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Original Article

Sepsis research is hampered by the lack of a clear definition of suspected infection

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ABSTRACT

INTRODUCTION. A prevalent approach in sepsis research is pairing obtained cultures with antibiotic treatment to identify suspected infections. However, cultures are insensitive and nonspecific. Therefore, the present study aimed to examine the proportion of patients with infections admitted to an emergency department (ED) with and without having cultures obtained and to estimate 28-day mortality and prognostic factors of mortality according to culture status.

METHODS. We conducted a secondary analysis of prospectively collected data from adult ED patients with suspected or documented infections (1 October 2017 – 31 March 2018). Patients receiving both cultures and antibiotics were compared to those treated solely with antibiotics. Logistic regression analyses assessed mortality differences.

RESULTS. Among 2,055 patients, 1,441 (70.1%) had at least one culture obtained in addition to antibiotic treatment. Among patients without cultures, 163 (26.6%) had a Sequential Organ Failure Assessment score (SOFA) ≥ 2 on admission, compared to 528 (36.6%) among patients with cultures obtained (difference: 5.7-14.3). The 28-day mortality was 7.3% and 7.7%, respectively (difference: –2.1-2.9). Age, SOFA and the Charlson Comorbidity Index were the most important prognostic factors in both groups.

CONCLUSIONS. Defining suspected infections using cultures and antibiotics may introduce bias in sepsis research. Data sources relying on these criteria should be validated to examine their applicability.

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TRIAL REGISTRATION. Not relevant.

Sepsis is a serious condition defined as organ dysfunction caused by a dysregulated host response to infection [1]. The Sequential Organ Failure Assessment (SOFA) score [2] is used to quantify organ dysfunction and define sepsis [1, 3]. Although Quick SOFA (qSOFA) was proposed as an early prompt for suspecting sepsis, international guidelines from 2021 recommend against using qSOFA as a stand-alone screening tool, favouring other broader clinical assessment tools such as the Systemic Inflammatory Response Syndrome (SIRS) criteria and the National Early Warning Score (NEWS) [4].

The incidence and mortality of sepsis vary by definition, clinical severity and geography [5-7]. Reliable sepsis data are limited due to inconsistent criteria, incomplete records and biased coding [6, 8, 9]. Sepsis-specific coding often underestimates the true occurrence, whereas indirect coding methods may lead to overestimation [6].

The Sepsis-3 definition [1, 3] identifies sepsis as infection-related organ dysfunction based on retrospective indicators such as blood culture positivity and antibiotic use; however, it does not provide a universally accepted definition of infection [10-12].

Most cohort studies identify suspected infection retrospectively using varying definitions [5-7]. A common method is combining antibiotic use and culture collection, as in Sepsis-3 [1, 3, 5, 10], though cultures have low sensitivity and specificity [13].

We hypothesised that some patients with suspected infection may not have cultures obtained due to physician behaviour and perceived clinical necessity [13]. Requiring cultures as a criterion could misclassify patients and bias sepsis incidence and mortality estimates. This study aimed to examine the proportion of emergency department (ED) patients with infection who had cultures collected and to assess 28-day mortality and prognostic factors by culture status.

Methods

This is a secondary analysis of a prospective cohort of adult patients acutely admitted with suspected bacterial infections to the ED at Slagelse Hospital in Denmark between 1 October 2017 and 31 March 2018 [5]. The ED serves an uptake area comprising approximately 198,000 adults, with 26,500 visits annually during the study period (2017-2018). Privately funded hospitals in Denmark do not admit acute patients.

Patients with suspected infections were identified through daily review of triage and electronic health records. All patients (N = 12,092) were triaged by a nurse who recorded vital signs. Patients were considered infected if they received intravenous or oral antibiotics within 24 hours of arrival [5]. Infection documentation was based on assessments by the on-call physicians, and confirmed by manual daily author electronic health record (EHR) review, also confirming if an infection was listed as a discharge diagnosis. ED staff followed protocols based on local and international guidelines [14].

At the time, clinical practice prioritised cultures and rapid treatment for patients with ≥ 2 SIRS criteria, qSOFA ≥ 2 or critical illness. The guidelines [14] recommended obtaining cultures before initiating treatment with antibiotics.

Definitions

The culture was defined as any microbiological sample (e.g., blood, urine or expectorate) collected within 24 hours of admission. Sepsis was defined as an increase in SOFA score of ≥ 2 points from baseline [1, 3, 5].

Sepsis database and data collection

Data were extracted from a sepsis research database containing demographics, comorbidities, vital signs, labs, infection source, antibiotics and outcomes. Collection procedures are described in detail elsewhere 5. A baseline SOFA score of zero was assumed unless comorbidities were present, in which case it was adjusted using a previously described method [5]. Microbiology data were integrated from the regional microbiology database.

Inclusion and exclusion criteria

Patients were included if they had suspected or confirmed infection, received antibiotics within 24 hours and continued treatment for ≥ 48 hours (or upon discharge, with home continuation). Supplementary Figure 1 illustrates the flow of patient inclusion and the reasons for exclusions.

Statistics

The primary outcome was 28-day mortality; secondary outcomes included in-hospital mortality and transfer to

the intensive care unit (ICU). We compared characteristics and outcomes by culture status using counts, percentages, medians, 95% CI and interquartile range (IQR). Differences were tested using exact methods.

Multivariable logistic regression was used to evaluate 28-day mortality, with backwards selection of clinically relevant variables. Bonferroni correction was applied. Lactate was excluded due to > 50% missing data and non-random missingness. Significance was set at $p < 0.05$. Model fit was assessed with Pearson goodness-of-fit; the area under the receiver operating curve (AUROC) measured discrimination.

Stata 17.0 SE (StataCorp), College Station, Texas, USA, was used for all analyses.

Ethics approval and consent to participate

The study was reported to the Danish Data Protection Agency (REG-105-2017). The data accessed complied with relevant data protection and privacy regulations. On 16 May 2017, the study was defined as a quality project by the Secretariat of the Committee on Health Research Ethics of Region Zealand. Therefore, it was not covered by the Committee Act and was not obligated to report to the ethics committee system. Administrative permission to access the data was achieved on 25 September 2018 from the Head of the Slagelse Hospital Administration. The data were anonymised.

Data sharing statement

The dataset used and/or analysed during the current study is available from the corresponding author upon reasonable request.

Trial registration: not relevant.

Results

Study cohort

Among the 12,092 ED patients, 3,176 received antibiotics [5]. After excluding 1,121 patients (Supplementary Figure 1), 2,055 patients (48.5% male, median age 73.1 years (IQR: 60.0-82.7)) were analysed. Among these, 1,441 patients (70.1%) had at least one sample collected for bacterial culture; 614 patients (29.9%) did not.

Baseline characteristics

Baseline characteristics by culture status are presented in **Table 1**. Compared to patients with cultures, those without were younger and exhibited a lower prevalence of a high Charlson Comorbidity Index (CCI ≥ 3). They also had a higher systolic blood pressure, lower respiratory and heart rates and were more frequently normothermic upon arrival. Laboratory findings in this group showed higher haemoglobin levels and lower concentrations of C-reactive protein, leukocytes, creatinine and glucose. Additionally, pulmonary involvement was less common among patients without cultures, whereas abdominal or skin infections were more common. The group without culture collection also received intravenous antibiotics less frequently (63.0% versus 81.8%; see **Table 2**) and had a shorter length of stay.

TABLE 1 Baseline characteristics by culture status among patients admitted with suspected infection.

	Cultures collected + antibiotic treatment (N = 1,441)	Only antibiotic treatment (N = 614)	Difference (95% CI)
Female sex, n (%)	746 (51.8)	313 (51.0)	0.8 (–3.9-5.5)
Age, median (IQR), yrs	73.7 (61.4-83.1)	71.5 (57.3-82.2)	2.0 (0.5-3.6)
Comorbidities, n (%)			
Charlson Comorbidity Index:			
0	440 (30.5)	209 (34.0)	3.5 (–0.9-7.9)
1-2	669 (46.4)	292 (47.6)	1.2 (–3.5-5.9)
≥ 3	332 (23.1)	113 (18.4)	4.7 (0.9-8.4)
Heart failure	157 (10.9)	61 (9.9)	1.0 (–1.8-3.9)
Ischaemic heart disease[a]	161 (11.2)	62 (10.1)	1.1 (–1.8-4.0)
Cerebrovascular disease[b]	208 (14.4)	76 (12.4)	2.0 (–1.2-5.2)
Chronic pulmonary disease	378 (26.2)	154 (25.1)	1.1 (–3.0-5.2)
Diabetes[c]	257 (17.8)	85 (13.8)	4.0 (0.6-7.4)
Malignancy[d]	194 (13.5)	80 (13.0)	0.5 (–2.6-3.7)
Chronic kidney disease[e]	78 (5.4)	37 (6.0)	0.6 (–1.6-2.8)
Chronic mild or severe liver disease	30 (2.1)	6 (1.0)	1.1 (0.01-2.2)
Hypertension	479 (33.2)	191 (31.1)	2.1 (–2.3-6.5)
Severity of disease upon admission			
Systolic blood pressure, median (IQR), mmHg	130 (115-147)	135 (120-152)	5 (3-7)
Systolic blood pressure < 90 mmHg, n (%)	44 (3.1)	15 (2.4)	0.7 (–0.8-2.2)
Respiratory rate, median (IQR), × min.$^{-1}$	20 (16-23)	18 (16-20)	1 (1-2)
Heart rate, median (IQR), × min.$^{-1}$	91 (78-105)	86 (74-99)	5 (3-7)
O_2 saturation, median (IQR), %	96 (94-98)	97 (95-99)	1 (0-1)
Core temperature, median (IQR), °C	37.4 (36.8-38.3)	37.0 (36.6-37.5)	0.4 (0.3-0.5)
Normothermia: 36.1-38.0 °C, n (%)	944 (65.5)	509 (82.9)	17.4 (13.5-21.2)
Hyperthermia: > 38.0 °C, n (%)	442 (30.7)	71 (11.6)	19.1 (15.6-22.6)
Hypothermia: < 36.1 °C, n (%)	55 (3.8)	34 (5.5)	1.7 (–0.4-3.8)
Altered mental state, n (%)	204 (14.2)	74 (12.1)	2.1 (–1.0-5.2)
Length of stay, median (IQR), days	4.9 (2.7-8.1)	3.2 (1.0-6.6)	1.5 (1.1-1.8)
Risk scores upon admission, n (%)			
SOFA ≥ 2	528 (36.6)	163 (26.6)	10.0 (5.7-14.3)
qSOFA ≥ 2	173 (12.1)	46 (7.5)	4.6 (1.9-7.3)
SIRS ≥ 2	764 (53.0)	211 (34.4)	18.6 (14.0-23.2)
NEWS2 ≥ 5	686 (47.6)	193 (31.4)	16.2 (11.7-20.7)
Laboratory results, median (IQR)			
Haemoglobin, mmol/l[f]	8.0 (7.2-8.8)	8.2 (7.3-8.9)	0.2 (0.1-0.3)
CRP, mg/l[g]	76 (24-145)	43 (13-105)	18 (13-24)
White blood cell count, × 10^9/l[g]	11.3 (8.6-15.3)	10.5 (8.2-13.5)	0.8 (0.4-1.2)
Creatinine, µmol/l[h]	83 (63-117)	79 (62-104)	4 (1-7)
Bilirubin, mmol/l[i]	9 (6-13)	8 (6-12)	1 (0-1)
Platelets, × 10^9/l[j]	241 (185-316)	245 (193-311)	5 (–3-14)
Lactate, mmol/l[k]	1.2 (0.8-2.0)	1.1 (0.8-1.6)	–0.1 (–0.2-0)
Glucose, mmol/l[l]	6.7 (5.8-8.2)	6.4 (5.6-7.7)	0.3 (0.2-0.5)

IQR = interquartile range; NEWS2 = National Early Warning Score 2; qSOFA = quick SOFA; SIRS = Systemic Inflammatory Response Syndrome; SOFA = Sequential Organ Failure Assessment.
a) Myocardial infarction or other ischaemic heart disease prior to admission.
b) History of cerebrovascular disease, including transient ischaemic attacks.
c) Uncomplicated or end-organ damage.
d) Tumour without metastasis, leukaemia, lymphoma or metastatic tumours.
e) Mild or severe kidney disease.
f) 11 missing.
g) 5 missing.
h) 10 missing.
i) 65 missing.
j) 26 missing.
k) 1,309 missing.
l) 96 missing.

TABLE 2 Time to antibiotic treatment, types of microbiological samples obtained and infection source according to culture status among patients admitted with suspected infection.

	Cultures collected + antibiotic treatment (N = 1,441)	Only antibiotic treatment (N = 614)	Difference (95% CI)
Antibiotic treatment	746 (51.8)	313 (51.0)	0.8 (–3.9-5.5)
Time to antibiotic treatment; median (IQR), h	5.6 (3.3-8.9)	5.9 (3.4-9.2)	0.23 (–0.18-0.65)
Antibiotics before hospitalisation, n (%)	284 (19.7)	145 (23.6)	3.9 (–0.04-7.8)
Intravenous antibiotics, n (%)	1,178 (81.8)	387 (63.0)	18.8 (14.4-23.2)
Peroral antibiotics, n (%)	263 (18.2)	227 (37.0)	18.8 (14.5-23.1)
Cultures collected in total cohort, n (%)[a]			
Blood	1,040 (50.6)	-	-
Urine	935 (45.5)	-	-
Expectorate	278 (13.5)	-	-
Faeces	62 (3.0)	-	-
Wounds/skin	75 (3.7)	-	-
Cerebrospinal fluid	13 (0.6)	-	-
Others	65 (3.2)	-	-
Influenza/viral tests[a]	131 (6.4)	-	-
Source of infection, n (%)[b]			
Lungs	796 (55.2)	279 (45.4)	9.8 (5.1-14.5)
Urine	381 (26.4)	148 (24.1)	2.3 (–1.8-6.4)
Abdomen	142 (9.9)	80 (13.0)	3.1 (0.02-6.2)
Wounds/skin	107 (7.4)	86 (14.0)	6.6 (3.5-9.7)
Endocarditis	9 (0.6)	0	0.6 (0.2-1.0)
Central nervous system	7 (0.5)	2 (0.3)[c]	0.2 (–0.4-0.8)
Devices	1 (0.07)	3 (0.5)	0.4 (–0.1-1.0)
Facial, teeth, others	6 (0.4)	5 (0.8)	0.4 (–0.4-1.2)
Other	10 (0.7)	1 (0.2)	0.5 (–0.05-1.1)
Unknown	92 (6.4)	46 (7.5)	1.1 (–1.3-3.5)

a) Total number of patients with the specific culture collected among the total number of patients in the cohort (n = 2,055).
b) Some patients had > 1 focus of infection.
c) No information available on cerebrospinal fluid cultures.

Regarding sepsis criteria, 36.6% of those with cultures had SOFA ≥ 2 versus 26.6% without. In the no-culture group, 7.5% met qSOFA ≥ 2, 34.4% met SIRS ≥ 2 and 31.4% met NEWS2 ≥ 5; all lower than in patients with cultures.

Mortality

The mortality rates were similar between groups; 28-day mortality was 7.7% (95% CI: 6.4-9.2) in patients with cultures and 7.3% (95% CI: 5.4-9.7) in those without. In-hospital mortality rates were 3.3% and 4.7%, respectively (**Table 3**). Patients with cultures were more frequently transferred to the ICU.

TABLE 3 Outcomes according to culture status among patients admitted with suspected infection.

	Cultures collected + antibiotic treatment (N = 1,441)		Only antibiotic treatment (N = 614)		Difference,
Outcome	n	% (95% CI)	n	% (95% CI)	% (95% CI)
Primary					
28-day mortality	111	7.7 (6.4-9.2)	45	7.3 (5.4-9.7)	0.4 (–2.1-2.9)
Secondary					
In-hospital mortality	48	3.3 (2.5-4.4)	29	4.7 (3.2-6.7)	1.4 (–0.5-3.3)
Transfer to ICU	115	8.0 (6.6-9.5)	27	4.4 (2.9-6.3)	3.6 (1.5-5.7)

ICU = intensive care unit.

Prognostic factors

Multivariate regression analyses (**Table 4**) demonstrated that in the culture group, age (odds ratio (OR) = 1.04; 1.02-1.06), SOFA score ≥ 2 (OR = 3.04; 1.79-5.17); CCI 1-2 (OR = 3.58; 1.67-7.69), CCI ≥ 3 (OR = 7.04; 3.25-15.27) were associated with 28-day mortality. Model fit was good (p = 1.0); AUROC = 0.778. In the no-culture group, age (OR = 1.05; 1.02-1.08) and SOFA ≥ 2 (OR = 3.97; 1.93-8.16) were associated with 28-day mortality. CCI ≥ 3 also increased the risk of mortality with an imprecise estimate (OR = 2,67; 0.99-7.22). Model fit was good (p = 0.99); AUROC = 0.80.

TABLE 4 Multivariate logistic regression model of odds ratio for 28-day mortality among patients with suspected infection, stratified by culture status.

	Model 1[a] cultures collected and treatment with antibiotics (N = 1,441)		Model 2[b] only treatment with antibiotics (N = 614)	
	OR (95%CI)	adjusted[c] p value	OR (95%CI)	adjusted[c] p value
Age	1.04 (1.02-1.06)	< 0.001	1.05 (1.02-1.08)	0.004
SOFA				
0	Reference		Reference	
1	1.48 (0.79-2.76)	-	0.63 (0.20-2.04)	-
≥ 2	3.04 (1.79-5.17)	< 0.001	3.97 (1.93-8.16)	< 0.001
CCI				
0	Reference		Reference	
1-2	3.58 (1.67–7.69)	0.008	1.78 (0.73-4.35)	-
≥ 3+	7.04 (3.25–15.27)	< 0.001	2.67 (0.99-7.22)	-

AUROC = area under the receiver operating curve, CCI = Charlson Comorbidity Index; OR = odds ratio; SOFA = sequential organ failure assessment.
a) Goodness-of-fit test after logistic model: p = 1.0; AUROC = 0.770.
b) Goodness-of-fit test after logistic model: p = 0.99; AUROC = 0.800.
c) Bonferroni correction.

Sensitivity analysis

A sensitivity analysis comparing patients with and without blood cultures showed no significant difference in 28-day or in-hospital mortality (Supplementary Table 1). Results were consistent across analyses restricted to patients with cultures and the full cohort of all patients treated with antibiotics. Additionally, patients with blood cultures were more likely to meet the criteria for SOFA ≥ 2, qSOFA ≥ 2, SIRS ≥ 2 and NEWS2 ≥ 5 (Supplementary Table 2).

Discussion

Approximately one-third of ED patients with suspected or confirmed infection did not have cultures obtained. Many met the sepsis criteria or other criteria for urgent sepsis evaluation. Mortality rates were similar between groups. Age, SOFA score and CCI were prognostic factors in both.

Our findings support our hypothesis that culture-based definitions risk excluding patients with sepsis and poor outcomes, introducing bias into cohort studies.

The Sepsis-3 definitions [1, 3] face criticism for challenges in distinguishing sepsis from non-infectious diseases [13]. The lack of a universal infection definition and the absence of a gold standard reduce diagnostic precision. The Infectious Diseases Society of America has criticized the Surviving Sepsis Campaign Guidelines for failing to address these challenges [15]. It is often unclear whether an infection is truly present or if organ dysfunction is due to another cause [15].

A key challenge in sepsis epidemiology is reliance on heterogeneous observational studies and biased administrative data [6]. These may underestimate sepsis incidence and mortality [6, 7, 12, 16, 17]. Research on sepsis incidence and mortality should be based on prospective studies using clinical data from patient records and community-based study designs [6, 8]. However, such studies are few, often small and population-specific, limiting generalisability [18].

These methodological problems in sepsis research call for more reliable tools to identify patients with infection and sepsis, standardisation of study designs and data reporting. In this context, comprehensive prospective studies based on chart- or EHR-based data in infection and sepsis research are preferable to retrospective cohort studies [8].

The identification of age, SOFA score and comorbidities as prognostic factors in both groups is not unexpected, as these are well-established markers of outcome in infection and sepsis, and their predictive value is likely to persist across varying culture status and baseline characteristics. However, our finding that these factors remained important in both groups of patients with suspected infection supports that those without cultures should not be excluded from sepsis studies. Despite some differences in baseline characteristics, overall risk profiles were similar. Therefore, sepsis research should consider that patients without cultures may experience illnesses of similar severity and have prognostic characteristics comparable to those with microbiological confirmation.

The study results confirm that clinical risk scores are associated with an increased likelihood of blood culture collection, which is consistent with established diagnostic protocols and what was observed for culture collection in general. However, mortality did not differ between patients with and without blood cultures, suggesting that while elevated risk scores may guide diagnostic decisions, the presence of a blood culture alone did not correspond to a higher observed mortality in this setting.

It remains unclear why some patients who met the sepsis criteria did not have cultures obtained. Clinical assessment may have deemed symptoms inconsistent with sepsis or cultures unnecessary, as sepsis may mimic other conditions [11, 19].

Taken together, our findings highlight the complexity of interpreting culture collection patterns in sepsis research. Cultures were more likely to be obtained in patients with elevated clinical risk scores, reflecting guideline-based practice. However, the absence of a corresponding difference in mortality — while acknowledging the limitations of statistical power —suggests that culture collection may reflect clinical judgment or perceived severity rather than reliably identifying higher-risk patients. These findings highlight that the clinical context and diagnostic behaviour should be considered when interpreting observational data on suspected infection.

Implications

Our study underlines the risk of significant misclassification bias in sepsis research due to unreliable diagnostic tools and inadequate criteria. Data sources in sepsis research that identify suspected infection based on frequently used criteria, such as culturing and antibiotic treatment [20], should be validated to confirm the applicability of these infection criteria.

Emphasising the importance of refining criteria and diagnostics and optimising culture collection strategies in clinical practice is also essential.

Strengths and limitations

We used prospective EHR data from patients admitted to the ED over six months, capturing all suspected infection patients from the area, thereby minimising selection bias. However, misclassification of infection may exist due to reliance on physician-ordered antibiotics. All patients registered with an infection based on the criteria of antibiotic treatment also had a discharge diagnosis of infection. However, disagreements between physicians about diagnosis and infection sources are common [10, 13], and a gold standard biomarker to confirm the diagnosis has yet to be established.

In the comparisons of mortality and clinical characteristics by culture status, confounding by indication may have influenced the results. Furthermore, there is a risk of selection bias in how clinicians choose which patients to culture. Furthermore, we only had the initial 24-hour microbiological data available.

We may have underestimated sepsis prevalence since SOFA scores were collected only at admission and were not validated for chronic disease adjustments. Finally, as this was a single-centre study, the findings reflect local practices; however, they also point to broader issues of bias in sepsis research.

Conclusions

Our findings demonstrate that a substantial proportion of patients with suspected infection and indicators of sepsis do not have cultures obtained. This challenges the validity of using culture collection and antibiotic treatment alone to define suspected infection. The lack of clear definitions for suspected infection and poor performance of the sepsis criteria challenge sepsis epidemiology. Further research is needed to provide valid data on sepsis incidence, prognosis and overall burden.

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