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Time to Grow Positive Blood Cultures and Its Impact on Clinical Outcomes in Patients with Bacteremia Admitted to Intensive Care Unit

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Time to positivity of blood cultures · Clinical outcomes · Bacteremia · Critical · Infectious · Inflammatory markers · Medicine

Abstract
Introduction: Bloodstream infections are one of the leading causes of mortality and morbidity. Time to positive blood culture may be reflective of the severity of infection. We aim to study the impact of time to positivity (TTP) of blood culture upon clinical outcome. ***Methods:*** Data from blood cultures for 17 months duration reviewed. Outcome measures included in-hospital mortality and length of stay in ICU (LOS-ICU). TTP was determined for each sample. Demographics (age, gender, BMI, and nationality), APACHE-2 score for severity of illness, comorbid conditions, and other confounding factors were recorded. ***Results:*** One hundred and one patients with 346 positive blood cultures with mean age of 62 and mean APACHE-2 score of 18.9 + 9.7 (mean +SD) with overall observed mortality of 61%. Median TTP was 20.2 h with quartiles cutoff Q1 = 15.3, Q2 = 20.2, Q3 = 28, and range 8–104 h. Only APACHE-2 scores predict LOSICU. TTP is not a significant predictor for mortality or LOSICU. ***Discussion:*** Data on TTP of blood cultures have a complex interaction with clinical outcomes. ***Conclusion:*** TTP of blood cultures does not predict mortality or length of stay in ICU.

Introduction

Bloodstream infections (BSIs) are one of the leading causes of mortality and morbidity due to infection in the USA [1]. Bacteremia may result from pneumonia, soft tissue or skin infection, urinary tract infection, urinary catheter related infection, or catheter related BSI. Blood cultures are cost effective measures for optimal management of septic shock [1, 2]. Time to positive blood culture in specimens taken concomitantly from catheters

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Table 1. Sample characteristic

Categorical variables	All	Died	Alive	*p* value
Total sample, *N*	101	62	39	
Gender male/female, *n*	55/46	31/31	23/16	0.2
Emirati/expatriate, *n*	35/66	23/39	12/27	0.3
Resistant organism (yes), *n* (%)	38 (37)	26 (25)	12 (11.8)	0.1
On antibiotic at blood culture draw time, *n* (%)	56 (55)	38 (37)	18 (17)	0.1
Follow-up cultures blood culture, *n* (%)	59 (58)	30 (29)	29 (28)	0.01
Follow-up culture with growth, *n* (%)	19 (18)	10 (9)	9 (9)	0.06
Patient in shock (yes), *n* (%)	54 (53)	39 (38)	15 (14)	0.01
Infiltrate on X-ray chest (yes), *n* (%)	52 (51)	36 (35)	16 (15)	0.04
Vasopressor (used), *n* (%)	61 (60)	42 (41)	19 (18)	0.06
MV, *n* (%)	70 (69)	52 (51)	18 (17)	0.01
Immunosuppressed (yes), *n* (%)	25 (24)	18 (17)	7 (6)	0.13
Hemodialysis (yes), *n* (%)	13 (12)	11 (10)	2 (2)	0.06
Cancer diagnosis (yes), *n* (%)	17 (16)	12 (11)	5 (5)	0.25
Chemotherapy (yes), *n* (%)	14 (13)	10 (9)	4 (4)	0.26
Prior steroids (yes), *n* (%)	28 (27)	19 (18)	9 (9)	0.29
Diabetes (present), *n* (%)	52 (51)	36 (35)	16 (15)	0.11
Prior antibiotics within 90 days, *n* (%)	65 (64)	46 (45)	19 (18)	0.01
Continuous variables	**All**	**Died**	**Alive**	***p* value**
Age, median (range), years	65 (61–72)	68 (64–72)	54 (43–74)	0.06
Time to positive median (range), h	20.2 (96)	20.7 (80)	20 (96)	0.30
Procalcitonin, ng/mL	1.8 (180)	2.1 (82.6)	1.19 (180)	0.1
CRP, mg/L	148 (445)	173 (396)	114 (442)	0.01
WBC, ×1,000/mm^3	13.5 (47.8)	14.9 (47.8)	13.2 (32)	0.1
Platelets, ×1,000/mm^3	167 (470)	150 (463)	197 (470)	0.4
APACHE-2 scores	21 (64)	23 (61)	21 (33)	0.2
LOSICU, days	6 (50)	5 (50)	8 (34)	0.05
LOSH, days	9 (248)	6 (247)	17 (100)	0.01

MV, mechanical ventilation; CRP, C-reactive protein; LOSICU, length of stay in ICU; LOSH, length of stay in hospital.

and peripheral blood help define if the catheter is the source of bacteremia [3]. It is plausible that early positivity (>2 h early) in specimens taken from a catheter suggests catheter is the source. Similarly, earlier growth of organisms in the specimen may suggest a bigger load of organisms in blood, which may be reflective of the severity of infection. Early detection of positive blood culture leads to early initiation of antimicrobial therapy, targeted therapy, or escalation or de-escalation of antimicrobial treatment. Therefore, these timings are important clinical parameters which may affect clinical outcomes. Giving early and correct antibiotics to patients with sepsis possibly within 1–3 h improves clinical outcomes [4]. Therefore, time to positivity (TTP) of culture in bacteremia is an important clinical variable which may impact outcome. Most studies are done on hospital population without focus on ICU. Most such studies also do not record and adjust many important parameters determining clinical outcomes as mostly conducted by infectious disease researchers or microbiologists. Clinical outcomes like mortality and length of stay in ICU (LOSICU) and length of stay in hospital (LOSH) are determined by multiple factors; age, gender, BMI, comorbid conditions [5], immune status of the patient, severity of the illness, virulence of the organism, resistance of the organism to antimicrobials, coinfection by multiple organisms, fluid therapy, corticosteroid use [6], glucose control, and adherence to protocols, including early goal-directed therapy and infection-control measures. Therefore, any study evaluating the relationship of TTP in bacteremia and clinical outcome must measure and adjust for all important clinical variables which is lack-

ing in most clinical studies on this issue. We aim to study the impact of TTP of blood culture upon clinical outcomes while recording and adjusting for these important clinical confounding parameters by conducting a retrospective chart review, single-center clinical study in the ICU population.

Methods

Records of all positive blood cultures for 17 months duration August 1, 2017 to December 31, 2018 were reviewed. Primary outcome measures included in-hospital mortality, LOSICU, and LOSH.

The TTP were determined from the time interval between the start of incubation and the detection of microbial growth, as documented using an automated monitoring system (BD BACTEC™ FX Blood Culture System – Becton Dickinson). When multiple cultures from the same time were positive, only the shortest TTP was selected for analysis. When a patient had multiple blood cultures at different times only the last incidence of bacteremia was included for analysis. Demographics (age, gender, BMI, and nationality), APACHE score for severity of illness, comorbid conditions (diabetes, hypertension, and COPD) type of blood culture (central catheter and cutaneous peripheral), results of respiratory culture, urine culture, catheter tip culture, antibiotic susceptibility pattern, start time of antimicrobial, use of mechanical ventilation (MV), presence of infiltrate on chest X-ray, usage of vasopressors, presence of renal failure, thrombocytopenia, and results of follow-up blood culture, were also recorded.

Laboratory Parameters

C-reactive protein (CRP), procalcitonin, and WBC count on the day of blood culture draw were recorded. Presence of immunosuppression from medication review (i.e., steroids) or from a pathology (leukemia) if present were also recorded. Other confounding variables include cancer, chemotherapy, prior use of antibiotics within 90 days of admission, need for MV, and need for renal replacement therapy.

LOSICU and hospital was measured from the day the blood culture was taken till the discharge of the patient. Ethical approval was approved by Dubai scientific Research Ethics Committee (DSREC-12/2018, 13 approved on January 13, 2019).

Statistical Analysis

Dependent variables include, in hospital mortality, LOSICU, and Hospital (LOSH). Primary independent variable of interest was TTP of blood cultures. All other variables were used as confounding variables with possible impact on clinical outcomes.

χ^2 tests were performed to compare all categorical variable between the two groups (died vs. survived) (Table 1 upper panel). Data were not normally distributed. Median test was performed for all continuous variables to compare medians between groups (Table 1 lower panel). For the outcome of mortality, logistic regression was performed. For the outcomes of LOSICU and LOSH (numerical), we normalized the LOSICU and LOSH data by log transformation and then ran the least square regression on the transformed data.

Table 2. Logistic regression analysis for outcome of mortality

	B	*p* value	Odds ratio
TTP (h)	−0.358	0.339	0.699
Gender (male/female)	−0.425	0.637	0.654
Age (years)	0.027	0.329	1.027
UAE (nationals/expatriates)	1.480	0.122	4.391
On antibiotics at culture time[a]	1.426	0.117	4.161
Follow-up blood cultures ordered	0.479	0.636	1.614
Follow-up culture with resistant organism	0.139	0.939	1.149
Procalcitonin	−0.050	0.013	0.951
CRP	0.009	0.049	1.009
WBC	0.108	0.039	1.114
Platelets	−0.006	0.161	0.994
Shock	3.429	0.038	30.85
Infiltrate on chest X-ray	0.091	0.924	1.096
Vasopressors	−2.568	0.084	0.077
MV	1.738	0.047	5.686
Immunosuppressed	3.100	0.080	22.18
Hemodialysis	2.204	0.185	9.064
Cancer	−0.469	0.787	0.626
Chemotherapy	−2.045	0.253	0.129
Prior steroids	−0.897	0.506	0.408
Diabetes	0.374	0.700	1.454
Prior antibiotics (90 days)	1.730	0.108	5.642
APACHE	0.029	0.526	1.029

MV, mechanical ventilation; CRP, C-reactive protein; TTP, time to positivity. [a] Where unit is not mentioned, it is odds of presence of variable versus absence of variables.

Results

Sample characteristics are presented in Table 1. Sample included 101 patients with 346 positive blood cultures (many patients had multiple occurrences of bacteremia) with a median age of 65 years and a median APACHE-2 score of 21 with an overall observed mortality of 61%. Median TTP was 20.2 h with quartiles cutoff; Q1 = 15.3, Q2 = 20.2, Q3 = 28, range 8–104 h. Patients who died were older, have significantly higher evidence for infiltrate on X-ray, MV, shock, use of antibiotics within 90 days of admission to ICU, and presence of repeated orders of blood cultures. Platelet count was significantly lower in those died.

For the outcome of mortality, logistic regression analysis was performed. We determined TTP does not predict mortality, only procalcitonin, CRP, WBC, shock, and MV predicted mortality (Table 2).

For the outcome of LOSICU, least square regression analysis on log transformed data showed TTP does not

Table 3. LSR (predictor of LOSICU)

Dependent variable	log-LOSICU	*p* value	95% CI for *B*	
			lower bound	upper bound
(Constant)	0.812	0.011	0.200	1.423
Gender (male/female)	0.009	0.937	−0.209	0.226
Age (years)	−0.004	0.274	−0.010	0.003
TTP (h)	0.002	0.392	−0.003	0.008
On antibiotics at culture drawn time[a]	−0.004	0.968	−0.217	0.208
Follow-up blood cultures ordered	0.253	0.073	−0.025	0.531
Procalcitonin (ng/mL)	0.000	0.834	−0.005	0.004
CRP (mg/L)	−0.001	0.118	−0.002	0.000
WBC (×1,000/mm^3)	0.002	0.794	−0.011	0.014
Platelets (×1,000/mm^3)	0.000	0.406	−0.002	0.001
Shock[a]	−0.144	0.428	−0.506	0.219
Infiltrate on chest X-ray[a]	−0.107	0.388	−0.355	0.141
Vasopressors[a]	0.196	0.270	−0.158	0.551
MV[a]	−0.077	0.508	−0.311	0.156
Immunosuppressed[a]	−0.149	0.383	−0.491	0.193
Hemodialysis[a]	0.074	0.674	−0.279	0.427
Cancer[a]	0.143	0.463	−0.246	0.532
Chemotherapy[a]	0.186	0.362	−0.221	0.594
Prior steroids[a]	0.015	0.927	−0.306	0.335
Diabetes[a]	0.043	0.753	−0.231	0.317
Prior antibiotics (90 days)[a]	0.118	0.368	−0.144	0.380
APACHE-2 scores	0.002	0.644	−0.008	0.013

LOSICU, length of stay in ICU; MV, mechanical ventilation; CRP, C-reactive protein; LSR, least square regression; TTP, time to positivity. [a] Where unit is not mentioned, it is odds of presence of variable versus absence of variables.

predict LOSICU. No other variable predicts LOSH (Table 3). Similar analysis for LOSH determines that TTP does not predict LOSH and no other variable predicts LOSH (Table 4).

Discussion

Our analyses suggest that TTP of a blood culture for the single incidence of bacteremia is not a significant predictor for mortality, LOSICU, and hospital. The issue is complex though, as multiple blood cultures in a patient at different time frames may have a cumulative effect which complicates the model to assess this relationship. Cillóniz et al. [7] showed that TTP on blood cultures in pneumococcal pneumonia is a significant predictor of clinical outcomes. Martín-Gutiérrez et al. [8] showed higher mortality in patient who either grow blood organism <12 h or >27 h comparing the patient whose blood culture grow organism in 12–27 h. Another study showed that BSI with *Pseudomonas* with TTP ≤18 h is independently associated with mortality [9]. Kim et al. [10] studied TTP for *Staphylococcus aureus* and found that patients with TTP ≤12 and >48 h suffered the higher case-fatality rate than those with TTP (12–48 h). The reasons for the difference in results between our study and these studies are few; population studied as they studied hospital patients (ICU and non-ICU), while we studied bacteremia as a group regardless of organism in ICU population. Moreover, our patients have more than one episode of bacteremia and more likely have cumulative effects of these events.

Most studies addressing the impact of TTP on mortality were focused on specific organisms and sites of infection with less focus on clinical coordinates and other variables affecting mortality, that is, comorbidities like cancer, chemotherapeutic agents, immunosuppression, presence of MV, shock, or pressers which are significant determinants of mortality and LOS. For example, Khatib et al. [11] showed that patients with TTP for *Staphylococcus aureus* within 14 h are more likely to have endovascular infection sources and complications, although they did not control for the severity of the underlying illnesses. Our sample was an ICU population with assessment of

Table 4. LSR (predictor of LOSH)

Dependent-variable	log-LOSH	*p* value	95% CI for *B*	
			lower bound	upper bound
Constant	1.465	0.001	0.639	2.291
Gender (male/female)	−0.116	0.433	−0.411	0.179
Age (years)	−0.003	0.463	−0.013	0.006
TTP (h)	−0.002	0.603	−0.010	0.006
On antibiotics at culture drawn time[a]	−0.072	0.619	−0.364	0.219
Follow-up blood cultures ordered	0.298	0.108	−0.069	0.665
Procalcitonin (ng/mL)	0.003	0.347	−0.003	0.009
CRP (mg/L)	−0.001	0.343	−0.002	0.001
WBC (×1,000/mm^3)	−0.004	0.666	−0.020	0.013
Platelets (×1,000/mm^3)	2.568E−05	0.973	−0.001	0.002
Shock[a]	−0.184	0.466	−0.687	0.320
Infiltrate on chest X-ray[a]	−0.308	0.078	−0.651	0.036
Vasopressors[a]	0.208	0.404	−0.289	0.705
MV[a]	−0.227	0.158	−0.545	0.092
Immunosuppressed[a]	−0.087	0.717	−0.565	0.391
Hemodialysis[a]	0.161	0.513	−0.330	0.651
Cancer[a]	0.068	0.802	−0.477	0.613
Chemotherapy[a]	0.206	0.470	−0.365	0.778
Prior steroids[a]	−0.066	0.765	−0.512	0.379
Diabetes[a]	−0.062	0.744	−0.446	0.321
Prior antibiotics (90 days)[a]	0.178	0.314	−0.175	0.531
APACHE-2 scores	0.001	0.932	−0.014	0.015

MV, mechanical ventilation; CRP, C-reactive protein; LOSH, length of stay in hospital; LSR, least square regression; TTP, time to positivity. [a] Where unit is not mentioned, it is odds of presence of variable versus absence of variables.

clinical variables without single organism focus, a real-life phenomenon in ICU. To our knowledge, there is no study on ICU population addressing impact of TTP on clinical outcomes. The difference could be from different organisms in the sample. In our sample, Gram-negative bacteria were >50%, Gram positives were 31%, while 13% were fungi, prevalence of resistance to antimicrobials in our sample was 45% for GN, 38% for Gram positive, and 15% for fungi. More than 50% of blood cultures in our sample comprised following 4 organisms in decreasing order of frequencies; *Klebsiella pneumoniae* (20%) with a fatality rate of 55%, *Candida* species (14%) with fatality a rate of 92%, *Escherichia coli* (13%) with fatality rate of 69%, and *Pseudomonas aeruginosa* (9%) with fatality rate of 66.6% (Table 5).

We identify the following weakness of our study. It is a single-center retrospective chart review study with relatively small sample size, which may not be enough to exclude this association. This study was without specific organism focus, although it is the real-life scenario in ICU that our study specifically addressed, where bacteremia is a clinical finding regardless of the organism, and its im-

Table 5. Organisms in blood cultures (*N* = 101)

	All	Died	Alive	Mortality rate, %
Klebsiella	20	11	9	55
Candida	14	13	1	92.8
E. coli	13	9	4	69.2
Pseudomonas	9	6	3	66.6
Staphylococcus epidermidis	9	2	7	22.2
Staphylococcus aureus	4	2	2	50
Acinetobacter	4	3	1	75
Staphylococcus capitis	3	2	1	66.6
Staphylococcus haemolyticus	3	2	1	66.6
MRSA	3	1	2	33.3
Enterococcus	3	0	3	0
Bacteroides	3	3	0	100
Streptococcus	3	0	3	0
Enterobacter	2	0	2	0
Stenotrophomonas	2	2	0	100
Staphylococcus hominis	1	1	0	100
Fusobacterium	1	0	1	0
Lactobacillus	1	1	0	100
Serratia	1	0	1	0
Providentia	1	1	0	100
Haemophilus	1	0	1	0

pact on clinical outcome is addressed with control of significant coexisting clinical factors affecting clinical outcomes which are not addressed before in any study on ICU population with bacteremia.

Conclusion

TTP in bacteremia is an important clinical variable. TTP of bacteremia does not predict mortality. Larger studies are required to evaluate impact of TTP upon clinical outcome.

Statement of Ethics

Ethical approval was provided by DSREC, DSREC-12/2018_03/ approved on January 13, 2019.

Conflict of Interest Statement

There are no conflicts of interest.

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Author Contributions

R.N.: research idea conception, proposal writing, data collection, data analysis, and manuscript writing. A.H.: idea conception, proposal writing, and review of final manuscript. L.S.: idea conception and data collection. M.M.: idea conception and data collection. I.B.; data collection. S.K.: idea conception and data collection. A.S.: idea conception and data collection. R.A.: idea conception and data collection. Z.O.: idea conception and data collection. M.E.: idea conception and data collection.

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