Active Surveillance Cultures in Critically ill Patients: Pathogens, Patterns, and Correlation with Eventual Bloodstream Infections

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ABSTRACT: **Background:** The role of routine active surveillance cultures (ASCs) in predicting consequent bloodstream infections is unclear.

Objectives: To determine prospectively whether routine screening ASCs obtained on admission to the intensive care unit (ICU) can predict the causative agent of subsequent bloodstream infections.

Methods: We prospectively studied a cohort of 100 mechanically ventilated patients admitted consecutively to a 16-bed ICU. On admission, ASCs were obtained from four sites: skin cultures (swabs) from the axillary region, rectal swabs, nasal swabs, and deep tracheal aspirates. Thereafter, cultures were obtained from all four sites daily for the next 5 days of the ICU stay.

Results: Of the 100 recruited patients 31 (31%) had culture-proven bacteremia; the median time to development of bacteremia was 5 days (range 1–18). Patients with bacteremia had a longer median ICU stay than patients without bacteremia: 14 days (range 2–45) vs. 5 days (1–41) ($P < 0.001$). ICU and 28 day mortality were similar in patients with and without bacteremia. Most ASCs grew multiple organisms. However, there was no association between pathogens growing on ASCs and eventual development of bacteremia.

Conclusions: ASCs obtained on ICU admission did not identify the causative agents of most subsequent bacteremia events. Therefore, bloodstream infections could not be related to ASCs.

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KEY WORDS: active surveillance cultures (ASCs), bloodstream infections, intensive care unit (ICU) infections

Nosocomial infections can affect as many as 30% of patients admitted to an intensive care unit [1,2]. Early knowledge of the causative pathogen in nosocomial and community-acquired infection is crucial for initiating and managing the correct antibiotic treatment. Furthermore, delaying early and appropriate antibiotic treatment until results of blood cultures are positive is associated with increased mortality [3-5]. Consequently, in most infectious events the causative agent at the start of the event is unknown or at best only suspected, thus mandating empiric antibiotic treatment.

In the present study we sought to determine whether active surveillance cultures obtained on ICU admission and during the first 5 days of ICU stay can predict the causative pathogen in subsequent bloodstream nosocomial or community-acquired infectious events and thus better manage eventual antimicrobial treatment.

PATIENTS AND METHODS

We recruited 100 consecutively admitted patients (men and women) to the ICU. Inclusion criteria included age over 18 and an expected ICU stay of more than 48 hours. Only patients who were mechanically ventilated were recruited. Excluded were patients who at the time of ICU admission were already receiving antibiotic treatment, patients with expected short ICU stay of less than 48 hours, and patients who were not mechanically ventilated. The study was approved by the local hospital ethics board (Helsinki committee). Since obtaining surveillance cultures was common practice in our ICU, a written informed consent was waived. Nevertheless, as all recruited patients were mechanically ventilated and thus sedated, a verbal consent was also obtained from patients' next of kin.

On admission, blood cultures were obtained along with surveillance cultures from four sites: skin cultures (swabs) from the axillary region, rectal swabs, nasal swabs, and deep tracheal aspirates. Cultures were obtained daily for the first 5 days of ICU stay.

Any positive blood culture was considered as bacteremia. However, pathogens likely to be contaminants (Staphylococcus coagulase negative or diphtheroids) were excluded. Bacterial and fungal cultures were processed by a commonly used

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ICU = intensive care unit

automated detection system, Vitek 2® (Bomerieux SA, Marcy l'etoile, France).

At admission all patients were placed under contact precautions. Thereafter, the following criteria for obtaining blood cultures during stay in the ICU for suspected bacteremia were followed: a) fever > 38°C, b) suspected sepsis defined as presence of a suspected infectious source, c) the presence of at least two SIRS criteria with or without shock, d) unexplained shock, or e) organ failure. Follow-up continued until ICU or hospital death, discharge, or 28 days after admission.

STATISTICAL ANALYSIS

The data were analyzed using BMDP statistical software [6]. Discrete variables were compared using Pearson's chi-square test or Fisher's exact test as applicable. Continuous variables were compared using Student's *t*-test. For variables such as length of ICU stay or time to development of bacteremia, which did not have Gaussian distributions, we used the non-parametric Mann-Whitney U-test to compare between groups. A *P* value ≤ 0.05 was considered significant.

RESULTS

During a 3 month period 100 patients were recruited consecutively. The average age of the 63 men and 37 women was 58 ± 19 years (range 18–95) [Table 1]. Average APACHE II score on admission was 16.3 ± 7 (range 3–39). The hospital stay before admission to the ICU was less than 48 hours in 52 patients and > 48 hours in 48 [Table 1]. Twenty-six percent of patients were admitted directly from the emergency room, 38% from internal medicine wards and 36% from the surgical division; of the latter, 17% were from surgical wards and 19% were admitted postoperatively. Overall, 61% of the admitted patients had comorbidities; 20% had diabetes mellitus.

Surveillance cultures were divided into four groups according to the site of collection. APACHE II score on ICU admission was 16.4 ± 6.0 in patients with bacteremia and 16.2 ± 7.9 in patients without (*P* non-significant). Of the 100 recruited patients 18 presented with APACHE II score > 25 (27.52 ± 3.4). However, only 4 of 18 (22%) developed bacteremia. The other 27 events of bacteremia occurred in patients with APACHE II score < 25 (13.81 ± 5.4).

Overall, 31 of the 100 recruited patients (31%) had culture-proven bacteremia. The median time to development of bacteremia was 5 days (range 1–18) [Table 2]. Of the 31 patients with bacteremia, 11 stayed less than 48 hours in hospital prior to their ICU admission. Their median time to development of bacteremia was 2 days (range 1–9) after their ICU admission. The remaining 20 bacteremia events occurred in patients who were hospitalized for more than 48 hours prior to ICU admission and occurred at a median of 6 days (range 1–18) after their ICU admission.

Table 3 presents the microbiologic profile of positive surveillance cultures and their relation to bacteremia. Staphylococcus

SIRS = systemic inflammatory response syndrome

Table 1. Patient characteristics on ICU admission

	Hospital stay < 48 hours prior to ICU admission (n=52)	Hospital stay > 48 hours prior to ICU admission (n=48)	*P* value
Age (yr)	48.9 ± 19.5	68.0 ± 15.2	< 0.001
APACHE II score	15.4 ± 8.3	17.2 ± 6.0	0.21
Medical patients	31/52 (64.6%)	29/48 (55.8%)	0.54
Surgical patients	19/52 (36.5%)	21/48 (43.8%)	0.54
Comorbidities	22/52 (42.3%)	40/48 (83.3%)	< 0.001
Diabetes mellitus	8/52 (15.4%)	12/48 (25%)	0.32

Table 2. Patient outcome according to length of hospital stay prior to ICU admission

	Hospital stay < 48 hours prior to ICU admission (n=52)	Hospital stay > 48 hours prior to ICU admission (n=48)	*P* value
ICU length of stay Median (range)	5.0 days (1–41)	9.5 days (1–45)	0.03
ICU mortality	8/52 (15.4%)	12/48 (25%)	0.32
28 day mortality	14/52 (26.9%)	13/48 (27.1%)	1.00
APACHE II score on ICU admission	15.4 ± 8.3	17.23 ± 6.0	0.21
Bacteremia events	11/52 (21.2%)	20/48 (41.7%)	0.03
Time to development of bacteremia (after ICU admission) Median (range)	2 days (1–9)	6 days (1–18)	0.01

Table 3. Microbiologic profile of positive active surveillance cultures

	Hospital stay < 48 hours prior to ICU admission (n=52)	Hospital stay > 48 hours prior to ICU admission (n=48)	*P* value
Medical patients	31/52 (64.6%)	29/48 (55.8%)	0.54
Surgical patients	19/52 (36.5%)	21/48 (43.8%)	0.54
Bacteremia events	11/52 (21.2%)	20/48 (41.7%)	0.03
MRSA	0/52	4/48 (8.33%)	0.05
MSSA	15/52 (28.8%)	7/48 (14.6%)	0.1
SCN	47/52 (90.4%)	44/48 (91.7%)	1.0
All gram-negative	34/52 (65.4%)	24/48 (50%)	0.16
All gram-positive	27/52 (51.9%)	19/48 (60.4%)	0.42
Pseudomonas spp.	3/52 (5.8%)	13/48 (27.1%)	0.005
Acinetobacter spp.	4/52 (7.7%)	18/48 (37.5%)	< 0.001
ESBL	2/52 (3.8%)	8/48 (16.7%)	0.04
Candida	14/52 (26.9%)	15/48 (31.3%)	0.66

MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-sensitive *Staph. aureus*, SCN = Staphylococcus coagulase negative, ESBL = extended-spectrum beta lactamase

coagulase-negative bacteria grew in all 4 sites in 81 patients. However, only 13 patients had bacteremia due to SCN bacteria. There was no statistical association between prevalence of SCN culture positivity on ICU admission and later positive blood cultures. *Staphylococcus aureus* methicillin-resistant and -sensitive bacteria (MRSA and MSSA) grew in all 4 sites in 22 patients who had 27 cultures positive for MSSA and 4 cultures positive for MRSA. However, only two patients in the study population subsequently had staphylococcal (MSSA) bacteremia, and neither of them was positive for MSSA on surveillance cultures obtained at the time of ICU admission.

In 15 patients the ASC was positive for an extended-spectrum beta lactamase-producing organism. However, there were only three subsequent ESBL bacteremias caused by *Escherichia coli*, none of them in patients with positive ASCs for ESBL on admission to the ICU. Similarly, ASCs were positive for MRSA in four patients, but not even one patient had MRSA bacteremia. Enterococci grew in 28% of surveillance cultures in rectal swabs and in 22% of sputum cultures. However, only one patient was subsequently found to have enterococcal bacteremia. Gram-negative bacteria growing in surveillance cultures were found in 58% of patients. However, only 10 patients had bacteremia caused by gram-negative bacteria (3 of them were due to *E. coli* ESBL that were not identified on surveillance cultures). Acinetobacter was found to colonize 22 patients on surveillance cultures, but was responsible for only two bacteremia events. Pseudomonas spp. grew in 16 patients on surveillance cultures, with 6 subsequent bacteremia events. Here too, there was no statistically significant association. Candida spp. grew on surveillance cultures in 29 patients, most of them in nasopharynx and sputum. However, only two patients had positive blood cultures for Candida.

Overall, we did not find any association between pathogens growing in surveillance cultures and eventual development of bloodstream infections. Bacteremia was only associated with the presence of diabetes mellitus on admission; 55% of bacteremia events occurred in patients with diabetes, whereas only 25% of patients without diabetes developed bacteremia ($P = 0.015$).

Patients with hospital stay less than 48 hours as compared to more than 48 hours prior to ICU admission. had a significantly shorter ICU length of stay, with a median of 5.0 days (1–41) vs. 9.5 (1–45) ($P < 0.03$) respectively [Table 2]. Death in the ICU occurred in 8 of 52 patients (15.4%) who stayed in the hospital for < 48 hours prior to their ICU admission vs. 12 of 48 (25%) ($P = 0.32$) staying > 48 hours prior to their ICU admission.

The 28 day mortality rate was 26.9% (14 of 52 patients), compared to 27% (13/48) ($P = 1.0$) in patients with more than 48 hours of hospital stay prior to ICU admission. Overall, ICU mortality in both groups was 20%, and another 7% died after ICU discharge. The median ICU length of stay was 14 days (range 2–45) in patients with bacteremia compared to 5 days (1–41) in those without ($P < 0.001$). ICU and 28 day mortality tended to be higher in patients with bacteremia. However, this did not reach statistical significance [Table 4].

Table 4. Patient outcome according to eventual development of bacteremia

	Patients with bacteremia* (n=31)	Patients without bacteremia (n=69)	*P* value
ICU length of stay Median (range)	4 days (2–45)	5 days (1–41)	‹ 0.001
ICU mortality	7/31 (22.6%)	13/69 (18.8%)	0.79
28 day mortality	11/31 (35.5%)	16/69 (23.2%)	0.23
APACHE II score on ICU admission	16.4 ± 6.0	16.2 ± 7.9	0.88
Time to development of bacteremia (after ICU admission) Median (range)	5 (1–18) days		

*Positive blood cultures

DISCUSSION

In intensive care units around the world much effort has been invested to reduce and control health care-associated infections. However, the results of these efforts are inconclusive [7,8] and there is growing political and public concern. Hospitals are under increasing pressure to perform active surveillance cultures for the detection of multidrug-resistant pathogens among newly admitted patients. Theoretically, results of these cultures could then be used for contact precautions, prevention of further transmission, and potentially to direct antimicrobial treatment in subsequent infections.

The use of active surveillance cultures is a resource-consuming intervention with the potential for undesirable consequences [9-11]. Furthermore, hospital staff adherence to and compliance with guidelines for active surveillance is inconsistent and at times may be poor [12]. Patients under contact isolation may have more adverse events as compared to patients not under isolation, and are less likely to be attended by senior physicians. Thus, the utility and benefits of ASCs are still controversial.

Many studies examining ACSs have focused on MRSA [13] and vancomycin-resistant enterococci [14-16], and to a much lesser extent on multidrug-resistant gram-negative bacteria. In 2003, the Society for Healthcare Epidemiology of America published a report entitled "SHEA Guideline for Preventing Nosocomial Transmission of Multidrug-Resistant Strains of *Staphylococcus aureus* and Enterococcus" [17]. The report

SCN = *Staphylococcus* coagulase negative
MSSA = methicillin-sensitive *Staphylococcus aureus*
MRSA = methicillin-resistant *Staphylococcus aureus*
ASCs = active surveillance cultures

SHEA = Society for Healthcare Epidemiology of America

included a recommendation for the use of active surveillance cultures. However, these ASC recommendations were not based on a systematic review, and much controversy still remains. Therefore, the question whether ASCs are effective in decreasing MRSA infection and its related mortality has not been answered conclusively.

Huang and Platt [18] reported an MRSA infection rate of 29% among 209 colonized patients; 28% of these infections were bacteremias. In another study by the same author [19] a retrospective analysis of a 9 year period showed that routine surveillance cultures were associated with a reduction in the incidence of MRSA bacteremia in ICUs and hospital-wide. However, this was a retrospective analysis. Olivier et al. [20] studied the risk of vancomycin-resistant enterococci bacteremia among patients previously colonized with the bacteria. Only 4% of colonized patients developed bacteremia caused by the same strain, as confirmed by genotype analysis [20].

Many other reports relate to hospital-acquired MRSA. A recent systematic review by McGinigle et al. [21] summarized the evidence available for ASCs in the intensive care unit. Most of the reviewed studies reported a significant reduction in MRSA infection after the application of ASCs. Although these studies were of poor quality and did not allow a conclusive recommendation, ASCs have been shown to be effective in reducing the colonization rate of various pathogens. The question remains whether reduction in colonization actually decreases the rate of subsequent bloodstream infectious events caused by the colonizing pathogen. A prospective observational study by Robicsek and co-authors [22] examined universal surveillance for MRSA and found a significant reduction in MRSA infections. In reporting the results of a 6 year surveillance screening cultures, Reddy and coworkers [23] identified 413 patients colonized with ESBL-producing Enterobacteriaceae; 35 (8.5%) of them developed a subsequent ESBL bloodstream infection. Similarly, Ben Ami et al. [21] performed fecal screening of 241 patients on hospital admission, 26 of whom were found to be colonized with ESBL-producing pathogens. Only 4 of 26 (15%) subsequently had ESBL bacteremia.

Our study was a prospective cohort of 100 consecutively admitted patients to a 16-bed multidisciplinary ICU. ASCs were obtained daily on the first 5 days after ICU admission. Most cultures were positive and grew multiple organisms. In 31% of the admitted patients bacteremia was proven in a subsequent culture. This rate may be higher than reported in the literature. We assume that this higher rate was mainly due to the fact that the most severe patients were selected for the study. While patients with bacteremia had a longer ICU stay than patients without bacteremia, ICU and 28 day hospital mortality were similar in both.

We were not able to demonstrate with statistical significance any association between results of screening ASCs and the causative agents of subsequent bacteremia. The causative agent of most bacteremia events could not be related to ASCs obtained on admission. Our results raise an important question: apart from identifying colonized patients, are ASCs also effective in identifying colonizing pathogens as the causative agents of subsequent bloodstream infectious events? Our results may not support that notion.

ASCs may help identify patients colonized by drug-resistant pathogens. This may further limit in-hospital transmission. However, obtaining ASCs is labor intensive and associated with increased cost. If ASCs cannot predict bloodstream infection, then besides limiting in-hospital spread its usefulness may be questionable. Furthermore, bacteremia events that cannot be related to surveillance cultures obtained on ICU admission cast doubt on the effectiveness of surveillance cultures as predictors of subsequent bloodstream infections.

Our study has some limitations. First, ASCs were collected only during the first 5 days after ICU admission. Perhaps the collection of additional samples during patients' entire stay in the ICU could provide additional information. Retrospectively, the samples might have been sufficient since blood cultures were positive mostly within the first 7 days of the ICU stay. Secondly, a sample size of 100 screened patients is relatively small. Nevertheless, we did not find any statistical association between ASC results and subsequent bacteremia.

CONCLUSIONS

ASCs may have an epidemiologic role in containing the spread of multidrug-resistant pathogens, but the role of positive ASCs in predicting subsequent bloodstream infectious events is limited. In fact, in most bacteremia events in our study, the causative pathogen causing the bacteremia event could not be identified on surveillance cultures obtained on the initial admission. This lack of correlation between admission ASCs and subsequent bacteremia events has implications for our practice, since we depend on prior positive cultures to direct empiric antimicrobial treatment. Our findings suggest that positive screening cultures on ICU admission serve merely to identify patient colonization with multidrug-resistant pathogens. It should be borne in mind that these pathogens, other than being colonizers, are not the causative agents of subsequent invasive infections. Therefore, when starting antimicrobial treatment for a presumed bacteremia, knowledge of prior colonizing pathogens is impractical, may be misleading, and probably should not be relied upon.

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