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Original Research Article

Time to positivity of blood culture as a prognostic marker in predicting the clinical outcome of blood stream infection

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ABSTRACT

Introduction: Automated blood culture systems provide continuous monitoring of bacterial growth, and time to positivity (TTP), may be used as good tool for diagnosis of blood stream infections. Objective of the study was to document bacterial profile and their susceptibility pattern and to evaluate the association between the TTP and clinical outcome in patients with BSIs.

Materials and Methods: A cross-sectional study was conducted (after obtaining waiver of consent from institute ethics committee), on 75 patients with positive blood culture. Laboratory data such as TTP, bacterial pathogen isolated from positive blood cultures and their susceptibility pattern, clinical parameters such as demographic characteristics, source of BSIs, severity of infection as per various clinical scores were analysed for patients with TTP ≤10 hours and > 10 hours using univariate analysis.

Results: *Escherichia coli* was the commonest gram-negative bacterial isolate (33.3%), and Staphylococcus aureus was the commonest gram-positive bacterial isolate (22.2%). Antimicrobial resistance rate in GNB was very high for cefotaxime (57%), ciprofloxacin (44%) and among gram-positive bacterial isolates was high for clindamycin (56.5%), and cefotaxime (50%). In the study, median TTP was 13 hours and short TTP of ≤10h was observed for *Escherichia coli*, and *Streptococcus pneumoniae*. There were statistically significant differences observed for end stage renal disease, diabetes association and neutropenia patients with short TTP.

Conclusion: Time to positivity is a useful tool for to-measure laboratory prognostic factor for patients with bacteremia. However, further studies with larger sample size, may be required to define its usefulness and the optimal cut-off points.

1. Introduction

Blood stream infection (BSI) has been closely associated with increased incidences of hospitalization, length of hospital stay, hospital cost and higher rates of mortality ranging from 21% to 69%.[1,2] Prompt and appropriate antibiotic therapy can reduce the mortality and morbidity among these patients. Isolation and identification of the pathogen by blood culture and antimicrobial susceptibility testing are vital steps in the diagnosis and management of BSI.[2–4] Blood culture techniques typically require minimum of 48 to 72 hours, even for a preliminary report. Hence, a test that would provide early evidence of blood stream infection would potentially be of clinical value.[5]

Bacterial load may be indirectly measured by considering the time to positivity (TTP) of blood cultures. TTP is defined as the length of time from the beginning of culture incubation to the detection of bacterial growth by an automated blood culture system, and has been proposed as a diagnostic and prognostic tool in early and prompt

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management of a case of blood stream infection.[3,6] TTP of blood culture may be influenced by the infecting pathogen, concentration of pathogen in the blood sample, patients clinical characteristics, presence of antimicrobial agents, blood collection time and processing parameters such as delay of sample transfer and thus, can provide information about source of infection and level of contaminants. As TTP would provide an early evidence of BSI, it may help in early modification of the empirical treatment and thereby contribute in reducing antibiotic resistance.[3,5,6]

2. Aims and Objectives

1. To document bacterial profile and their susceptibility pattern among patients with blood stream infection.
2. To evaluate the association between the time to positivity of blood cultures (TTP) and clinical outcome in patients with blood stream infections such as mortality indicator (infection related deaths), morbidity indicators such as severity of infection and duration of hospital stay.

3. Material and Methods

A cross-sectional study was conducted after obtaining a waiver of consent from Institute Ethics Committee (IEC:RC/18/13). All consecutive eligible patients (n=75) admitted in various wards of a tertiary care hospital during the two months' period from 15^{th} May 2018 to 15^{th} July 2018, with positive blood culture were included in the study. Repeat isolates from the same patient, all the blood cultures reported as contaminants grown, and polymicrobial infections were excluded from the study.

3.1. Brief procedure

Data of all included patients, were collected and analysed.

1. The following data were collected from laboratory records-
   (a) Time to positivity (TTP) of blood cultures
   (b) Gram stain report from positive blood culture bottles was noted.
   (c) Bacterial pathogen isolated from positive blood cultures was documented.
   (d) Antimicrobial susceptibility pattern of organisms isolated from blood cultures was recorded.
2. Clinical data collection and case definition

The data on patient outcome was recorded from the clinical records. The following data were collected:

1. Age and gender
2. Location of the patient
3. Presence of predisposing clinical factors
4. Sources of secondary BSIs- this was identified by cultures of samples obtained from any other the primary site of infection that yielded the same pathogen as obtained from blood.
5. Adverse outcomes occurred during the course of hospitalization.
6. The severity of the underlying disease preceding the positive blood culture was classified according to Charlson weighted comorbidity index and the McCabe classification.[7]
7. The patient's physiological condition on the day of the BSI was assessed by using the APACHE II score.[8]
8. Severity of bacteraemia was assessed by Pittsburg bacteraemia score.[9]
9. Nosocomial infection was defined as an infection that occurs > 48 hours after hospital admission.
10. Adequate empirical antimicrobial treatment was defined as therapy that is administered within 24 hours after samples for blood culture were obtained and that includes any antimicrobial agent to which the isolated organism is tested susceptible.
11. Patients who received antimicrobial therapy prior to blood culture sent.
12. At the onset of the BSI, the clinical condition of each patient was classified as sepsis and septic shock by using criteria by American Medical Association 2016.[10]
    (a) Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in total SOFA (Sequential [Sepsis-related] Organ Failure Assessment) score $\geq$ 2 points consequent to the infection.
    (b) Patients with septic shock were identified as subset of patients with sepsis presented with persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) > 65 mmHg.

3.2. Parameters studied

1. Analysis was conducted in two groups: i) patients with short TTP of $\leq$10 hours and ii) patients with long TTP of > 10hours. The demographic distribution and clinical characteristics of patients with TTP $\leq$10 hours and > 10 hours were compared such as: age, gender, location, severity of illness, underlying illness/condition, source of infection, adequate empirical therapy, bacterial pathogen associated, outcome indicators such as length of hospital stay, presence of organ failure and mortality.
2. The following parameters were compared between the survival group and death group such as: age > 60 years, female gender, APACHE II score > 20 at BSI

onset, Organ failure (at least one), inadequate antibiotic therapy, and receiving antimicrobial therapy prior to blood culture, Charlson score ≥ 3, hospital-acquired bacteremia, MDR-GNB and MRSA, TTP < 10 hr.

3.3. Methods of statistical analysis

1. Data was entered in Microsoft excel and analysed using SPSS software for Windows (Release 21.0; SPSS, Chicago, IL, USA).
2. The demographic distribution and clinical characteristics of patients with TTP ≤ 10 hours and >10 hours were compared using univariate analysis.
3. Means and standard deviations were calculated for continuous variables. Percentages were used for categorical variables.

3.4. Ethical consideration

As study involved only analysis of data collected from the laboratory and hospital clinical case records, necessary permission was requested from the hospital management. Confidentiality of the data was maintained. Waiver of consent was requested from the Institute Ethics Committee.

4. Results

4.1. Study population and patient characteristics

Out of 75 patients included in this study, age of these patients varied from 3 months to 80 years and maximum patients [26 (35%)] were in the age group of 60 years or older, followed by 24 (32%) patients were in the age group of 51-60 years. Mean age of the study population was 54 ± 14.89 years. Of the total of 75 patients, 49 (65%) were males and 26 patients (35%) were females. Average length of hospitalization of these patients was 10 ± 14.2 days.

Commonest source of blood stream infection was urinary tract (37.3%), followed by 18.7% patients had primary bacteremia, respiratory tract infections (14.7%), skin and soft tissue infections (14.6%), GIT infections (5.3%), intravascular catheter related BSIs (4%), bone and joint infections and CNS infections (2.7% each).

4.2. Bacterial profile and susceptibility pattern

Of the total of 75 patients included in this study, gram-negative bacteria were isolated from 48 (64%) cases and gram-positive bacteria from 27 cases (36%). Among the gram-negative bacteria, *Escherichia coli* was the commonest isolate (33.3%), followed by *Klebsiella pneumoniae* (18.8%), *Pseudomonas aeruginosa* (12.5%), non-fermenting gram-negative bacteria [NFGNB (8.3%)], *Salmonella* Typhi, and *Salmonella* Paratyphi A (6.3%) each, *Salmonella* Enteritidis, *Acinetobacter baumannii*, and *Aeromonas* spp. (4.4%) each.

Among the gram-positive bacteria, *Staphylococcus aureus* was the commonest isolate (22.2%), followed by methicillin resistant *Staphylococcus aureus* (MRSA) and Viridans streptococci (14.8%) each, *Enterococcus faecium* and *Streptococcus pneumoniae* (11.1%) each, *Streptococcus pyogenes,* Coagulase negative *staphylococci* (CONS) and MRCONS 7.4% each.

Among 48 gram-negative bacterial isolates, the overall antimicrobial resistance rate is shown in Figure 1. Among the 27 gram-positive bacterial isolates, overall antimicrobial resistance rate is shown in Figure 2.

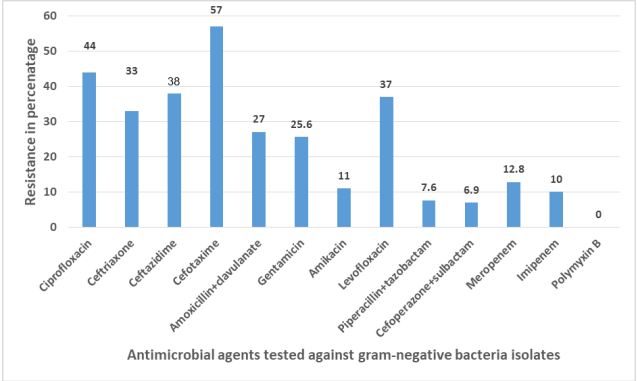

Fig. 1: Antimicrobial agents tested for gram-negative bacterial isolates and their resistance pattern (n=48)

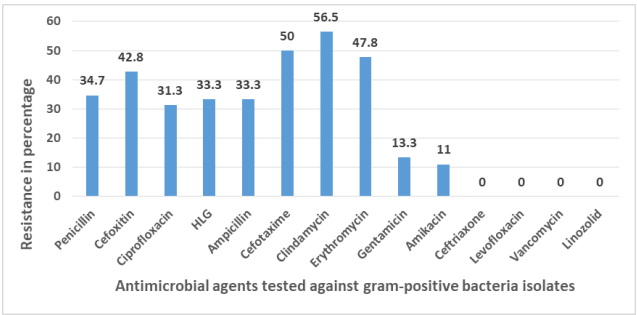

Fig. 2: Antimicrobial agents tested for gram-positive bacteria isolates and their resistance pattern (n=27)

4.3. Time to positivity of blood cultures

Time to positivity (TTP) ranged from five hours to 83 hours among 75 positive blood cultures and median TTP was 13 hours with 13.32 standard deviation. Short TTP of ≤10h was observed for 23 (30.6%) isolates. Median TTP in hours with standard deviation for commonly isolated etiological agents is depicted in Table 1.

Patients demographic characters (male gender, age >60 years, ICU stay), underlying clinical conditions and risk factors (underlying genitourinary infections, respiratory conditions, GIT infections, CNS infections and skin/ soft

Table 1: Median TTP with standard deviation in hours for commonly isolated etiological agents from BSIs

Etiological agents	Median TTP	Standard deviation
Escherichia coli	8.5	8.622
Klebsiella pneumoniae	12	20.507
Acinetobacter baumannii	11	1
Pseudomonas aeruginosa	12.5	2.671
Salmonella spp.	18	5.498
Streptococcus pneumoniae	8	2.828
Enterococcus faecium	10.4	1.5
Viridans streptococci	16	13.294
Staphylococcus aureus	18	3.226
CoNS*	18	8.81

*CoNS- Coagulase negative Staphylococcus

tissue infections), organ failures, mortality and common bacterial etiology were compared and analyzed for TTP of ≤10h or > 10h (Table 2).

There was no significant difference in between short TTP and long TTP with regarding to demographic characteristics. There were significant differences in end stage renal disease with Odds ratio (OR) of 13.33; CI: 2.551- 69.69 (P value=0.0008, extremely significant) and also diabetes association with OR of 4.333; CI: 1.521-12.347 (P value=0.0075, highly significant). Neutropenia patients had short TTP as compared to the other group with OR of 10.200; CI: 1.073-96.974 (P value: 0.0322, considered significant).

By comparison of clinical conditions in between two TTP groups, no statistically significant differences were observed for APACHE II score ≥20 at BSI onset, Pitt Bacteremia Score, and adequate antibiotic therapy. However, for hospital acquired bacteremia we observed Odds ratio of 2.24 with CI of 0.744 to 6.737, but P value was 0.156, which was considered not very significant.

Univariate analysis revealed blood stream infection originated from urinary tract had shorter TTP (<10h) as compared to BSI from other sources and primary bacteremia. By comparison of source of BSI as urinary tract, in between two TTP groups, statistically significant difference was observed with OR of 5.042, CI: 1.658 - 15.335 (P value of 0.0080; considered highly significant). Clinical conditions and common source of BSI associated with two groups of TTP is summarized in Table 3.

Analysis of outcome parameters such as septic shock, respiratory failure, renal failure, hepatic failure and overall in-hospital mortality, no statistically significant differences were observed between the two TTP groups. However, we observed higher odds ratio (OR) of 3.750 for septic shock, 5.263 for renal failure and for hepatic failure and in-hospital mortality 4.8 each. By comparison of etiological agents in between two TTP groups, statistically significant difference was observed for *Escherichia coli* BSI, with Odds ratio of 8.617; CI 2.511- 29.566 (P value=0.0005, considered extremely significant). These findings are summarized in Table 4.

5. Discussion

The time to positivity of blood cultures in automated blood culture system, can be influenced by multiple factors such as blood volume, greater burden of pathogen in blood, endovascular or genitourinary source of infection, and duration of bacteremia.[11,12] The present study revealed that selected microorganisms, underlying risk factors, clinical conditions, sources of infection are independently associated with time to positivity at which detectable growth occurs in automated blood culture bottles.

Escherichia coli was the commonest isolate (33.3%), followed by *Klebsiella pneumoniae* (18.8%) among gram-negative bacteria isolates and Staphylococcus aureus was the commonest isolate (22.2%), followed by MRSA and Viridans streptococci (14.8%) each, among gram-positive bacteria isolates. Similar observations were also done in various other studies.[2,13,14] This could be due to the reason that commonest source of BSI observed in these studies was renal source and *Escherichia coli* was the commonest organism causing UTI.

Among 48 gram-negative bacteria isolates, antimicrobial resistance was observed maximum for cefotaxime (57%), ciprofloxacin (44%), ceftazidime (38%), ceftriaxone (33%), and less for imipenem (10%), piperacillin+azobactam (7.6%), and cefoperazone+sulbactam (6.9%). Among gram-positive bacterial isolates, no resistance was observed to ceftriaxone, levofloxacin, vancomycin, teicoplanin and linezolid. Similar results were also observed in other studies.[13,14] Observations made in the study suggests the use of either imipenem, piperacillin+tazobactam or cefoperazone+sulbactam for empiric treatment for BSIs in combination with ceftriaxone or vancomycin for gram-positive coverage, in our tertiary care hospital.

Time to positivity ranged from five hours to 83 hours among 75 positive blood culture isolates and median TTP was 13 hours with 13.32 standard deviation. Among gram-negative bacteria BSIs, *Escherichia coli* had the shortest median TTP of 8.5h±8.622 and among gram-positive BSIs

Table 2: Demographic characteristics and underlying conditions associated with time to positivity (≤ 10h or >10h) in patients with blood stream infections

Variable	TTP ≤10 hours (n=23)		TTP >10 hours (n=52)		P value	OR	95% CI
	Patients		Patients				
	No.	%	No.	%			
1. Demographic characteristics							
Age (≥60 years)	7	30	19	30	0.79	0.76	0.26- 2.17
Male	16	69	33	63	0.793	1.316	0.459 - 3.771
ICU stay	12	52	18	34.6	0.203	2.061	0.759- 5.591
2.Underlying conditions							
Charlson score ≥ 3	7	30	22	42.3	0.442	0.597	0.209- 1.696
Ultimately fatal disease#	11	48	17	32.6	0.301	1.887	0.692- 5.144
End-stage renal disease	8	35	2	3.8	0.0008***	13.33	2.551- 69.69
Diabetes	13	56	12	23	0.0075**	4.333	1.521-12.347
Neutropenia	4	17	1	2	0.0322*	10.200	1.073 - 96.974
Endocarditis	1	4.3	1	2	0.522	2.318	0.138 - 38.784

TTP: Time to positivity
#- Ultimately fatal disease as per MacCabe classification
***–Extremely significant; **–Highly significant; *–Significant

Table 3: Clinical conditions and common source of blood stream infections associated with time to positivity (≤ 10h or >10h)

Variable	TTP ≤10 hours (n=23)		TTP >10 hours (n=52)		P value	OR	95% CI
	Patients		Patients				
	No.	%	No.	%			
1. Conditions related to the clinical course							
APACHE II score ≥20 at BSI onset*	4	17	4	7.6	0.239	2.526	0.5724 to 11.149
Pitt score >4	3	8.7	6	11.5	1.000	1.15	0.261 to 5.064
Hospital acquired bacteremia	8	35	10	19	0.156	2.240	0.744 to 6.737
Adequate antibiotic therapy	14	61	29	55.7	0.8017	1.234	0.453 to 3.356
2. Common source of infection							
Urinary tract	11	48	8	15.3	0.0080**	5.042	1.658 to 15.335
Intravascular catheter	1	4.3	2	3.8	1.000	1.136	0.0977 to 13.207
Respiratory tract	5	21	6	11.5	0.2960	2.130	0.576 to 7.863
Skin and soft tissue	1	4.3	3	5.7	1.000	0.7424	0.07304 to 7.547
Bone and joint	1	4.3	2	3.8	1.000	1.136	0.0977 to 13.207
Gastro-intestinal	1	4.3	3	5.7	1.000	0.7424	0.07304 to 7.547
Wound	2	8.7	5	9.6	1.0000	0.8952	0.1605 to 4.995
Primary bacteremia	2	8.7	10	19.2	0.3232	0.4000	0.08024 to 1.994

Table 4: Patient outcome and common etiological agent associated with time to positivity (≤ 10h or >10h) in patients with blood stream infections

Variable	TTP ≤10 hours (n=23) Patients		TTP >10 hours (n=52) Patients		P value	OR	95% CI
	No	%	No.	%			
1. Outcome							
Septic shock #	3	13	2	3.8	0.1647	3.750	0.582-24.168
Respiratory failure	3	13	3	5.7	0.363	2.450	0.455-13.187
Renal failure	4	17.3	2	3.8	0.0675	5.263	0.8892-31.151
Hepatic failure	2	8.7	1	2	0.2211	4.857	0.4174-56.527
In-hospital mortality	2	8.7	1	2	0.2211	4.857	0.4174-56.527
2. Common etiological agent							
Escherichia coli	11	48	5	9.6	0.0005***	8.617	2.511- 29.566
Klebsiella pneumoniae	2	8.7	7	13.4	0.7129	0.612	0.1170-3.204
Pseudomonas aeruginosa	2	8.7	4	7.6	1.0000	1.143	0.1940- 6.734
Staphylococcus aureus	1	4.3	5	9.6	0.6598	0.4273	0.0470- 3.881
Streptococcus pneumoniae	2	8.7	1	2	0.2211	4.857	0.4174-56.527
Enterococcus faecium	1	4.3	2	3.8	1.000	1.136	0.0977-13.207

TTP- time to positivity
#- Septic shock as calculated by quick SOFA score –Quick sequential-organ-failure-assessment-score
***- Extremely significant.

Streptococcus pneumoniae had the shortest TTP of 8hours ±2.828. Several previous studies have revealed that short TTP is related to high bacteria load in the blood and is related to bad outcome. In our study we did not observe any significant association for various 'conditions related to the clinical course' and TTP. Various studies have revealed that short TTP of <7h was associated with high mortality.[6,11] As this study involved a very small sample size, probably failed to observe these findings.

Among two TTP groups, there were significant differences in BSIs with end stage renal disease with Odds ratio (OR) of 13.33; CI: 2.551- 69.69 (P value=0.0008, extremely significant), BSIs originated from urinary tract with OR of 5.042, CI: 1.658-15.335 (P value of 0.0080; considered highly significant) and also BSIs and diabetes association with OR of 4.333; CI: 1.521-12.347 (P value=0.0075, highly significant). In contrast to our findings, study by Liao et al., revealed *E.coli* BSIs of renal origin had longer TTP, and they have predicted better clinical outcome.[1,11] However in a study by Martinez et al., stated faster-growing species were usually involved in UTIs, hence BSIs originated from urinary tract might present with short TTP.[11] For better correlation regarding TTP as a predictor of outcome large sample size may be required.

Analysis of outcome parameters such as septic shock, respiratory failure, renal failure, hepatic failure and overall in-hospital mortality, we observed higher Odds ratio for all these outcome parameters, but statistically significant differences were not observed between the two TTP groups, probably due to small sample size or may be due to differences in host immunity. As we had patients of varied demographic and clinical characteristics, drawing conclusions would have been difficult as sample size for each variable was not sufficient enough to show the exact statistical significance as observed in other studies.

Overall comparison of median TTP for BSIs due to gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae, Acinetobacter baumannii* and *Pseudomonas aeruginosa* was less than 12 hours; Similar observations were also made by other researchers.[1,5,11,12] These are gram-negative bacteria with short generation time, rapidly multiply and hence have a shorter TTP. Comparison of TTP of two groups for BSIs due to *Escherichia coli* revealed significant risk for adverse outcome with OR of 8.617, CI: 2.511- 29.566 with P value of 0.0005, which is statistically extremely significant. Median TTP of *Streptococcus pneumoniae* BSIs was eight hours and *Enterococcus faecium* was 10 hours. Similar to our observations study by Martinez et al., stated that gram-positive cocci in pairs or chains following a positive blood culture, with TTP of >21h, ruled out beta haemolytic streptococci or *Streptococcus pneumoniae*.[11] For other organisms and other sources of BSIs, the sample sizes were probably too low for accurate predictions to be

made. Average TTP for BSIs due to *Staphylococcus aureus* (including MRSA) and *Coagulase Negative Staphylococcus* (including MRCoNS) was 18 hours. We have not made any observations regarding fatal outcome among methicillin resistant staphylococci isolates as compared to susceptible isolates.[3] As reported by Ning et al., for gram-positive cocci in clusters with TTP of >100h, can be considered as skin contaminants.[5] A larger sample size may be required for better prediction of the above stated findings by the other researchers.

We had some limitations such as blood volume cultured, the time that elapsed between blood drawing and loading into automated blood culture system were not recorded, assuming that variations occurred randomly. Due to small statistical differences for many of the microbiological and clinical parameters (clinical source), it remains unclear whether the results of this study will have a real impact on prediction of clinical outcome of individual patients.

6. Conclusion

Time to positivity is an attractive candidate for an easy-to-measure laboratory prognostic factor for patients with bacteremia. This study supports the usefulness of TTP as a tool for prognosis and for defining the origin (mainly renal source) or risk factors associated (diabetes/neutropenia/end stage renal disease) with blood stream infection; especially, *Escherichia coli* BSIs. Further studies with larger sample size, may be required to define its usefulness and the optimal cut-off points for blood stream infections caused by other organisms.

Despite of usefulness of TTP as a prognostic tool, it has a relatively low sensitivity in predicting mortality. However, short TTP is independently related to septic shock by gram-negative bacteria and this information may be very useful to raise the alarm when septic shock goes clinically unnoticed.

7. Source of Funding

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8. Conflict of Interest

The authors declare no conflict of interest.

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