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Controversy

Implications of culture collection after the first antimicrobial dose in septic emergency department patients

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ABSTRACT

Background: Previous research has illustrated the importance of collection of microbiologic cultures prior to first antimicrobial dose (FAD) in septic patients to avoid sterilization of pathogens and thus allowing confirmation of infection, identification of pathogen(s), and de-escalation of antimicrobial therapy. There is currently a lack of literature characterizing the implications and clinical courses of patients who have cultures collected after FAD.
Methods: In this single-center, retrospective chart review of 163 sepsis cases in the emergency department, the primary outcome was positive-cultures from appropriate sources. Secondary outcomes included time to FAD (TFAD); ICU and hospital lengths of stay (LOS); rate of antibiotic restart; secondary infection rate; readmission; and mortality. Cases were divided based on culture timing relative to FAD: culture-first (CF) or antimicrobial-first (AF) cohorts.
Results: Cultures were more frequently positive in the CF cohort vs. AF cohort overall (80.4% vs. 46.7%, $p < 0.005$). TFAD was greater in the CF cohort (202 min vs. 153 min, $p = 0.036$) and these cases trended toward shorter ICU and hospital LOS (6.8 days vs. 8.4 days, $p = 0.122$; 11.5 days vs. 13.5 days, $p = 0.218$). Antibiotic restart was less frequent in the CF cohort (10.7% vs. 17.8%, $p < 0.005$). *C. difficile* infection and mortality trended toward lower incidence in the CF cohort, and readmission rates were similar.
Conclusions: Sepsis patients who have cultures obtained after FAD (represented in the AF cohort) had less positive-cultures, shorter TFAD, a trend toward longer ICU and hospital LOS, and perhaps higher risk of *C. difficile* infection, and mortality.

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1. Background

The Surviving Sepsis Campaign (SSC) guidelines recommend that appropriate microbiologic cultures be obtained prior to starting antimicrobial therapy if doing so does not result in substantial delay in the initiation of antimicrobials [1]. Sterilization of cultures in patients may occur within hours of the first antimicrobial dose (FAD) affecting the yield of cultures, and decreasing the likelihood of identifying a pathogen [1-3]. Isolating the infecting organism(s) allows for antimicrobial de-escalation after receipt of the susceptibility profile, therefore decreasing the prevalence of resistant organisms, limiting side effects, lowering costs, and improving survival [3-5]. The SSC guidelines also recommend that administration of intravenous antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock, as reducing time to FAD (TFAD) has also been shown to improve outcomes [1]. These two recommendation statements present conflicting priorities of minimizing TFAD and collecting appropriate cultures prior to starting antimicrobial therapy.

To our knowledge, there has been no research evaluating patient outcomes based specifically upon timing of culture relative to FAD. With mortality rates as high as 40% in septic shock, there is a need to better characterize and understand the implications on patient outcomes when cultures are obtained after FAD to improve practices [1].

2. Methods

2.1. Study design

This single-center, Internal Review Board approved, retrospective cohort study was performed at The University of Kansas Health System (TUKHS), Kansas City, Kansas, aiming to compare and contrast clinical courses of septic emergency department (ED) patients with cultures collected before FAD compared to patients who had cultures collected after FAD.

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The timing of multiple outcome measures required the use of "time-zero" to determine a standardized starting point. Centers for Medicare and Medicaid Services (CMS) defines time-zero for sepsis patients for purposes of hospital quality measurements. It is defined when three clinical criteria are met within 6 h of each other, in no particular order. Time-zero is reached when there is electronic medical record (EMR) documentation of a suspected infection source, two or more manifestations of systemic infection per the Systemic Inflammatory Response Syndrome (SIRS) criteria, and organ dysfunction is evidenced by predetermined thresholds of pertinent laboratory values or vital signs.

Broad-spectrum antibiotics are defined in Table 1 and based upon the relevant infection sites' practice guidelines with consideration given to the established practice habits at TUKHS.

Data were extracted from the EMR by a residency-trained Doctor of Pharmacy skilled in data extraction using a standardized electronic data collection form. Data analysis was performed with SPSS version 25, and p-values of <0.05 were considered statistically significant. Chi-squared and ANOVA tests were used for statistical analysis of outcome measures that were binomial or nominal, and t-test was used for evaluation of continuous outcome data.

2.2. Patient selection

Patient cases were identified using reports generated within the utilized at TUKHS EMR (Epic Systems Corporation, Verona, Wisconsin). Reports were specified to include patients 18 years or older who presented to the ED between August 1, 2016 and January 31, 2017 with an admitting diagnosis corresponding to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes for "sepsis," "severe sepsis," or "septic shock." The time frame under review was chosen as a convenience sample given the time necessary for manual chart review and considering the magnitude of these implications were unclear during study inception. Patients must have been administered broad-spectrum antimicrobials, as defined in Table 1, and then be admitted to an intensive care unit (ICU). Patients whose first level of care was an ICU after admission were selected to promote homogeneity within the sample groups as these patients may have similar acuity and would receive the same level of care. Patient baseline characteristics are compared in Table 2.

Patients were excluded if the source of infection was not clearly identified or suspected in the history and physical note documented in the patients' EMR; if infection was ruled out after admission; if no appropriate cultures were collected from the suspected source (as defined in Table 1); if patients presented with *Clostridium difficile* infection; if the causative organism was identified as fungal or viral; if the identified source was non-purulent cellulitis or another infection which cannot be routinely cultured; or if the patient was discharged within 72 h from admission (Fig. 1).

Table 1
Defined broad-spectrum antibiotics and appropriate culture sites.

Infection	Antibiotics	Relevant culture site
Health-care associated pneumonia (HCAP) or hospital acquired pneumonia (HAP)	Anti-MRSA agent + anti-PSa agent(s)	Sputum or BAL
Community acquired pneumonia (CAP)	Fluoroquinolone (monotherapy) OR beta-lactam + [fluoroquinolone/macrolide/doxycycline]	
Urinary tract infection (UTI)	Beta-lactam/fluoroquinolone	Urine
Meningitis	Two anti-Streptococcal agents	Cerebrospinal fluid
Intra-abdominal infections	Anaerobic + Gram-negative agent(s)	Relevant site swab or collection
Skin and skin-structure infections	Anti-MRSA agent	

MRSA: methicillin-resistant *Staphylococcus aureus*; PSa: *Pseudomonas aeruginosa*; BAL: bronchial alveolar lavage.

Table 2
Patient demographics.

Characteristic		Overall	CF cohort	AF cohort	p value
Number of cases		163	56	107	–
Age (years), range		60.5, 20–98	59.7, 20–98	60.9, 25–96	0.650
Male gender, n (%)		96 (58.9)	28 (50.0)	68 (64.0)	0.950
Ethnicity, n (%)	Caucasian	117 (71.8)	45 (80.4)	72 (67.3)	0.318
	African American	29 (17.8)	6 (10.7)	23 (21.5)	
	Other	17 (10.4)	5 (8.9)	12 (11.2)	
Body mass index (mean)		29.1	29.2	29.0	0.901
Systemic inflammatory response syndrome (SIRS) criteria (mean)		2.9	2.7	3.0	0.293
Required mechanical ventilation, n (%)		57 (35.0)	18 (32.1)	39 (36.4)	0.584
Required vasopressor(s), n (%)		65 (39.9)	27 (48.2)	38 (35.5)	0.116
Number of vasopressor(s) (mean)		1.6	1.5	1.7	0.286
ICD-10 diagnosis codes, n (%)	Sepsis	29 (17.8)	13 (23.2)	16 (15.0)	0.111
	Severe sepsis	67 (41.1)	17 (30.4)	50 (46.7)	
	Septic shock	67 (41.1)	26 (46.4)	41 (38.3)	

CF: culture-first; AF: antimicrobial-first.

2.3. Outcomes and assessments

The primary outcome measure was incidence of positive-culture from an appropriate site. A positive-culture was defined as a microbiologic culture collected from the relevant source (as defined in Table 1) resulting any organism that is not reported as normal flora or a contaminant by TUKHS laboratory. Secondary outcome measures included the incidence of FAD administered within 60 min and 180 min from presentation (SSC and CMS recommended timeframes, respectively); TFAD from time-zero (hours); time to first antimicrobial de-escalation (days); time to anti-methicillin resistant *Staphylococcus aureus* (anti-MRSA) agent discontinuation (days); number of consecutive days on antimicrobials; incidence of positive *C. difficile* polymerase chain reaction (PCR) and documented fungal infection after antimicrobial initiation during the admission; ICU and hospital lengths of stay (LOS) (days); readmission rate at 30 days; and in-hospital mortality at

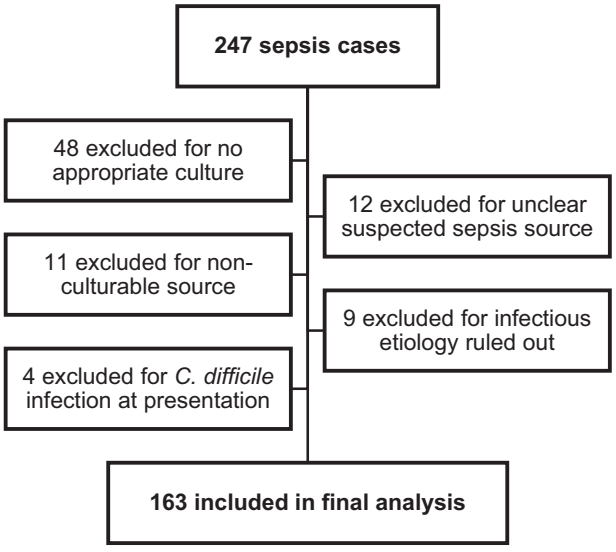

Fig. 1. Case selection.

28 days. These outcomes were compared between the culture-first (CF) and antimicrobial-first (AF) cohorts. The CF cohort included cases in which the appropriate culture was collected prior to FAD, and conversely, the AF cohort were cases in which an antimicrobial was given prior to appropriate culture collection.

Antibiotic restart was defined as having all antimicrobials discontinued from the patient's EMR for a period of at least 24 h before the same or other antimicrobials were ordered. Rate of antibiotic restart was evaluated as a surrogate marker for appropriate discontinuation and treatment duration.

Baseline characteristics included age; gender; race; body mass index (BMI); vasopressor utilization, number of discrete vasoactive agents required, and mechanical ventilation dependence in the first 24 h from presentation; body temperature, heart rate, respiratory rate, and white blood cell count (peak or nadir as appropriate according to SIRS criteria) in the first 24 h from presentation to the ED.

3. Results

In the study period, 247 cases met criteria to be included. Forty-eight were excluded for no appropriate culture collected, 12 were excluded for unclear suspected sepsis source, 11 were excluded for non-culturable sepsis source, nine were excluded for infectious etiology rule out, and four were excluded for *C. difficile* infection at presentation. There were two patients who had two distinct suspected sources documented in the history and physical note and had appropriate cultures collected for both sites. For these two patients all data points were duplicated to allow each suspected source to be isolated and analyzed as separate septic cases in their respective sepsis source groups. Altogether, this resulted in 163 cases to be included for final analysis.

Sepsis sources included pulmonary infections (39.3%), urinary tract infections (35.6%), intra-abdominal infections (8.0%), skin and skin-structure infections (SSSI) (6.7%), bacteremia/infective endocarditis (5.5%), meningitis (3.1%), and bone/joint infections (1.8%). CF and AF cohorts accounted for 56 (34.4%) and 107 (65.6%) cases, respectively (Table 3).

The CF cohort was 50% male and 80.4% Caucasian. On average the cases were 59.7 years old, with a mean SIRS criterion of 2.7, 32.1% required mechanical ventilation, and 48.2% required vasopressors (mean of 1.5 vasoactive agents). Comparatively, the AF cohort was 64% male and 67.3% Caucasian. On average the cases were 60.9 years old, with a mean SIRS criterion of 3.0, 36.4% required mechanical ventilation, and 35.5% required vasopressors (mean of 1.7 vasoactive agents). Incidence of sepsis, severe sepsis, and septic shock ICD-10 codes were not difference between groups ($p = 0.111$). No baseline characteristics were found to be statistically significantly different between the CF and AFs cohorts (Table 2).

Table 3
Sepsis sources.

Sepsis Source	Overall, *n* = 163	CF cohort, *n* = 56	AF cohort, *n* = 107	*p* value*
Pulmonary, *n* (%)	64 (39.3)	6 (9.4)	58 (90.6)	<0.005
Urinary tract, *n* (%)	58 (35.6)	37 (63.8)	21 (36.2)	<0.005
Intra-abdominal, *n* (%)	13 (8.0)	3 (23.1)	10 (76.9)	0.372
Skin and skin structure, *n* (%)	11 (6.7)	2 (18.2)	9 (81.8)	0.242
Bacteremia/infective endocarditis, *n* (%)	9 (5.5)	7 (77.8)	2 (22.2)	0.005
Meningitis, *n* (%)	5 (3.1)	1 (20.0)	4 (80.0)	0.492
Bone/joint, *n* (%)	3 (1.8)	0 (0)	3 (100.0)	–

CF: culture-first; AF: antimicrobial-first.
* *p* values describe the difference in CF vs. AF cohort distribution per sepsis source group.

There was a significantly higher incidence of positive-cultures in the CF cohort compared to the AF cohort overall (80.4% vs. 46.7%, $p < 0.005$). Isolating the UTI sepsis source group, cultures were also more frequently positive in the CF cohort (89.2% vs. 47.6%, $p = 0.01$). Conversely, isolating all non-UTI sepsis source groups, there was a trend toward increased positive-cultures in the CF cohort (63.2% vs. 46.5%, $p = 0.189$) (Table 4).

FAD was administered within 60 min from time-zero in 14.3% vs. 19.6% of cases in the CF cohort vs. AF cohort ($p = 0.397$) and within 180 min from time-zero in 58.9% vs. 73.8% of cases ($p = 0.051$), respectively. Mean TFAD was greater in the CF cohort (202 min vs. 153 min, $p = 0.036$). Time to first de-escalation in the CF and AF cohort was 3.0 days vs. 2.6 days ($p = 0.313$), and time to anti-MRSA de-escalation was 4.5 vs. 4.8 days ($p = 0.755$), respectively. There was a trend toward less consecutive days on antibiotics in the CF cohort (6.8 days vs. 7.7 days, $p = 0.350$). CF cohort cases tended to have shorter ICU and hospital LOS (6.8 days vs. 8.4 days, $p = 0.122$; 11.5 days vs. 13.5 days, $p = 0.218$, respectively) (Table 5).

C. difficile and fungal secondary infections occurred infrequently in both cohorts, but *C. difficile* infections were slightly more common in the AF cohort although not statistically different compared to the CF cohort (1.9% vs. 5.7%, $p = 0.270$). Secondary fungal infections occurred in similar incidence between groups as well (1.8% vs. 0.9%, $p = 0.639$). Readmission at 30 days was similar between cohorts (17.9% vs. 16.8%, $p = 0.868$), and in-hospital mortality at 28 days was marginally lower in the CF cohort although not statistically different compared to the AF cohort (7.1% vs. 10.3%, $p = 0.149$). Antibiotic restart was less frequent in the CF cohort (10.7% vs. 17.8%, $p < 0.005$) (Table 6).

In a post-hoc analysis of culture positivity based on site of collection, it was clarified that positive-cultures from any site were obtained in 63.8% (104/163) of cases. Of these positive-culture cases, appropriate site cultures were positive in 91.3% (95/104) of cases, whereas blood cultures were positive in only 42.3% (44/104) of cases ($p < 0.005$). Furthermore, among cases with positive appropriate cultures, blood cultures were negative in 63.2% (60/95) of cases; representing a significant population that would have failed to identify a pathogen had blood cultures been the only culture collected (Table 7).

4. Discussion

The 163 sepsis cases can be more specifically stratified into six distinct sepsis sources (pulmonary, urinary tract, intra-abdominal, SSSI, bacteremia/infective endocarditis, meningitis, bone/joint). Pulmonary infections, intra-abdominal infections, SSSI, meningitis, and bone/joint infections all more frequently had cultures collected after FAD. Conversely, UTI and bacteremia/IE more frequently had cultures collected before FAD. This is most likely due to the nature of collecting the cultures relevant to these sepsis sources. Urine samples are typically easily produced by patients, and blood cultures are very often the first cultures collected for all septic patients. Alternatively, the remaining sepsis sources may have more difficult to obtain appropriate cultures (e.g. cerebrospinal fluid from a lumbar puncture).

Due to heterogeneity of sepsis sources in the overall analysis, wherein all suspected groups are combined, statistical analysis is

Table 4
Culture outcomes.

Sepsis source	Positive appropriate culture		*p* value*
	CF cohort	AF cohort	
Overall, *n* (%)	45/56 (80.4)	50/107 (46.7)	<0.005
UTI, *n* (%)	33/37 (89.2)	10/21 (47.6)	0.01
Non-UTI, *n* (%)	12/19 (63.2)	40//86 (46.5)	0.189

CF: culture-first; AF: antimicrobial-first; UTI: urinary tract infection.
* *p* values describe the difference in incidence of positive-culture in the CF vs. AF cohorts.

Table 5
Temporal outcomes.

Outcome		CF cohort, $n = 56$	AF cohort, $n = 107$	p value
FAD ≤ 60 min*, n (%)		8 (14.3)	21 (19.6)	0.397
FAD ≤ 180 min*, n (%)		33 (58.9)	79 (73.8)	0.051
TFAD*, mean (minutes)		201.8	152.9	0.036
Time to de-escalation, mean (days)	Any ABX	3.0	2.6	0.313
	Anti-MRSA	4.5	4.8	0.755
Consecutive days on ABX, mean (days)		6.8	7.7	0.350
LOS, mean (days)	ICU	6.8	8.4	0.122
	Hospital	11.5	13.5	0.218

CF: culture-first; AF: antimicrobial-first; FAD: first antimicrobial dose; *from time zero; TFAD: time to FAD; ABX: antibiotic(s); MRSA: methicillin-resistant *Staphylococcus aureus*; LOS: length of stay; ICU: intensive care unit.

potentially flawed, and differences found between cohorts in this manner should be taken with caution. When evaluating the discrete sepsis sources to examine the primary outcome measure, there was only one sepsis source group which had sufficient cases in both cohorts to perform an appropriate analysis. The UTI sepsis source group had 58 cases (37 in the CF cohort and 21 in the AF cohort) and analysis of this group reaffirmed the overall hypothesis that cultures are more likely to result positive in the CF cohort. While we theorize that this validates the results seen in the overall analysis, it is probable that the UTI sepsis source group is driving the difference seen as it is a part of the overall analysis. A larger study population would be required to achieve sufficient incidence in both cohorts among multiple sepsis source groups to more accurately validate the results found in this study.

Percent of FAD being administered within 60 min from time zero was substantially lower than expected given the urgent nature of antimicrobial initiation in septic patients. It is plausible that time-zero is calculated unsuitably early in the sepsis work up process, falsely portraying a delay of FAD.

The mean TFAD was greater in the CF cohort compared to the AF cohort. This was somewhat expected and warned of in the SSC guidelines. Cases in the CF cohort may very well have had FAD delayed while appropriate cultures were being obtained.

Consecutive days on antibiotics was on average 0.9 days less in the CF cohort, although this was not found to be statistically significant. It was hypothesized that the AF cohort would have greater time to first de-escalation and anti-MRSA de-escalation due to inability to evaluate culture data, but this was not seen in the analysis. It may stand to reason that there is a mixture of de-escalating early due to positive-cultures (i.e. narrowing of antibiotics) and de-escalating early due to no positive-cultures (i.e. decision that MRSA coverage is unnecessary).

ICU LOS and overall hospital LOS between the groups were on average longer in the AF cohort, though not statistically different. However, any additional days in an ICU or hospital may be considered clinically relevant.

Secondary infections of *C. difficile* occurred more frequently in the AF cohort and may have found statistical significance if this study were larger. Readmissions at 30-days were approximately the same between cohorts. Lastly, mortality at 28-days was 3.2% greater in the AF group but also not statistically significant. Overall mortality for this study was 9.2%. Again, a larger study may reveal differences which this study's results trended toward.

The AF cohort had a greater incidence of antibiotic restart compared to the CF cohort. This suggests antibiotics were discontinued earlier than indicated, potentially based upon negative-cultures, which were more common in this cohort. To test this theory, the same outcome was analyzed with cases divided by positive and negative-cultures. There was no difference found when the cohorts were re-evaluated this way (Table 6). We propose that antibiotics were discontinued in the CF cases with knowledge of properly timed culture collection, and therefore physicians were less inclined to restart antibiotics due to confidence in the initial course of therapy or lack thereof.

The post-hoc analysis of culture positivity suggests that appropriate cultures are perhaps as valuable, if not more valuable, than blood cultures. This is evidenced by blood cultures failing to identify a pathogen that was identified by an appropriate culture in 63.2% of cases. Importantly, this represents patients that would have failed to have an identified pathogen had blood cultures been the only culture collected. Conversely, appropriate cultures failed to identify a pathogen that was identified by a blood culture in only 20.5% (9/44) of cases.

Limitations of this research include the single center, retrospective nature required for studying these clinical questions, which a randomized interventional study could not perform. The asymmetrical distribution into sepsis sources (Table 3) hindered the robustness of statistical analyses. Additionally, for overall analyses, results must be taken with caution because heterogenous sepsis sources may not be entirely intercomparable. Lastly, this study is focused on patients admitted to the ICU, thus results may not be generalizable to non-ICU patients. Future research on this topic in non-ICU patients is needed.

5. Conclusions

If the results of this study are generalizable to sepsis management elsewhere, it is concerning to find that 19.4% of cases did not have appropriate cultures collected from relevant sites. Note, these cases were excluded from the study and may be an area which future research explores. While it may be appropriate to collect blood cultures on all sepsis patients, blood cultures inconsistently result with organism(s) present at the source of the infection. Furthermore, appropriate cultures from relevant, suspected sites should be obtained if this does not delay TFAD. Further analysis of these clinical questions with a larger study population will be required to confirm several outcomes which trended toward difference but did not reach significance.

Sepsis management includes many variables that play significant roles in patient outcomes. Healthcare providers must be cognizant of these variables to aid in improving outcomes. Appropriately timed cultures from relevant sources are crucial to providing optimal antimicrobial stewardship for septic patients. Considering these results, the SSC guideline bundle recommendations regarding culture collection may warrant clarification that appropriate cultures from the suspected site is crucial for pathogen identification. ED healthcare providers should

Table 6
Complications outcomes.

Outcome	CF cohort, $n = 56$	AF cohort, $n = 107$	p value
Clostridium difficile infection, n (%)	1 (1.9)	6 (5.7)	0.270
Fungal infection, n (%)	1 (1.8)	1 (0.9)	0.639
Readmission at 30 days, n (%)	10 (17.9)	18 (16.8)	0.868
In-hospital mortality at 28 days, n (%)	4 (7.1)	11 (10.3)	0.149
Antibiotic restart, n (%)	6 (10.7)	19 (17.8)	<0.005

Outcome	Positive-culture	Negative-culture	p value
Antibiotic restart, n (%)	16/95 (16.8%)	9/68 (13.2)	0.529

CF: culture-first; AF: antimicrobial-first.

Table 7
Culture result.

Outcome	Positive-culture	Negative-culture	*p* value
Overall, *n*/163 (%)	104 (63.8)	59 (36.2)	–
Appropriate site culture, *n*/163 (%)	95 (58.3)	68 (41.7)	–
Blood cultures, *n*/163 (%)	44 (27.0)	119 (73)	–
Outcome	Appropriate Site	Blood	*p* value
Positive-culture, *n*/104 (%)	95 (91.3)	44 (42.3)	<0.005

take steps to evaluate their culture collection practices as it may carry significant implications on patient outcomes.

In conclusion, this research validates the sensical hypothesis that cultures may be sterilized if collected after FAD. Patients are at risk of having antimicrobials delayed while collecting appropriate cultures, and patients who had FAD prior to culture obtainment have less positive-cultures, a trend toward longer ICU and hospital LOS, and perhaps a higher risk of *C. difficile* infection and mortality.

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