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ORIGINAL ARTICLE

Time to Positivity of Blood Cultures in Infants 0 to 90 Days Old Presenting to the Emergency Department: Is 36 Hours Enough?

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Background. Continuous monitoring blood culture systems (CMBCS) now allow for more rapid detection of microbial growth. We aimed to determine whether a 36-hour period was sufficient to detect all blood cultures positive for pathogenic bacteria in infants 0 to 90 days old undergoing a septic workup in the emergency department of a tertiary care pediatric center.

Methods. We performed a retrospective study of all positive blood cultures collected in these infants over a 5-year time period (from March 13, 2008 to July 29, 2013). Bottles were incubated in a CMBCS. The time to positivity (TTP) was calculated from time of blood culture registration into the laboratory system to time of Gram stain. Medical charts were reviewed for relevant clinical information. Cultures were classified as pathogenic or contaminant using microorganism type and clinical presentation.

Results. Three thousand five hundred fifty-nine blood cultures were collected. Of these, 98 (2.8%) were positive. Fifty-two (53.1%) were deemed pathogenic and 46 (46.9%) were deemed contaminant, for a true prevalence of bacteremia of 1.5%. At 24, 36, 48, and 50 hours, 87.8% (86 of 98), 96.9% (95 of 98), 99% (97 of 98), and 100% (98 of 98) of all cultures were positive. Considering only pathogenic organisms, 96.1% (50 of 52) and 100% (52 of 52) were positive at 24 and 36 hours. Mean TTP for pathogens and contaminants was 14.40 and 23.18 hours, respectively ($P < .001$).

Conclusions. An incubation period of 36 hours is sufficient to detect 100% of blood cultures positive for a pathogenic organism in our population.

Keywords. bacteremia; blood culture; infant; serious bacterial infections.

Infants younger than 90 days are at increased risk of serious bacterial infection (SBI) [1]. Because of this, and their often nonspecific presentation during infection, when they present with fever, an extensive workup is often done including a blood culture, a urine culture, and, sometimes, a lumbar puncture [2]. These infants are then often treated with empiric antibiotic therapy and hospitalized while awaiting culture results.

In the 1970s, the advent of automated blood culture detection instruments allowed for more rapid identification of positive cultures. As a result, the time deemed necessary to safely consider a blood culture negative was reduced from 72 hours to 48 hours [3–6]. Since the 1990s, continuous monitoring blood culture systems (CMBCS) have been in use, allowing for more frequent surveillance of cultured specimens. Many studies have demonstrated these CMBCS' ability to even more rapidly detect bacterial growth [7–10]. However, there is a paucity of data on the specific impact CMBCS might have on blood culture time to positivity (TTP) in infants 0 to 90 days old. For this reason, there is a lack of consensus between clinicians and no clear guidelines as to what constitutes a safe observation period for a clinically well infant without evidence of focal infection who has had a workup for SBI [11].

In a recent study, Biondi et al [12] published a multicenter evaluation of blood culture TTP in febrile infants using the BACTEC CMBCS that suggested most pathogens are identified within 24 hours of blood culture collection. This was the first study to look specifically at TTP in febrile infants since the advent of CMBCS. However, these results might not be applicable to countries other than the United States due to differences in bacteremia epidemiology resulting from variation in vaccine schedules and intrapartum prophylaxis guidelines, to name a few. Furthermore, the Biondi et al [12] study used only 1 of the 2 most widespread CMBCS adopted by US clinical laboratories, the other being the VersaTREK (Thermo Scientific, Oakwood Village, Ohio), and it is not yet known whether a different CMBCS would yield similar results.

As a result, we aimed to determine whether a period of 36 hours is sufficient to detect all blood cultures positive for pathogenic bacteria in infants between the ages of 0 and 90 days

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presenting to the emergency department (ED) of a Canadian urban tertiary care pediatric center and undergoing a workup for SBI, using a different CMBCS, the VersaTREK.

PATIENTS AND METHODS

We performed a retrospective study of all positive blood cultures collected in the ED of the Centre Hospitalier Universitaire (CHU) Sainte-Justine, from infants 0 to 90 days old, over a 5-year period (from March 13, 2008 to July 29, 2013). Located in Montréal, Québec, the CHU Sainte-Justine is one of the largest Canadian pediatric hospitals, with over 60 000 emergency room visits each year.

In our institution, blood culture bottles are loaded on site, 24 hours a day, 7 days a week in a CMBCS (VersaTREK). Blood cultures are generally drawn by a nurse or a trained laboratory technician after topical disinfection and are placed directly in a VersaTREK REDOX 1 (aerobic) culture bottle. The bottles are monitored 24 hours a day at 12-minute intervals by the VersaTREK system, which detects microbial growth by sensing changes in bottle headspace pressure due to gas consumption and production by microorganisms. Bottles that are identified as positive are removed from the CMBCS, and a Gram stain is performed within 30 minutes. The time and result of the Gram stain are recorded in the microbiology Laboratory Information System (LIS) (SoftMic, Medisolution, Montreal, Canada), and a notification of the result is sent to the physician. A sample of the blood culture is then plated on culture media for organism identification and antimicrobial susceptibility testing.

Positive blood cultures matching our inclusion criteria were identified through the microbiology LIS. The TTP was calculated using the time interval from blood culture registration into the LIS upon arrival to the microbiology laboratory to the time of Gram stain. Other information collected from the LIS included the following: date of birth, patient's age, and Gram stain and culture results. When 2 cultures matching our inclusion criteria were drawn during separate ED visits from the same infant, both results were considered separately.

Medical charts were reviewed to obtain relevant clinical information, including concurrent antibiotic use, presence of central venous catheters, and concomitant urine or cerebral spinal fluid analysis and culture results.

To determine the pathogenicity of a cultured organism, the main determinant was bacterial species. Organisms generally considered to be pathogenic (eg, *Escherichia coli*, *Streptococcus pneumoniae*, group B *Streptococcus*) were considered as such, whereas common contaminants (Coagulase-negative staphyloccoci, viridans streptococci) were classified accordingly. A microbiologist-infectious disease specialist (C. R.) and a pediatrician (C. C.) then confirmed appropriate classification, using additional information obtained from medical charts, such as the patient's clinical course and the treating team's management decisions (such as whether or not to continue antimicrobial therapy). This study was approved by the CHU Sainte-Justine Institutional Review Board.

RESULTS

Three thousand five hundred fifty-nine blood cultures were collected during the study period. Of these, 98 (2.8%) were positive, collected from 96 infants (63 boys; 33 girls) with a mean age of 40.4 days (range, 3–89). Two infants had 2 blood cultures each included in the final analysis that were obtained, in both cases, from 2 completely separate ED visits and were therefore considered to represent 2 distinct episodes of bacteremia.

Among the positive cultures, 52 (53.1%) were deemed pathogenic, for a prevalence of true bacteremia of 1.5% in our population, whereas 46 blood cultures (46.9%) grew organisms considered to be contaminants (Figure 1). Two blood cultures growing common contaminants were ultimately classified as pathogenic after the medical chart review: one growing a *Staphylococcus hominis* in an 83-day-old infant admitted to the intensive care unit and intubated for severe pneumonia and another growing *Streptococcus viridans* in a 16-day-old infant with hypotension necessitating fluid resuscitation.

By 24, 36, 48, and 50 hours of incubation, 87.8% (86 of 98), 96.9% (95 of 98), 99% (97 of 98), and 100% (98 of 98) of all cultures were positive, respectively. Considering only the cultures that were positive for organisms deemed pathogenic, 96.2% (50 of 52) and 100% (52 of 52) were positive by 24 and 36 hours, respectively (Figure 2).

The mean (standard deviation [SD]) TTP for pathogens was 14.4 hours (4.4), and the median TTP was 13.5 hours. For contaminants, the mean and median (SD) TTP was 23.2 hours (7.3) and 21.14 hours, respectively. The difference between the mean TTP for pathogens and contaminants was statistically significant ($P < .001$). Figure 3 shows the scatter plot of the TTP for the most commonly isolated microorganisms.

Only 3 cultures became positive after 36 hours, and all were deemed contaminants. A *Kocuria kristinae* was identified at 40 hours in a 19-day-old boy with a positive urine culture for *Enterococcus* spp. A *Corynebacterium* spp grew in 49 hours in a febrile but otherwise well 19-day-old infant who tested positive for influenza A. Finally, a *Micrococcus* spp was identified at 45.5 hours in a 13-day-old infant who had been discharged home from the ED and whose follow-up blood culture was negative.

Among infants with positive pathogenic blood cultures, 15 of 52 (28.8%) had isolated bacteremia. The other 37 incidences of bacteremia (71.1%) were associated with focal infections: 23 urinary tract infections, 8 meningitis, 2 septic arthritis and/or osteomyelitis, 1 cellulitis, and 1 polymicrobial bacteremia (*E coli* and *Morganella morganii*) associated with an intestinal hernia reduction. One group B β-haemolytic *Streptococcus* (GBS) bacteremia was associated with both meningitis and osteomyelitis

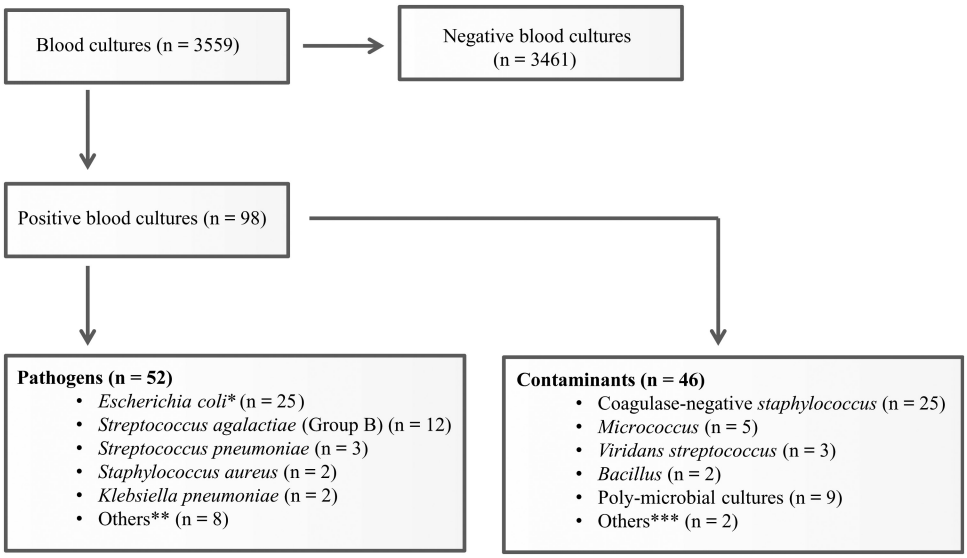

Figure 1. Breakdown of 3559 blood cultures included in the study. *Includes 2 polymicrobial cultures: *Escherichia coli* and *Morganella morganii* (bacteremia with intestinal hernia reduction); *E coli* and *Staphylococcus haemolyticus* (*E coli* bacteremia plus contaminant). ***Neisseria meningitidis*, group A *Streptococcus, Pasteurella multocida, Pseudomonas, Enterobacter cloacae, Enterococcus fecalis, Staphylococcus hominis, Streptococcus* sp. ***Corynebacterium, Kocuria kristinae.

in a 29-day-old infant. The mean TTP did not differ significantly between isolated bacteremia (15.1 hours) versus bacteremia associated with focal infection (14.1 hours).

DISCUSSION

The question of blood culture TTP, particularly in the infant population where ruling out SBI is an important cause of hospital admissions and empiric antibiotic use, is a crucial one for pediatric hospitalists [11]. Recent studies have started to challenge the traditional 48-hour observation period [12, 13].

In our study, all blood cultures positive for pathogenic organisms were detected within 33 hours. The only 3 cultures that became positive beyond 36 hours were deemed contaminants based on the bacterial species and the patient clinical information. Thus, in our population, no clinically significant bacteremia would have been overlooked after a 36-hour observation period.

Most studies examining pediatric blood culture TTP, although demonstrating similar results to ours, have focused on infants hospitalized in neonatal intensive care units, who have very different risk factors for infectious disease [14–19]. Studies within the broader pediatric population have either used very

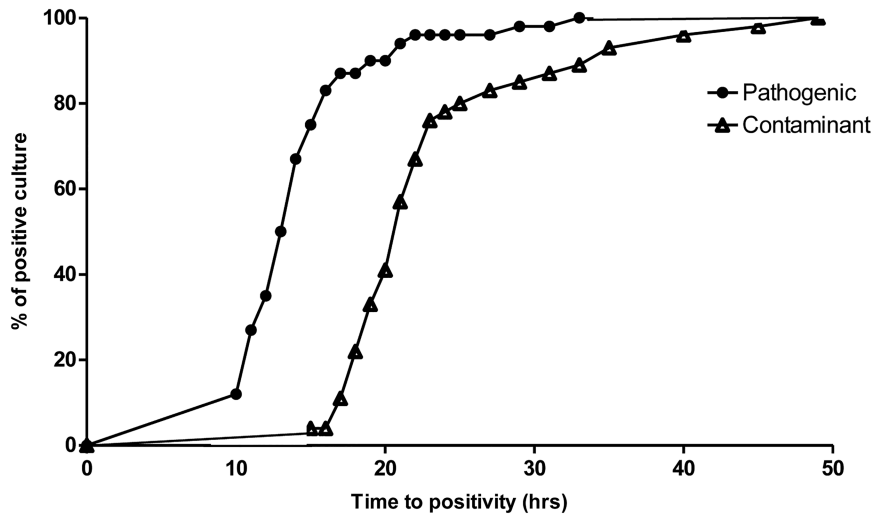

Figure 2. Graphic representation of blood culture time to positivity by pathogen and by contaminant.

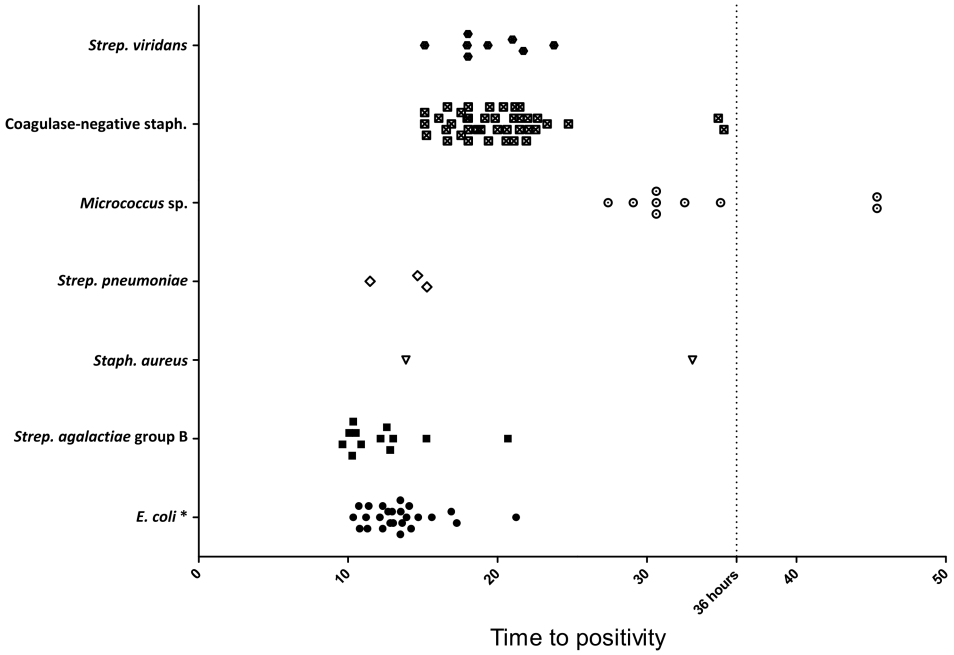

Figure 3. Blood culture time to positivity for the most commonly isolated microorganisms. *Includes 2 polymicrobial cultures (*Escherichia coli* and Staphylococcus haemolyticus; *E coli* and *Morganella morganii*).

broad age ranges [15], excluded infants under 28 days [14], or focused on bacteremia in the context of central venous catheters [20]. The only other study focusing specifically on infants 0 to 90 days old, mentioned previously, suggested that an observation period beyond 36 hours would detect only 1 additional case of bacteremia for every 1250 to 2778 febrile infants evaluated [12].

This study offers the first Canadian data on TTP of infant blood cultures using the newest CMBCS technology. These results are undoubtedly influenced by local epidemiology and vaccine calendars. During the study period, Canadian GBS prophylaxis guidelines [21] were in use as well as universal vaccination against *Haemophilus influenzae type B* and *S pneumoniae* (7-valent 2008–2009; 10-valent 2009–2010; 13-valent 2011–2013) starting at 2 months of age.

This study is also the first of its kind to use the VersaTREK CMBCS. Many earlier studies evaluating TTP have used the BacT/ALERT system or, as in the Biondi et al [12] study, the more recent BACTEC system, which both detect carbon dioxide production within the incubated bottles. Alternatively, the VersaTREK system detects changes in bottle headspace pressure. Studies comparing these systems have not shown a statistically significant difference between TTP [22]. Approximately two thirds of clinical laboratories in the United States now use either the VersaTREK or BACTEC systems as their CMBCS [23]. Therefore, our study is crucial in supporting the generalizability of the results from the recent Biondi et al [12] study by providing data on TTP in the infant population using the VersaTREK system.

Our bacteremia prevalence of 1.5% over 5 years closely resembles that of other studies [13, 14, 24–25], and our contamination rate (1.3% of all blood cultures drawn during the study period) was lower than that of other studies in the general pediatric population [15, 24], which might reflect our use of specialized laboratory technicians for blood culture draws [26].

Our study had some limitations. Because of its retrospective nature, the study design did not allow us to control for factors such as inoculated blood volume. Between 1 and 5 mL of blood should be inoculated as per laboratory protocol, but specimens were incubated regardless of sample volume. Ensuring sufficient blood volume inoculation would be important before recommending a 36-hour observation period.

Because our study included only blood cultures collected in the ED, our results may not be generalizable to hospitalized infants exposed to nosocomial flora and presenting risk factors for fungal or pathogenic coagulase-negative staphylococcus infections that may have significantly longer times to positivity [16, 17]. It is also important to note that only 1 infant was already on antibiotics at the time of her blood culture, meaning that these results may not be applicable to infants recently exposed to antibiotics, such as follow-up blood cultures drawn after the start of therapy as well as those collected in the immediate postpartum period from infants whose mothers received intrapartum prophylaxis.

During the study period, we did not recover all bacterial species known to be pathogenic in this patient population. For example, in the 5 years of our study, no case of listeriosis was

identified. However, the larger national US study [12] also failed to identify any *Listeria*, demonstrating the rarity of this organism as a cause of bacteremia in this population.

More importantly, the decision to discontinue antibiotics and discharge an infant at 36 hours, in light of a negative blood culture, should rely on the clinical course and the results of urine and cerebrospinal fluid cultures, when drawn. Evaluation of these factors is beyond the scope of our study. However, considering the availability of rapid analysis that are highly sensitive for the presence of urinary tract infection and meningitis [25, 27] it may be safe to discontinue antibiotics if these are negative, the clinical suspicion of SBI was low at presentation, and the child is clinically well.

CONCLUSIONS

An incubation period of 36 hours was sufficient to detect all blood cultures positive for a pathogenic organism in our population. In light of this, and other recent studies, the practice of observing infants 0–90 days for 48 hours before considering a blood culture negative should be re-evaluated. This could have a potential impact on duration of hospitalization, nosocomial infections and iatrogenic effects of empiric antibiotics, and intravenous infusion [28].

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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