effect on the outcome (90-day survival; Table 3).

Table 3. Cox regression analysis

Infection site	Variable	Hazard ratio	95% CI	p-value
Pulmonary:				
	Age	1.02	1.00-1.03	0.0009
	Gender	1.19	0.80-1.76	0.3803
	BMI	1.00	0.97-1.03	0.7058
	Diabetes mellitus (IDDM)	1.29	0.75-2.19	0.3450
	History of cancer	1.26	0.81-1.95	0.2921
	No history of surgery	1.37	0.87-2.14	0.1634
	Pulmonary infection	1.05	0.72-1.55	0.7675
Intra-abdominal:				
	Age	1.02	1.00-1.03	0.0007
	Gender	1.17	0.79-1.73	0.4302
	BMI	1.00	0.97-1.03	0.6497
	Diabetes mellitus (IDDM)	1.28	0.75-2.16	0.3534
	History of cancer	1.33	0.85-2.06	0.2036
	No history of surgery	1.25	0.80-1.97	0.3209
	Intra-abdominal infection	0.71	0.46-1.08	0.1142
Bloodstream:				
	Age	1.02	1.01-1.03	0.0007
	Gender	1.18	0.80-1.75	0.3956
	BMI	1.00	0.97-1.03	0.7930
	Diabetes mellitus (IDDM)	1.07	0.61-1.88	0.7877
	History of cancer	1.36	0.87-2.12	0.1719
	No history of surgery	1.30	0.84-2.02	0.2290
	Bloodstream infection	2.10	1.14-3.86	0.0166

Disease severity

During the observational period, patients with bloodstream infections presented significantly higher mean SOFA scores compared with patients in the other groups (8.5±4.7, 7.3±3.4 and 5.8±3.5, respectively; Table 2). Four of the six organ-specific SOFA scores (respiratory,

central nervous system (CNS), renal and hepatic) varied significantly among the study groups. The patients with pulmonary infections presented higher SOFA-respiratory scores than did patients with intra-abdominal and bloodstream infections (2.2±0.6, 1.5±0.7 and 1.9±0.9, respectively; Table 2). The patients with pulmonary and bloodstream infections required more mechanical ventilation than patients with intra-abdominal infections (85%, 76% and 62%, respectively; Table 2). Patients with mechanical ventilation usually received lung-protective ventilation (Tidal volume of 6–8 ml/kg predicted body weight) and were treated according to structured weaning protocols of the ICUs. Weaning protocols included daily trials of spontaneous breathing, gradual reduction in pressure support and use of non-invasive mechanical ventilation for extubated patients. The patients with pulmonary and bloodstream infections presented higher SOFA-CNS scores than those of the patients with intra-abdominal infections (2.1±1.0, 2.0±1.2 and 1.4±1.0, respectively; Table 2). Analysis of the SOFA-renal scores indicated that the patients with bloodstream infections presented higher SOFA-renal scores over the study period in the ICU compared with the patients with pulmonary and intra-abdominal infections (1.6±1.4, 0.8±1.1 and 0.7±1.0, respectively; Table 2). These patients also required significantly more renal replacement therapy (29%, 11% and 12%, respectively; Table 2). The SOFA-hepatic score was significantly higher in the patients with intra-abdominal and bloodstream infections compared with the patients with pulmonary infections (0.5±0.8, 0.5±0.6 and 0.3±0.6, respectively; Table 2). Additional results regarding disease severity were added to the supplemental data (see online supplementary data; Table1).

In addition, the gram-negative infection rate was significantly higher among the patients with pulmonary infections (75%) compared with those whose sepsis had intra-abdominal and bloodstream infection origins (57% and 54%, respectively; Table 4). Additional results regarding microbiological findings and anti-infective therapy were added to the supplemental data (see online supplementary data, Table 2 and Table 3; respectively).

Table 4. Infection types over the observational period

Infection site	Pulmonary	Intra-abdominal	Bloodstream	p-value
Infection type				
Gram-negative bacteria	75%	57%	54%	0.0026
Gram-positive bacteria	78%	84%	79%	0.5142
Fungus	52%	76%	42%	<0.0001
Virus	0.08%	0.06%	0.13%	0.4941

Furthermore, septic patients with intra-abdominal infections presented a higher incidence of fungal infections (76%) compared with the patients with pulmonary and bloodstream infections (52% and 42%, respectively; Table 4). In this study, blood cultures and cultures of samples from other sites, such as urine, cerebrospinal fluid, surgical wounds, respiratory secretions, or other body fluids that may be the source of infection, were taken at sepsis onset and over the observational period in the ICU in accordance with clinical judgment, as indicated. The bacteremia findings were only cultural.

Sometimes, infection foci could not be microbiologically verified, especially if the patients were pretreated with antibiotics on normal wards before they were admitted to the ICU.

DISCUSSION

The present study addressed whether common infection sites among patients with sepsis are associated with the survival rate.

The primary endpoint, the mortality risk within 90 days of the onset of sepsis, was higher in patients with primary bloodstream infections compared with those with respiratory or intra-abdominal infections (58%, 35% and 32%, respectively; Fig. 1). Primary bacteremia remained a significant covariate for mortality in the multivariate analysis (Table 3).

According to the SOFA and APACHE II scores, the infection site was not associated with the acute-illness severity at the onset of sepsis (Table 1). We believe that the similarity in SOFA and APACHE II scores at sepsis onset among the three groups can be attributed to the phenotypic heterogeneity of sepsis. This heterogeneity is affected by several factors, including the causative organism of the infection and the amount of time elapsed since the infection began, as well as by individual patient characteristics, such as comorbidities and genetic makeup[28].

The most significant result of this study with respect to 90-day mortality risk was that the mortality rate (58%) was higher among patients with primary bloodstream infections; this result is in agreement with the results of several previous investigations that found similar mortality rates in patients with nosocomial bloodstream infections; e.g., Garrouste-Orgeas et al. found that patients with nosocomial BSI had a mortality rate of 61.5%[14 15]. Our study also goes beyond previous investigations by evaluating a longer-term end point (90 days); this end point was investigated because sepsis patients continue to face an increased risk of mortality, even after ICU and hospital discharge[32].

Severe morbidity, quantified by the SOFA mean score in patients with primary bloodstream infections, resulted in an increased 28-day mortality rate compared with the patients with pulmonary and intra-abdominal infections (50%, 32% and 17%, respectively; Table 2).

The strengths of our study include that it is the first to investigate organ-specific manifestations associated with common sepsis infection sites (respiratory, intra-abdominal and bloodstream) by quantifying SOFA scores and evaluating the requirements for organ support in the ICU (Table 2). The more pronounced types of respiratory failure, which are quantified by the SOFA-respiratory score and the need for mechanical ventilation (Table 2), among patients with pulmonary infections are plausible because these patients frequently present comprised pulmonary function. Patients with primary bacteremia are also at a high risk of respiratory failure due to systemic inflammatory response syndrome, release of pro-inflammatory cytokines (such as tumor necrosis factor (TNF), IL-1 and IL-6,[33]) and recruitment of neutrophils to the lungs, which induces the release of toxic mediators, such as reactive oxygen species and proteases, thus contributing to lung damage and respiratory failure[34].

We believe that the difference in the SOFA-CNS score between the genotypes (with higher scores in the respiratory and the bloodstream groups) occurred because patients in these groups required much more mechanical ventilation, causing them to be treated more frequently with sedating medication, which impacts the CNS and thus affects the SOFA-CNS score.

The observed distinct renal failure among bloodstream infection patients indicated by the SOFA-renal score, which was accompanied by frequent renal replacement therapy (Table 2), was in accordance with former observations indicating that bloodstream infections are associated with a higher incidence of renal failure[35]. The frequent utilization of renal replacement therapy suggests persistent organ dysfunction, which is a well-known contributor to sepsis-related mortality and may explain the higher mortality among bloodstream infection patients observed in our study (Table 2, Figure 1)[36].

The SOFA-hepatic score was higher among patients with intra-abdominal and primary bloodstream infections compared with patients with pulmonary infections (Table 2). This

result can be attributed to the fact that Kupffer cells release several cytokines able to induce hepatocellular dysfunction in response to endotoxemia in patients with bloodstream infections[37].

There are some limitations to this study, along with potential confounding. One limitation to this study is the possibility of selection bias; for example, the patients in this study may have had a higher mortality rate in general than septic patients in other ICUs (e.g., in secondary medical care centers) because patients admitted to our surgical ICUs frequently had more severe coexisting diseases than did patients in other ICUs (non-tertiary care center ICUs). A second potential limitation to this study is measurement bias. For example, many clinical parameters (e.g., blood pressure, heart rate, and respiratory frequency) were registered automatically in the electronic patient record system, and we cannot guarantee that all registered clinical parameters were always correct because of potential measurement errors. However, we did check all clinical records for plausibility before conducting our statistical analysis. Finally, one uncontrolled confounder that was not adjusted for is appropriate antibiotic therapy; although patients with clinical signs of infection were routinely promptly given antibiotic therapy, data regarding the exact times at which patients received antibiotic doses after sepsis onset are unavailable.

To the best of our knowledge, this investigation is the first to evaluate 90-day survival rates with respect to common sepsis infection sites (respiratory, intra-abdominal and primary bloodstream). This study revealed a significantly higher mortality rate among patients with primary bloodstream infections (58%) compared with patients with respiratory and intra-abdominal infections, although all patients were treated according to current guidelines for the treatment of sepsis (Surviving Sepsis Campaign)[6]. Because of this dramatically higher mortality rate among patients with primary bloodstream sepsis, we believe that future sepsis trials should focus on this vulnerable group of high-risk patients. More appropriate interventions and further improvements in prevention and care are urgently needed.

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Contributors All authors contributed to the study design, data acquisition (clinical and experimental), or the analysis and interpretation of data. Specifically, YK collected clinical data and participated in the statistical analysis and interpretation of the data. AP, JE, MG and MB contributed to the study design, supervised patient enrollment and clinical data monitoring and interpreted data. TB contributed to the study design and conception and performed and approved the statistical analyses. AM and JH designed the study, supervised the sample and data collection, interpreted the data and drafted the manuscript. All authors were involved either in writing or revising the manuscript. All authors have approved the final version of the manuscript.

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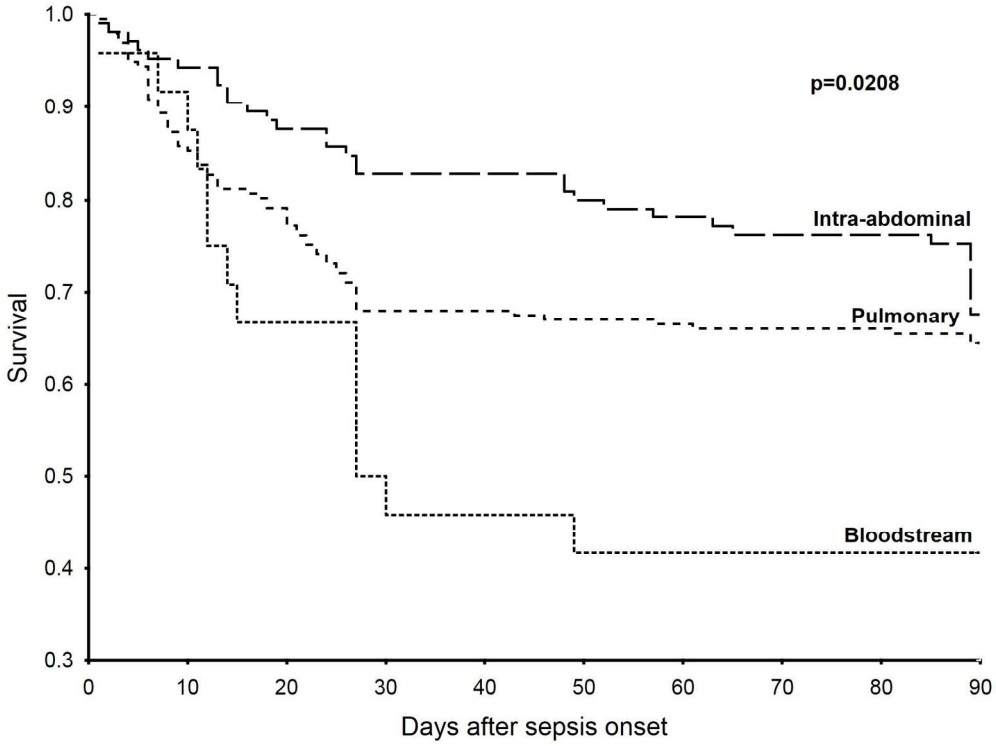

Figure 1. Kaplan-Meier survival analysis
The Kaplan-Meier curve shows the survival curves until day 90 for the three infection site groups. The mortality risk among the patients under study was higher among the patients with bloodstream infections compared with those in the pulmonary and intra-abdominal infection groups (p=0.0208, log-rank test).
165x123mm (300 x 300 DPI)

Primary bacteremia is associated with a higher mortality risk compared with pulmonary and intra-abdominal infections in patients with sepsis: a prospective observational cohort study

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ABSTRACT

Objective: To investigate whether common infection foci (pulmonary, intra-abdominal and primary bacteremia) are associated with variations in mortality risk in sepsis patients.

Design: Prospective, observational cohort study.

Setting: Three surgical intensive care units (ICU) at a university medical center.

Participants: A total of 327 adult Caucasian patients with sepsis originating from pulmonary, intra-abdominal and primary bacteremia participated in this study.

Primary and secondary outcome measures: The patients were followed for 90 days, and mortality risk was recorded as the primary outcome variable. To monitor organ failure, sepsis-related organ failure assessment (SOFA) scores were evaluated at the onset of sepsis and throughout the observational period as secondary outcome variables.

Results: A total of 327 critically ill patients with sepsis were enrolled in this study. Kaplan-Meier survival analysis showed that the 90-day mortality risk was significantly higher among patients with primary bacteremia than among those with pulmonary and intra-abdominal foci (58%, 35% and 32%, respectively; p=0.0208). To exclude the effects of several baseline variables, we performed multivariate Cox regression analysis. Primary bacteremia remained a significant covariate for mortality in the multivariate analysis (hazard ratio, 2.10; 95% CI, 1.14-3.86; p=0.0166). During their stay in the ICU, the patients with primary bacteremia presented significantly higher SOFA scores than those of the patients with pulmonary and intra-abdominal infection foci (8.5±4.7, 7.3±3.4 and 5.8±3.5, respectively). Patients with primary bacteremia presented higher SOFA-renal score compared with the patients with other infection foci (1.6±1.4, 0.8±1.1 and 0.7±1.0, respectively); the primary bacteremia patients required significantly more renal replacement therapy than the patients in the other groups (29%, 11% and 12%, respectively).

Conclusions: These results indicate that sepsis patients with primary bacteremia present a higher mortality risk compared with patients with sepsis of pulmonary or intra-abdominal origins. These results should be assessed in sepsis patients in larger, independent cohorts.

Strengths and limitations of this study

- This is the first study to evaluate mortality risk among sepsis patients with primary bloodstream infections compared with those with respiratory or intra-abdominal infections over an observational period of 90 days.
- The strengths of our study include that it is the first to investigate organ-specific manifestations associated with common sepsis infection sites (respiratory, intra-abdominal and bloodstream) by quantifying SOFA scores and evaluating the requirements for organ support in the ICU.
- One potentially uncontrolled confounder that was not adjusted for is appropriate antibiotic therapy.

INTRODUCTION

Sepsis is defined as a systemic inflammatory response that occurs during severe infection[1-3]. Sepsis affects more than 750,000 patients in the United States each year and remains one of the leading causes of death worldwide[4]. Although the incidence of this major health care problem has been increasing, the implementation of early goal-directed therapy in patients with severe sepsis and septic shock has in part successfully reduced mortality[5]. Guidelines for disease control have been written by the Surviving Sepsis Campaign (SSC), a joint collaboration between the Society of Critical Care Medicine and the European Society of Intensive Care Medicine committed to reducing mortality from severe sepsis and septic shock worldwide[6]. These guidelines contain clear recommendations for improving disease outcomes (e.g., guidelines for resuscitation and recommendations pertaining to infections, including for the use of diagnostics, hemodynamic support and adjunctive therapy and for supportive therapy for severe sepsis)[6].

Respiratory, intra-abdominal, urinary and primary bloodstream infections make up 80% of all infection sites[7]. According to epidemiological data, the lung is the most common site of infection, followed by the abdomen and the blood[2].

Pneumonia, hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP) and subsequent sepsis remain important causes of morbidity and mortality in critically ill patients despite advances in antimicrobial therapy, better supportive care modalities, and a wide range of preventive measures[8-10].

Intra-abdominal infections are a common cause of sepsis. These infections comprise a markedly heterogeneous group of infectious processes that share an anatomical site of origin between the diaphragm and the pelvis[11]. Their clinical course is dictated by a number of infection-related factors, including the microbiology of the infection, the anatomical location,

the degree of localization, and the presence of correctable anatomical derangements involving intra-abdominal viscera[12 13].

Bloodstream infections (BSIs) are a major cause of death due to nosocomial events in intensive care units (ICUs)[14]. Immunosuppression and invasive health care procedures act together to create a high risk of nosocomial BSIs in critically ill patients[15]. The outcomes of BSIs have been the focus of many case-control and cohort studies[15-17]. BSIs lead to poor patient outcomes[16 18], prolonged patient stays in the ICU and in the hospital[16 19 20], and substantial extra medical costs[21 22].

Whether the characteristics of the infection, infection site and pathogenic organism independently affect the outcome in patients with sepsis remains a subject of debate. Whereas previous studies have shown an independent, significant contribution of the infection site and the pathogenic organism to the survival of sepsis patients[23], recent investigations have not found any significant impact of the infection site on mortality among patients with sepsis[24].

This study aimed to explore whether common origins of sepsis infections, in particular respiratory, intra-abdominal and bloodstream infection sites, are associated with changes in the 90-day survival rate among patients with sepsis in a representative university medical center, where patients are treated according to the most recent sepsis guidelines.

MATERIALS AND METHODS

Patients

Adult Caucasian patients admitted to ICUs at the University Medical Center-Goettingen (UMG) between April 2012 and May 2013 were screened daily according to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) criteria for sepsis, severe sepsis, or septic shock[25 26]. This study was approved by the University of Goettingen ethics committee in Goettingen, Germany (1/15/12) and conformed to the ethical principles of the Declaration of Helsinki (Seoul, 2008). For each patient, written, informed consent was obtained from either the patient or his or her legal representative. Patients were enrolled if they presented sepsis of a respiratory, intra-abdominal or primary bloodstream origin. Because interracial genetic differences may affect the clinical course of infectious diseases, we have exclusively recruited Caucasians, who form the majority of patients admitted to our surgical ICUs, into this clinical investigation. Caucasian origin was assessed by questioning the patients, their next of kin or their legal representatives.

Definitions

In this study, patients with sepsis of respiratory origin had hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP). HAP is the most frequent infection in surgical intensive care units and is defined as a pulmonary infection that was not incubating at the time of admission and that occurred at least 48 h after hospital admission[27]. Ventilator-associated pneumonia (VAP) is defined as either a pulmonary infection arising more than 48 h after tracheal intubation with no evidence of pneumonia at the time of intubation or the diagnosis of a new pulmonary infection if the initial ICU admission was due to pneumonia[27].

Typically, patients with intra-abdominal infections in the surgical ICU develop secondary peritonitis as a result of microbial infection of the peritoneal space following perforation,

abscess formation, ischemic necrosis, or a penetrating injury of the intra-abdominal contents[11].

Primary BSI comprises BSI of unknown origin in patients without an identifiable focus of infection, and intravascular catheter-related BSI (catheter, implantable cardioverter-defibrillator or pacemaker related); according to The International Sepsis Forum Consensus Conference on Definitions of Infection in the Intensive Care Unit[11].

Exclusion criteria

As described previously[28 29], the patient exclusion criteria were the following: (1) age less than 18 years; (2) being pregnant or nursing an infant; (3) immunosuppressive therapy (e.g., cyclosporine or azathioprine) or cancer-related chemotherapy; (4) documented or suspected acute myocardial infarction within the previous 6 weeks; (5) a history of New York Heart Association functional class IV chronic heart failure; (6) human immunodeficiency virus infection; (7) a do not resuscitate or do not treat order or the patient and/or his or her legal representative not being committed to aggressive management; (8) not being expected to survive the 28-day observation period or not being likely to be placed on life support because of an uncorrectable medical condition, including a poorly controlled neoplasm or end-stage lung disease; (9) a chronic vegetative state or a similar long-term neurological condition; (10) current participation in any interventional study (of a drug or device); (11) inability to be fully evaluated during the study period; and (12) being a study-site employee or a family member of a study-site employee involved in conducting this study.

Data collection

Patients were followed up for 90 days, and mortality risk was recorded as the primary outcome variable. Sequential Organ Failure Assessment (SOFA)[30] and Acute Physiology and Chronic Health Evaluation (APACHE) II[31] scores were evaluated at the onset of sepsis. Organ function was reassessed over 28 days in the ICU to monitor morbidity as previously described[28]. Organ failure, organ support requirements and the length of ICU stay were recorded as secondary outcome variables. All relevant clinical data were extracted from the electronic patient record system (IntelliSpace Critical Care and Anesthesia (ICCA); Philips Healthcare, Andover, Massachusetts, USA); all medical records, including microbiology reports, can be found in this system. We sought to determine whether patients suffered from preexisting conditions, for example, comorbidities, by examining physicians' notes, administering an anamnestic questionnaire to the patients or their legal representatives and consulting each patient's family doctor.

Statistical analyses

Statistical analyses were performed using Statistica software (version 10; StatSoft, Tulsa, Oklahoma, USA). Based on contingency tables, significance was calculated using two-sided Fisher's exact or chi-square tests, as appropriate. Two continuous variables were compared using the Mann-Whitney test. Time-to-event data were compared using the log-rank test from the Statistica package for Kaplan-Meier survival analysis. For variables identified as significant in univariate survival analyses (respiratory infections, intra-abdominal infections and primary bacteremia), potential confounders (age, gender and BMI) and covariates that varied at baseline (diabetes mellitus (IDDM), history of cancer and "No history of surgery"), we performed multivariate Cox regression analysis to examine survival times. A value of $p<0.05$ was considered statistically significant.

RESULTS

Study population

A total of 327 adult Caucasian patients with sepsis were enrolled in this study. At enrollment, 61% of the patients had a pulmonary infection; 32% suffered from an intra-abdominal infection; and 7% presented with a primary bloodstream infection (Table 1). Patients' ages ranged from 19 to 91 years (median, 65 years). At baseline, patients' SOFA and APACHE II scores, which measure disease severity, were 9.3±4.0 and 21.5±7.3, respectively (Table 1). Comorbidities included hypertension, myocardial infarction history, chronic obstructive pulmonary disease (COPD), renal dysfunction, non-insulin-dependent diabetes mellitus, insulin-dependent diabetes mellitus, chronic liver diseases, history of cancer, and a history of stroke (Table 1). Many patients were discharged before 90 days. We were able to follow all of these patients. If the patient or legal representative could not be reached by telephone or mail, we confidentially contacted the local registry office and inquired whether the patient was still alive (still registered).

Table 1. Patient baseline characteristics with regard to the infection site

	All n=327	Pulmonary n=198	Intra-abdominal n=105	Bloodstream n=24	p-value
Age, mean ± SD	62±15	61±15	65±13	60±16	0.2426
Male, %	67%	70	61	62	0.2614
Body mass index, mean ± SD	27±6	27±7	27±5	29±5	0.0885
SOFA score, mean ± SD	9.3±4.0	9.4±3.6	8.9±4.7	10.5±5.1	0.3099
APACHE II score, mean ± SD	21.5±7.3	21.8±6.8	20.6±8.1	22.8±7.6	0.3538
Organ support, %					
Mechanical ventilation	85	90	74	87	0.0008
Use of vasopressor	64	62	65	70	0.6778
Renal replacement therapy	8	7	9	20	0.0781
Comorbidities, %					
Hypertension	57	55	59	66	0.5395
History of myocardial infarction	8	9	7	8	0.9087
COPD	17	17	17	16	0.9880
Renal dysfunction	11	10	9	25	0.0857
Diabetes mellitus (NIDDM)	9	10	8	8	0.8928
Diabetes mellitus (IDDM)	11	8	11	33	0.0015

Chronic liver diseases	5	3	8	8	0.1538
History of cancer	18	15	30	0	0.0003
History of stroke	6	8	4	0	0.2192
Recent surgical history, %					
Elective surgery	30	27	37	25	0.1730
Emergency surgery	48	45	56	42	0.1401
No history of surgery	21	28	7	33	<0.0001

The data are presented as the means±SDs or percentages. NIDDM, noninsulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus.

Disease severity at the onset of sepsis

No differences in age, gender, or body mass index were found among the three groups of study subjects. Moreover, no differences were found in the SOFA and APACHE II scores with respect to the infection sites at the onset of sepsis. The patients in the group with intra-abdominal infections required significantly less mechanical ventilation compared with the other groups with pulmonary and bloodstream infections (74%, 90% and 87%, respectively). The patients with bloodstream infections suffered significantly more from insulin-dependent diabetes mellitus compared with patients with pulmonary or intra-abdominal infections (33%, 8%, 11%, respectively). In contrast, none of the patients with bloodstream infections had a history of cancer, unlike the patients with pulmonary and intra-abdominal infections (15% and 30%, respectively; Table 1).

Mortality analysis

Kaplan-Meier survival analysis showed that the 90-day mortality risk was significantly higher among patients with primary bacteremia than among those with pulmonary and intra-abdominal foci (58%, 35% and 32%, respectively; Figure 1). Analysis of the 28-day mortality data similarly revealed that the patients with bloodstream infections had a significantly increased risk of death compared with the patients with pulmonary and intra-abdominal infections (50%, 32% and 17%, respectively; Table 2). Moreover, 90-day mortality analysis suggested a higher incidence of death among the patients with bloodstream infections, although this finding was not significant (p=0.0544; Table 2).

Table 2. Disease severity with regard to infection site

	All n=327	Pulmonary n=198	Intra-abdominal n=105	Bloodstream n=24	p-value
SOFA	6.9±3.6	7.3±3.4	5.8±3.5	8.5±4.7	0.0002
SOFA Subscores					
SOFA-Respiratory	1.9±0.7	2.2±0.6	1.5±0.7	1.9±0.9	<0.0001
SOFA-Cardiovascular	1.5±0.9	1.5±0.9	1.3±0.9	1.7±1.2	0.4567
SOFA-Central nervous system	1.8±1.1	2.1±1.0	1.4±1.0	2.0±1.2	<0.0001
SOFA-Renal	0.8±1.1	0.8±1.1	0.7±1.0	1.6±1.4	0.0028
SOFA-Coagulation	0.3±0.5	0.3±0.6	0.2±0.5	0.6±0.8	0.4662
SOFA-Hepatic	0.4±0.7	0.3±0.6	0.5±0.8	0.5±0.6	0.0030
Organ support*, (%):					
Mechanical ventilation		85	62	76	<0.0001
Use of vasopressor		54	45	49	0.8355
Renal replacement therapy		11	12	29	0.0069
Length of stay in ICU (days)	18±15	17±14	20±16	16±13	0.5061
Mortality analysis, (%):					
Death by day 28	94 (28)	64 (32)	18 (17)	12 (50)	0.0012
Death by day 90	118 (36)	70 (35)	34 (32)	14 (58)	0.0544

The data are presented as means±SDs or percentages.
*Based on the total number of observations during the follow-up period.

Multivariate analysis

To exclude the effects of several baseline variables on survival among the three groups being investigated, we performed multivariate Cox regression analysis. Bloodstream infection remained a significant covariate for mortality in the multivariate analysis (hazard ratio, 2.10; 95% CI, 1.14-3.86; p=0.0166; Table 3). This finding indicates that, despite baseline differences in some variables (i.e., IDDM, Cancer and "No history of surgery"), the presence of a primary bloodstream infection remains a prognostic variable with a significant effect on the outcome (90-day survival; Table 3).

Table 3. Cox regression analysis

Infection site	Variable	Hazard ratio	95% CI	p-value
Pulmonary:				
	Age	1.02	1.00-1.03	0.0009
	Gender	1.19	0.80-1.76	0.3803
	BMI	1.00	0.97-1.03	0.7058
	Diabetes mellitus (IDDM)	1.29	0.75-2.19	0.3450
	History of cancer	1.26	0.81-1.95	0.2921
	No history of surgery	1.37	0.87-2.14	0.1634
	Pulmonary infection	1.05	0.72-1.55	0.7675
Intra-abdominal:				
	Age	1.02	1.00-1.03	0.0007
	Gender	1.17	0.79-1.73	0.4302
	BMI	1.00	0.97-1.03	0.6497
	Diabetes mellitus (IDDM)	1.28	0.75-2.16	0.3534
	History of cancer	1.33	0.85-2.06	0.2036
	No history of surgery	1.25	0.80-1.97	0.3209
	Intra-abdominal infection	0.71	0.46-1.08	0.1142
Bloodstream:				
	Age	1.02	1.01-1.03	0.0007
	Gender	1.18	0.80-1.75	0.3956
	BMI	1.00	0.97-1.03	0.7930
	Diabetes mellitus (IDDM)	1.07	0.61-1.88	0.7877
	History of cancer	1.36	0.87-2.12	0.1719
	No history of surgery	1.30	0.84-2.02	0.2290
	Bloodstream infection	2.10	1.14-3.86	0.0166

Disease severity

During the observational period, patients with bloodstream infections presented significantly higher mean SOFA scores compared with patients in the other groups (8.5±4.7, 7.3±3.4 and 5.8±3.5, respectively; Table 2). Four of the six organ-specific SOFA scores (respiratory,

central nervous system (CNS), renal and hepatic) varied significantly among the study groups. The patients with pulmonary infections presented higher SOFA-respiratory scores than did patients with intra-abdominal and bloodstream infections (2.2±0.6, 1.5±0.7 and 1.9±0.9, respectively; Table 2). The patients with pulmonary and bloodstream infections required more mechanical ventilation than patients with intra-abdominal infections (85%, 76% and 62%, respectively; Table 2). Patients with mechanical ventilation usually received lung-protective ventilation (Tidal volume of 6–8 ml/kg predicted body weight) and were treated according to structured weaning protocols of the ICUs. Weaning protocols included daily trials of spontaneous breathing, gradual reduction in pressure support and use of non-invasive mechanical ventilation for extubated patients. The patients with pulmonary and bloodstream infections presented higher SOFA-CNS scores than those of the patients with intra-abdominal infections (2.1±1.0, 2.0±1.2 and 1.4±1.0, respectively; Table 2). Analysis of the SOFA-renal scores indicated that the patients with bloodstream infections presented higher SOFA-renal scores over the study period in the ICU compared with the patients with pulmonary and intra-abdominal infections (1.6±1.4, 0.8±1.1 and 0.7±1.0, respectively; Table 2). These patients also required significantly more renal replacement therapy (29%, 11% and 12%, respectively; Table 2). The SOFA-hepatic score was significantly higher in the patients with intra-abdominal and bloodstream infections compared with the patients with pulmonary infections (0.5±0.8, 0.5±0.6 and 0.3±0.6, respectively; Table 2). Additional results regarding disease severity were added to the supplemental data (see online supplementary data; Table1).

In addition, the gram-negative infection rate was significantly higher among the patients with pulmonary infections (75%) compared with those whose sepsis had intra-abdominal and bloodstream infection origins (57% and 54%, respectively; Table 4). Additional results regarding microbiological findings and anti-infective therapy were added to the supplemental data (see online supplementary data, Table 2 and Table 3; respectively).

Table 4. Infection types over the observational period

Infection site	Pulmonary	Intra-abdominal	Bloodstream	p-value
Infection type				
Gram-negative bacteria	75%	57%	54%	0.0026
Gram-positive bacteria	78%	84%	79%	0.5142
Fungus	52%	76%	42%	<0.0001
Virus	0.08%	0.06%	0.13%	0.4941

Furthermore, septic patients with intra-abdominal infections presented a higher incidence of fungal infections (76%) compared with the patients with pulmonary and bloodstream infections (52% and 42%, respectively; Table 4). In this study, blood cultures and cultures of samples from other sites, such as urine, cerebrospinal fluid, surgical wounds, respiratory secretions, or other body fluids that may be the source of infection, were taken at sepsis onset and over the observational period in the ICU in accordance with clinical judgment, as indicated. The bacteremia findings were only cultural.

Sometimes, infection foci could not be microbiologically verified, especially if the patients were pretreated with antibiotics on normal wards before they were admitted to the ICU.

DISCUSSION

The present study addressed whether common infection sites among patients with sepsis are associated with the survival rate.

The primary endpoint, the mortality risk within 90 days of the onset of sepsis, was higher in patients with primary bloodstream infections compared with those with respiratory or intra-abdominal infections (58%, 35% and 32%, respectively; Fig. 1). Primary bacteremia remained a significant covariate for mortality in the multivariate analysis (Table 3).

According to the SOFA and APACHE II scores, the infection site was not associated with the acute-illness severity at the onset of sepsis (Table 1). We believe that the similarity in SOFA and APACHE II scores at sepsis onset among the three groups can be attributed to the phenotypic heterogeneity of sepsis. This heterogeneity is affected by several factors, including the causative organism of the infection and the amount of time elapsed since the infection began, as well as by individual patient characteristics, such as comorbidities and genetic makeup[28].

The most significant result of this study with respect to 90-day mortality risk was that the mortality rate (58%) was higher among patients with primary bloodstream infections; this result is in agreement with the results of several previous investigations that found similar mortality rates in patients with nosocomial bloodstream infections; e.g., Garrouste-Orgeas et al. found that patients with nosocomial BSI had a mortality rate of 61.5%[14 15]. Our study also goes beyond previous investigations by evaluating a longer-term end point (90 days); this end point was investigated because sepsis patients continue to face an increased risk of mortality, even after ICU and hospital discharge[32].

Severe morbidity, quantified by the SOFA mean score in patients with primary bloodstream infections, resulted in an increased 28-day mortality rate compared with the patients with pulmonary and intra-abdominal infections (50%, 32% and 17%, respectively; Table 2).

The strengths of our study include that it is the first to investigate organ-specific manifestations associated with common sepsis infection sites (respiratory, intra-abdominal and bloodstream) by quantifying SOFA scores and evaluating the requirements for organ support in the ICU (Table 2). The more pronounced types of respiratory failure, which are quantified by the SOFA-respiratory score and the need for mechanical ventilation (Table 2), among patients with pulmonary infections are plausible because these patients frequently present comprised pulmonary function. Patients with primary bacteremia are also at a high risk of respiratory failure due to systemic inflammatory response syndrome, release of pro-inflammatory cytokines (such as tumor necrosis factor (TNF), IL-1 and IL-6,[33]) and recruitment of neutrophils to the lungs, which induces the release of toxic mediators, such as reactive oxygen species and proteases, thus contributing to lung damage and respiratory failure[34].

We believe that the difference in the SOFA-CNS score between the genotypes (with higher scores in the respiratory and the bloodstream groups) occurred because patients in these groups required much more mechanical ventilation, causing them to be treated more frequently with sedating medication, which impacts the CNS and thus affects the SOFA-CNS score.

The observed distinct renal failure among bloodstream infection patients indicated by the SOFA-renal score, which was accompanied by frequent renal replacement therapy (Table 2), was in accordance with former observations indicating that bloodstream infections are associated with a higher incidence of renal failure[35]. The frequent utilization of renal replacement therapy suggests persistent organ dysfunction, which is a well-known contributor to sepsis-related mortality and may explain the higher mortality among bloodstream infection patients observed in our study (Table 2, Figure 1)[36].

The SOFA-hepatic score was higher among patients with intra-abdominal and primary bloodstream infections compared with patients with pulmonary infections (Table 2). This

result can be attributed to the fact that Kupffer cells release several cytokines able to induce hepatocellular dysfunction in response to endotoxemia in patients with bloodstream infections[37].

There are some limitations to this study, along with potential confounding. One limitation to this study is the possibility of selection bias; for example, the patients in this study may have had a higher mortality rate in general than septic patients in other ICUs (e.g., in secondary medical care centers) because patients admitted to our surgical ICUs frequently had more severe coexisting diseases than did patients in other ICUs (non-tertiary care center ICUs). A second potential limitation to this study is measurement bias. For example, many clinical parameters (e.g., blood pressure, heart rate, and respiratory frequency) were registered automatically in the electronic patient record system, and we cannot guarantee that all registered clinical parameters were always correct because of potential measurement errors. However, we did check all clinical records for plausibility before conducting our statistical analysis. Finally, one uncontrolled confounder that was not adjusted for is appropriate antibiotic therapy; although patients with clinical signs of infection were routinely promptly given antibiotic therapy, data regarding the exact times at which patients received antibiotic doses after sepsis onset are unavailable.

To the best of our knowledge, this investigation is the first to evaluate 90-day survival rates with respect to common sepsis infection sites (respiratory, intra-abdominal and primary bloodstream). This study revealed a significantly higher mortality rate among patients with primary bloodstream infections (58%) compared with patients with respiratory and intra-abdominal infections, although all patients were treated according to current guidelines for the treatment of sepsis (Surviving Sepsis Campaign)[6]. Because of this dramatically higher mortality rate among patients with primary bloodstream sepsis, we believe that future sepsis trials should focus on this vulnerable group of high-risk patients. More appropriate interventions and further improvements in prevention and care are urgently needed.

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Supplementary Data; Table 1: Vital parameters, laboratory parameters, kidney parameters and inflammation values

	All n=327	Pulmonary n=198	Intra-abdominal n=105	Bloodstream n=24	P value
vital parameters, mean ± SD					
Temperature (°C), max	37.9±0.5	38.0±0.5	37.7±0.4	37.8±0.6	0.0032
Temperature (°C), min	36.8±0.5	36.9±0.4	36.7±0.5	36.6±0.6	0.0054
Heart rate (bpm), max	103±12	103±12	103±11	102±15	0.5067
Heart rate (bpm), min	72±11	72±11	74±11	73±12	0.4774
MAP (mmHg), max	100±11	101±12	99±10	94±15	0.0781
MAP (mmHg), min	66±9	66±9	67±8	62±9	0.0243
Vasopressor (µg/kg/min) (n)	10±9 (247)	10±9 (147)	10±7 (83)	10±9 (17)	0.2268
laboratory parameters, mean ± SD					
Lactate (mmol/l)	1.7±1.1	1.6±1.0	1.7±1.1	2.0±1.2	0.1278
Thrombocytes (1000/µl)	295±148	281±133	329±168	257±154	0.0344
Quick (%) (n)	83±16 (325)	83±16 (196)	84±17 (105)	77±16 (24)	0.1528
kidney values					
Urine output (ml/day)	3055±1406	2900±1281	3555±1443	2144±1535	<0.0001
Urine output (ml/kg/h)	1.6±0.8	1.5±0.8	1.8±0.8	0.9±0.6	<0.0001
Creatinine (mg/dl)	1.3±0.9	1.3±0.9	1.2±1.0	1.6±1.0	0.0148
inflammatory values					
Leukocytes (1000/µl)	13±5	12±4	15±5	14±5	0.0001
CRP (mg/l) (n)	150±85 (175)	141±97 (70)	154±69 (90)	168±107 (15)	0.2159
Procalcitonin (ng/dl) (n)	4.8±12.0 (280)	3.3±9.7 (176)	7.4±15.6 (81)	7.1±11.3 (23)	<0.0001

CRP=C-reactive protein; MAP=Mean arterial pressure; The data are presented as the mean±SD or percentages. Min and Max indicate the lowest/highest value that has been recorded daily within the observation period.

Supplementary Data; Table 2. Recorded microbiological findings

	All n=327	Pulmonary n=198	Intra-abdominal n=105	Bloodstream n=24
Bacteria				
Gram-negative, n (%)				
Acinetobacter genomospecies 3	2 (0.6)	2 (1.0)	0 (0.0)	0 (0.0)
Bacteroides fragilis	11 (3.4)	0 (0.0)	11 (10.5)	0 (0.0)
Bacteroides ovaters	2 (0.6)	1 (0.5)	1 (1.0)	0 (0.0)
Bacteroides species	3 (0.9)	0 (0.0)	3 (2.9)	0 (0.0)
Bacteroides thetaiotaomicron	4 (1.2)	1 (0.5)	3 (2.9)	0 (0.0)
Bacteroides uniformis	4 (1.2)	0 (0.0)	4 (3.8)	0 (0.0)
Chlamydia pneumoniae IgA	6 (1.8)	6 (3.0)	0 (0.0)	0 (0.0)
Chlamydia pneumoniae lgG	2 (0.6)	1 (0.5)	0 (0.0)	1 (4.2)
Chlamydophila pneumoniae	2 (0.6)	2 (1.0)	0 (0.0)	0 (0.0)
Citobacter braakii	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
Citrobacter freundii	3 (0.9)	2 (1.0)	1 (1.0)	0 (0.0)
Citrobacter koseri	2 (0.6)	1 (0.5)	1 (1.0)	0 (0.0)
Enterobacter aerogenes	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Enterobacter asburiae	2 (0.6)	1 (0.5)	1 (1.0)	0 (0.0)
Enterobacter cloacae	22 (6.7)	14 (7.0)	5 (4.8)	3 (12.5)
ESBL E.coli	5 (1.5)	2 (1.0)	2 (1.9)	1 (4.2)
Escherichia coli	53 (16.2)	35 (17.7)	15 (14.3)	3 (12.5)
Haemophilus influenza	12 (3.7)	12 (6.1)	0 (0.0)	0 (0.0)
Haemophilus parainfluenzae	3 (0.9)	2 (1.0)	1 (1.0)	0 (0.0)
Hafnia alvei	2 (0.6)	2 (1.0)	0 (0.0)	0 (0.0)
Klebsiella oxytoca	8 (2.5)	8 (4.0)	0 (0.0)	0 (0.0)
Klebsiella pneumoniae	13 (4.0)	10 (5.1)	3 (2.9)	0 (0.0)
Morgonella morganii	3 (0.9)	3 (1.5)	0 (0.0)	0 (0.0)
Pantoea agglomerans	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Proteus mirabilis	9 (2.8)	8 (4.0)	1 (1.0)	0 (0.0)
Proteus species	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Proteus vulgaris	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
Pseudomonas aeruginosa	26 (8.0)	20 (10.1)	5 (4.8)	1 (4.2)
Pseudomonas korrensis	1 (0.3)	0 (0.0)	0 (0.0)	1 (4.2)
Serratia marcescens	8 (2.5)	7 (3.5)	0 (0.0)	1 (4.2)
Serratia ureilytica	1 (0.3)	0 (0.0)	0 (0.0)	1 (4.2)
Stenotrophomonas maltophila	5 (1.5)	3 (1.5)	1 (1.0)	1 (4.2)
Gram-positive, n (%)				
Aerococcus urinae	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Clostridium difficile	5 (1.5)	1 (0.5)	3 (2.9)	1 (4.2)
Clostridium innocuum	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
Clostridium perfringens	3 (0.9)	0 (0.0)	3 (2.9)	0 (0.0)
Enterococcus avium	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
Enterococcus casseliflavus	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
Enterococcus faecalis	33 (10.1)	10 (5.1)	23 (21.9)	0 (0.0)
Enterococcus faecium	35 (10.7)	4 (2.0)	27 (25.7)	4 (16.7)

Enterococcus mundtii	1 (0.3)	0 (0.0)	0 (0.0)	1 (4.2)
Enterococcus species	29 (8.9)	25 (12.6)	3 (2.9)	1 (4.2)
Coagulase negative Staphylococci	12 (3.7)	8 (4.0)	3 (2.9)	1 (4.2)
Lactobacillus paracasei	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
MRSA	6 (1.8)	5 (2.5)	0 (0.0)	1 (4.2)
Peptostreptococcus species	2 (0.6)	1 (0.5)	1 (1.0)	0 (0.0)
Rothia mucilaginosa	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Staphyloccocus aureus	52 (15.9)	47 (23.7)	1 (1.0)	4 (16.7)
Staphylococcus capitis	7 (2.1)	5 (2.5)	1 (1.0)	1 (4.2)
Staphylococcus epidermidis	36 (11.0)	24 (12.1)	9 (8.6)	3 (12.5)
Staphylococcus haemolyticus	2 (0.6)	2 (1.0)	0 (0.0)	0 (0.0)
Staphylococcus hominis	4 (1.2)	3 (1.5)	1 (1.0)	0 (0.0)
Staphylococcus wameri	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Streptococcus agalactiae	4 (1.2)	3 (1.5)	1 (1.0)	0 (0.0)
Streptococcus anginosus	3 (0.9)	0 (0.0)	2 (1.9)	1 (4.2)
Streptococcus constellatus	5 (1.5)	3 (1.5)	2 (1.9)	0 (0.0)
Streptococcus pneumonia	4 (1.2)	4 (2.0)	0 (0.0)	0 (0.0)
Streptococcus viridans	2 (0.6)	1 (0.5)	0 (0.0)	1 (4.2)
Fungi, n (%)				
Aspergillus flavus	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Aspergillus fumigatus	3 (0.9)	1 (0.5)	1 (1.0)	1 (4.2)
Candida albicans	110 (33.6)	67 (33.8)	38 (36.2)	5 (20.8)
Candida dubliniensis	3 (0.9)	2 (1.0)	1 (1.0)	0 (0.0)
Candida glabrata	25 (7.7)	16 (8.0)	6 (5.7)	3 (12.5)
Candida guilliermondii	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
Candida IgG	3 (0.9)	1 (0.5)	2 (1.9)	0 (0.0)
Candida krusei	5 (1.5)	2 (1.0)	2 (1.9)	1 (4.2)
Candida lusitaniae	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
Candida palmioleophila	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
Candida parapsilosis	4 (1.2)	3 (1.5)	1 (1.0)	0 (0.0)
Candida tropicalis	14 (4.3)	6 (3.0)	8 (7.6)	0 (0.0)
Viruses, n (%)				
Adenovirus-Ag-IFT	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
CMV	5 (1.5)	3 (1.5)	1 (1.0)	1 (4.2)
H1N1 (2009 RNA)	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)
H1N1 DNA	4 (1.2)	4 (2.0)	0 (0.0)	0 (0.0)
HSV	4 (1.2)	1 (0.5)	2 (1.9)	1 (4.2)
RS-Virusantigen IFT	2 (0.6)	2 (1.0)	0 (0.0)	0 (0.0)
Varizella zoster virus	1 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)

CMV: Cytomegalovirus; MRSA: Methicillin-resistant Staphylococcus aureus; RS-Virus: Respiratory Syncytial Virus.

Supplementary Data; Table 3. Anti-infective agents

	All n=327	Pulmonary n=198	Intra-abdominal n=105	Bloodstream n=24
Antibiotics, n (%)				
Penicillins	168 (51)	133 (67)	21 (20)	14 (58)
Aminopenicillins	43 (13)	30 (15)	11 (10)	2 (8)
2. generation cephalosporines	49 (15)	42 (21)	4 (3)	3 (12)
3. generation cephalosporines	87 (26)	60 (30)	23 (21)	4 (16)
Carbapenems	215 (65)	107 (54)	91 (86)	17 (70)
Macrolides	84 (25)	70 (35)	6 (5)	8 (33)
Aminoglycosides	15 (4)	7 (3)	6 (5)	2 (8)
Fluorchinolones	50 (15)	29 (14)	17 (16)	4 (16)
Imidazoles	38 (11)	14 (7)	22 (20)	2 (8)
Glycopeptides	125 (38)	44 (22)	63 (60)	18 (75)
Lipopeptides	2 (0.6)	1 (0.5)	1 (0.9)	0 (0)
Lincosamides	11 (3)	8 (4)	1 (0.9)	2 (8)
Oxazolidinones	106 (32)	60 (30)	39 (37)	7 (29)
Glycylcyclines	4 (1)	0 (0)	3 (2)	1 (4)
Rifampicin	4 (1)	3 (1)	0 (0)	1 (4)
Sulfamethoxazol/Trimethoprim	12 (3)	7 (3)	4 (3)	1 (4)
Antifungals, n (%)				
Echinocandin	60 (18)	25 (12)	25 (23)	10 (41)
Triazole derivatives	91 (27)	22 (11)	62 (59)	7 (29)
Polyene	5 (1)	5 (2)	0 (0)	0 (0)
Antivirals, n (%)				
Aciclovir	5 (1)	3 (1)	2 (1)	0 (0)
Ganciclovir/Valganciclovir	2 (0.6)	1 (0.5)	0 (0)	1 (4)
Oseltamivir	4 (1.2)	4 (2)	0 (0)	0 (0)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(*b*) Report category boundaries when continuous variables were categorized	12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-17
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.