Concise Communication

Time to positivity of blood cultures among a veteran population: How long to wait before discontinuing antimicrobial therapy when suspicion of infection is low

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Abstract

Time to positivity (TTP) of blood cultures can guide antimicrobial therapy. This single-center retrospective cohort study aimed to determine the yield of clinically significant organisms from blood cultures that were initially negative at 24 hours. Clinically significant organisms were uncommon after 24 hours (1.5%) and more common in intensive care unit settings.

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Time to positivity (TTP) is the time from the start of culture incubation to the detection of organism growth. Evidence indicates that TTP may be used to direct antimicrobial therapy. Antibiotics are often continued until blood cultures have been negative for 48–72 hours, even when suspicion of infection is low.[1,2] Continuing unnecessary antibiotics can increase the risk for antimicrobial resistance, *Clostridium difficile* infection, and other adverse effects.[3] Antimicrobial stewardship programs should focus on the optimal selection, dose, route, and duration of antimicrobial therapy resulting in the best clinical outcome for the patient with minimal toxicity and minimal impact on subsequent resistance.[3] Knowledge that a clinically significant organism is unlikely to result after 24 hours could lead to a more accurate differential diagnosis and appropriate de-escalation or discontinuation of antibiotics. Retrospective studies analyzing TTP in adult neutropenic patients and infants with bacteremia have found that most blood cultures have a TTP ≤24 hours and that a TTP >24 hours for an organism of clinical significance is rare.[1,2] However, these studies may not be applicable to the general or veteran population.

The primary objective of this study was to determine what percentage of blood cultures grow an organism of clinical significance if initially negative at 24 hours (TTP, >24 hours). Secondary objectives were to determine whether isolates with a TTP ≤24 hours are more likely to be clinically significant than isolates with a TTP >24 hours; to determine differences in TTP between intensive care unit (ICU) and non-ICU patients; and to evaluate differences in organisms isolated with a TTP ≤24 hours and >24 hours.

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Methods

This single-center retrospective cohort study at the Iowa City Veterans' Affairs Medical Center included consecutive blood cultures from December 2014 through May 2018. The TTP, distribution of isolates among positive cultures, and other variables were evaluated. Blood cultures were excluded from review if the culture order was not performed (including records accessioned in error, duplicate orders, test patients, mislabeled specimens, and insufficient blood quantity). When evaluating the primary objective, isolates that had a TTP ≤24 hours were also excluded. All organisms from positive blood cultures were characterized as clinically significant, likely contaminant, or organisms that were unlikely to be significant as they were only gram stained and no additional formal work-up was performed or requested (eg, identification or susceptibly results). Clinically significant bacteria included *Staphylococcus aureus*, Streptococci, Enterococci, gram-negative organisms, and *Candida*. Coagulase-negative Staphylococci, diphtheroids (eg, *Corynebacterium*), and gram-positive or gram-negative organisms that were not further identified were deemed to be contaminants and not clinically significant when evaluating the primary outcome as many studies indicate it is rare for these organisms to be of clinical significance if the TTP exceeds 16–24 hours.[4–9] Viridans group streptococci were not categorized as contaminants due to studies showing a lack of correlation between pathogenicity and TTP and contamination in only 50% of viridans streptococci cases compared to coagulase-negative staphylococci being in excess of 80%.[7] Descriptive statistics were used to summarize blood culture results among positive isolates. Differences in the TTP (≤24 hours compared to >24 hours) were compared using a 2-tailed Pearson's χ^2 analysis. *P* values <.05 were considered statistically significant. Our local institutional review board determined that this study was a quality improvement project and not human subjects research.
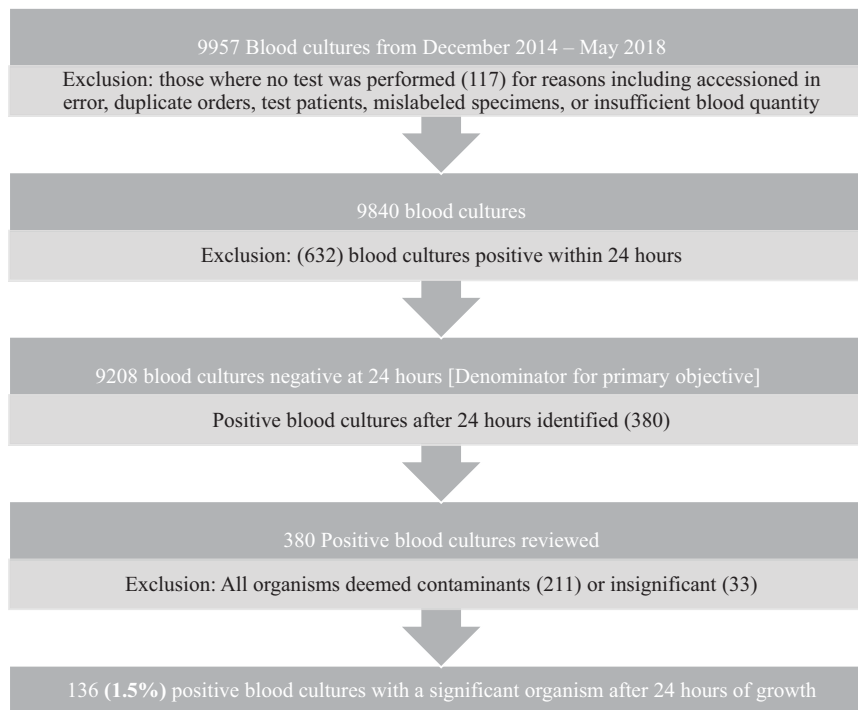
Fig. 1. Probability of a clinically significant organism with a time to positivity >24 hours.
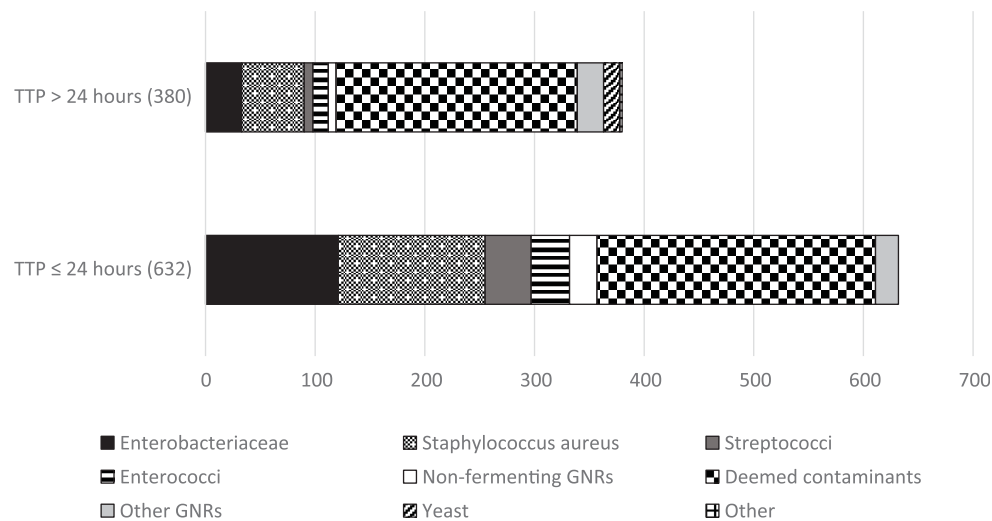

Fig. 2. Positive blood culture isolates with respect to time to positivity (TTP).

TTP ≤24 hours (n = 632). **Enterobacteriaceae**: *E. coli*, 58; *Klebsiella* sp, 31; *Enterobacter* sp, 17; *Proteus* sp, 8; *Citrobacter* sp, 2; *Serratia* sp, 1; and other, 4. ***Staphylococcus aureus***: MRSA, 64 and MSSA, 70. **Streptococci:** *S. pneumoniae*, 16; other streptococci, 26 (*S. anginosus*, 4; *S. gallolyticus*, 4; *S. bovis*, 4; *S. agalactiae*, 3; *S. mitis/oralis*, 3; *S. salivarius*, 1; viridans streptococci, 1; alpha-hemolytic streptococci, 1; and other group streptococci, not otherwise identified, 5. **Enterococci**: *E. faecalis*, 32 and *E. faecium*, 3. **Nonfermenting GNRs**: *Pseudomonas* sp, 17; *Aeromonas* sp, 2; *Morganella* sp, 2; *Acinetobacter* sp, 1; *Pasteurella* sp, 1; *Providencia* sp, 1; and *Burkholderia* sp, 1. **Deemed contaminants**: organism deemed contaminants, including CoNS, diptheroids, and unidentified gram-positives, 254. **Unidentified GNRs**: 21.

TTP >24 hours (n = 380). **Enterobacteriaceae**: *E. coli*, 15; *Klebsiella* sp, 10; *Proteus* sp, 5; *Enterobacter* sp, 2; and *Serratia* sp, 1. ***Staphylococcus aureus***: MRSA, 13 and MSSA, 44. **Streptococci**: *S. pneumoniae*, 1; other streptococci, 7 (*S. anginosus*, 3; *S. bovis*, 1; *S. salivarius*, 1; *Streptococcus* group G, 1; and viridans streptococci, 1. **Enterococci**: *E. faecalis*, 13 and *E. faecium*, 1. **Nonfermenting GNRs:** *Pseudomonas* sp, 2; *Pasteurella*, 2; *Providencia* sp, 1; *Salmonella* sp, 1; and *Stenotrophomonas*, 1. **Deemed contaminants**: organism deemed contaminants, including CoNS, diptheroids, and unidentified gram positives, 220. **Unidentified GNRs**: 24. **Yeast**: presumed *Candida* spp, 15. **Other**: *Nocardia* sp, 1 and *Bacteroides* sp, 1.

Results

During the study period, 9,957 consecutive blood cultures were collected of which 9,840 met the initial inclusion criteria (Fig. 1). Of the 9,840 blood cultures, 9,208 (93.6%) were negative at 24 hours. Subsequently, 136 (1.5%) grew an organism of clinical significance (TTP, >24 hours). Of the 9,208 cultures that were negative at 24 hours, 994 were collected from ICU patients. Cultures collected from ICU patients were more likely to have a

TTP >24 hours for a clinically significant organism (25 of 994, 2.5%) than non-ICU patients (111 of 8,214, 1.4%; *P* = .0063).

Overall, 1,012 positive cultures (10.3%) were identified from the 9,840 cultures that met initial inclusion criteria. Regarding TTP, 632 of 1,012 isolates had a TTP ≤24 hours, and 380 had a TTP >24 hours. A clinically significant organism was more common if the TTP was ≤24 hours (357 of 632, 56.4%) compared to >24 hours (136 of 380, 35.8%; *P* < .0001). Among cultures positive for a clinically significant organism, 357 of 493 (72.4%) had a TTP ≤24 hours. Staphylococci and Enterobacteriaceae were the most common organisms isolated, with *Staphylococcus aureus* being the leading pathogen regardless of the TTP (Fig. 2) or the clinical setting (ICU vs non-ICU, data not shown).

Discussion

In this study, few blood cultures (1.5%) yielded a clinically significant organism after 24 hours of incubation, which is similar to the findings of other TTP studies. In this study, our population was more heterogeneous than those of previous studies.[1,2,4] Furthermore, we evaluated all isolates, whereas other studies focused on specific organisms or a group of organisms.[5–8] Enterobacteriaceae was the second most common group of organisms isolated regardless of TTP or clinical setting, which may be reflective of the veteran patient population. The estimated rate of blood culture contamination was similar to those of other studies (30%–50%).[9,10] Consensus has not been reached regarding how long to wait to discontinue or de-escalate antimicrobial therapy based on negative blood cultures. Our findings suggest that when suspicion for infection is low, it may be reasonable to stop antimicrobial therapy if blood cultures are negative after 24 hours. These data are likely not applicable when suspicion is high for presumed infection. In those cases, antimicrobial therapy may be de-escalated targeting the most likely pathogens based on presumed source(s) of infection and other variables.

Our study has several limitations. As a retrospective study, only associations can be determined. Given the single-center design within a VA population, the generalizability of our study is limited. Data did not include any patient-specific, pharmacologic, or clinical information; thus, our determination of clinically significant organisms was based on our a priori definitions (see the Methods section). We did not exclude repeat cultures due to lack of patient-specific information, which may have influenced our findings. Lastly, the data did not include quantification of bacterial load, blood culture volume, or relation of culture collection and administration of antibiotics, which could have aided in the determination of clinical significance.

In conclusion, this study demonstrated that few clinically significant organisms have a TTP >24 hours. Incorporation of microbiologic data, including TTP, with other clinical findings can be used to guide treatment decisions. Future prospective studies evaluating TTP and potential risk factors for clinically significant organisms are needed to guide appropriate and timely de-escalation and discontinuation of antimicrobial therapy.

References

1. Biondi EA *et al.* Blood culture time to positivity in febrile infants with bacteremia. *JAMA Pediatrics* 2014;168:844–849.
2. Lambregts MC, *et al.* Distribution and clinical determinants of time-to-positivity of blood cultures in patients with neutropenia. *Eur J Haematol* 2018;100:206–214.
3. Barlam TF, *et al.* Implementing an antibiotic stewardship program: guidelines by the Infectious Disease Society of America and Society of Healthcare Epidemiology of America. *Clin Infect Dis* 2016;62(10):e51–e77.
4. Martinez JA, *et al.* Microbial and clinical determinants of time-to-positivity in patients with bacteraemia. *Clin Microbiol Infect* 2007;13:709–716.
5. Morioka S, Ichikawa M, Mori K, et al. Coagulase-negative staphylococcal bacteraemia in cancer patients. Time to positive culture can distinguish bacteraemia from contamination. *Infect Dis (Lond)* 2018;16:1–6.
6. Kassis C, Rangaraj G, Jiang Y, et al. Differentiating culture samples representing coagulase-negative staphylococcal bacteremia from those representing contamination by use of time-to-positivity and quantitative blood culture methods. *J Clin Microbiol* 2009;47:3255–3260.
7. Swenson FJ, Rubin SJ. Clinical significance of viridans streptococci isolated from blood cultures. *J Clin Microbiol* 1982;15:725–727.
8. Palmer HR, *et al.* Clinical and microbiological implications of time-to-positivity of blood cultures in patients with Gram-negative bacilli bacteremia. *Eur J Clin Microbiol Infect Dis* 2013;32:955–959.
9. Hall KK, Lyman JA. Updated review of blood culture contamination. *Clin Microbiol Revs* 2006;19:788–802.
10. Dargère S, Cormier H, Verdon R. Contaminants in blood cultures: importance, implications, interpretation and prevention. *Clin Microbiol Infect* 2018;24:964–969.