Comparison of 2 Blood Culture Media Shows Significant Differences in Bacterial Recovery for Patients on Antimicrobial Therapy

Rebecca Zadroga,[1,2] David N. Williams,[2,3] Richard Gottschall,[4] Kevan Hanson,[4] Vickie Nordberg,[4] Marcia Deike,[4] Mike Kuskowski,[5] Lisa Carlson,[6] David P. Nicolau,[7] Christina Sutherland,[7] and Glen T. Hansen[2,4,8]

[1]Veterans Affairs Medical Center, [2]Department of Infectious Disease, University of Minnesota, [3]Department of Infectious Disease and [4]Department of Microbiology, Hennepin County Medical Center, [5]Geriatric Research, Education and Clinical Center, Minneapolis VA Medical Center, University of Minnesota, and [6]Department of Pharmacy, Hennepin County Medical Center, Minneapolis, Minnesota; [7]Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, Connecticut; and [8]Department of Pathology and Laboratory Medicine, University of Minnesota, Minneapolis

Background. Antimicrobial removal devices in blood culture media are designed to remove antibiotics from the blood culture solution, thereby facilitating bacterial growth. How well these devices function clinically has not been established.

Methods. All blood drawn for culture from adult inpatients and emergency department visitors in a level I trauma center was placed in paired BACTEC Plus and BacT/Alert FAN culture media and studied simultaneously, consecutively, and prospectively between 1 February and 30 September 2011. All cultures were processed per standard laboratory protocols.

Results. Of 9395 total cultures collected, 1219 (13%) were positive, 831 were included, and 524 (33%) contained pathogens. BACTEC had a 4.5-hour faster detection time ($P < .0001$), and isolated exclusively 182 of 524 (35%; $P < .001$) pathogens, 136 of 345 (39%) of the gram-positive cocci ($P < .001$), 48 of 175 (27%; $P = .02$) of the gram-negative rods, 101 of 195 (52%) of *Staphylococcus aureus* ($P < .001$), and 59 of 120 (49%; $P = .004$) septic events. If active antibiotics had been dosed 0–4 or 4–48 hours prior to culture collection, the odds of that culture growing in BACTEC were 4.8- and 5.2-fold greater, respectively, than of growing in BacT/Alert ($P < .0001$). Both were equivalent in the recovery of yeast and when no antimicrobials were dosed.

Conclusions. BACTEC media has faster time to detection and increased bacterial recovery over the BacT/Alert media in the following categories: overall growth, pathogens, septic events, gram-positive cocci, gram-negative rods, *Staphylococcus aureus*, and cultures where antimicrobials were dosed up to 48 hours before culture collection.

Keywords. Blood cultures; BACTEC; BacT/Alert; septicemia; antibiotic removal device.

Bloodstream infections are a leading cause of morbidity and mortality in the United States and impact length of hospital stay and associated healthcare costs. Between 2000 and 2008, the number of hospital admissions for septicemia more than doubled [1]. In 2011, the Agency for Healthcare Research and Quality identified hospital mortality rates for septicemia at levels 8 times higher than mortality derived from other hospital stays, and in 2009 septicemia was deemed the most expensive reason for hospitalization [1]. In response to the rising incidence and increasing mortality from septicemia, numerous studies have attempted to qualify the laboratory's role in the diagnosis and identification of bloodstream pathogens and in guiding appropriate therapeutic interventions [2, 3].

Over the decades, significant advances have been made in laboratory blood culture systems, including the additions of enriched growth media, advances in automated agitation systems, and development of software that allows faster detection of bacterial growth via improved algorithms designed to track growth curves. Despite these technological advances, obtaining blood cultures (BCs) before initiating anti-infective therapy and ensuring appropriate fill volumes of 20–40 mL of blood per venipuncture within a single BC order remain key factors in the detection of adult bacteremia [3–5].

Initiation of prompt and appropriate antimicrobial therapy in patients at risk for sepsis is a clinical goal [2, 4]. However, there has been concern that initiation of antimicrobial therapy before culture collection can delay pathogen recovery, or in some cases, artificially sterilize BCs. In an effort to address this, BC manufacturers have incorporated blood-broth ratios and/or proprietary antimicrobial removal systems into BC media to minimize the impact of antimicrobials present in the media. The Becton Dickinson BACTEC Plus and the bio-Mérieux BacT/Alert FAN (hereafter referred to as BACTEC and BacT/Alert, respectively) are 2 of the more frequently used aerobic BC media that incorporate the use of proprietary antimicrobial removal systems. BACTEC utilizes proprietary binding resin beads incorporated into the media, while BacT/Alert utilizes Ecosorb, a blend of Fuller's earth and activated charcoal, to neutralize the effects of antimicrobials present in aerobic BCs submitted for laboratory testing.

BACTEC and BacT/Alert have been compared head to head clinically [6–8], and no demonstrable differences between the media were observed, whereas in vitro data indicate that there are differences between the 2 systems [9, 10]. This study was a prospective, simultaneous, head-to-head comparison of aerobic BACTEC and BacT/Alert BC media in a clinical setting focusing on the impact of prior antimicrobial exposure on bacterial recovery, time to detection (TTD), and identification of septic events.

MATERIALS AND METHODS

Patient Population
The study was conducted between 1 February 1 and 30 September 2011 in a 462-bed, acute care, urban, level I trauma center with medical and surgical intensive care units (ICUs) and an emergency department with >96 000 visits annually. The study was evaluated and approved by the hospital's institutional review board.

BC Collection and Processing
Adults on inpatient units and those seen in the emergency department were enrolled. A BC order/set consisted of 3 bottles: a BACTEC aerobic, a BACTEC anaerobic, and a BacT/Alert aerobic bottle. The bottles were randomly inoculated at the bedside and were submitted to the microbiology laboratory, accessioned, loaded into their respective instruments, and incubated according to the manufacturer's specifications under a 5-day incubation protocol. All clinical cultures were Gram stained and called to clinical providers caring for the patient (Supplementary Methods).

Exclusion Criteria
A BC set meeting any of the following criteria was excluded from the study: (1) collected in the outpatient setting, (2) collected from a pediatric patient, (3) growth exclusively in the BACTEC anaerobic bottle, or (4) lack of collection of a paired BACTEC–BacT/Alert bottle.

Clinical Assessment
The decision to initiate antimicrobial therapy in response to positive BCs is not always straightforward and is dependent on the clinical presentation, known virulence of the recovered organism, severity of disease, patient risk factors, length of hospital stay, and additional laboratory findings suggestive of infection. Organisms were classified as pathogens, contaminants, or indeterminants based on documentation of infection by the treating provider in the medical record, an independent assessment from an infectious disease specialist, and correlation with the clinical scenario. In cases where an organisms of questionable clinical significance were isolated in patients without obvious symptoms of infection, the recovered organism was classified as indeterminant. Each septic event was defined as the isolation of a unique pathogen or the repeated isolation of the same organism after 7 days of the last known positive culture. Discordant cultures were defined as recovery of an organism from one of the media in the absence of growth from the comparator media. Each culture was reviewed to determine if the source patient had received an antimicrobial(s) between 0–4 hours, 4–8 hours, 8–12 hours, 12–24 hours, or 24–48 hours prior to the culture collection (PCC). An active antimicrobial was defined as an antimicrobial with proven in vitro susceptibility against the cultured microorganism.

In Vitro Evaluation
Aliquots of paired BC media from discordant cases were filtered and tested by high-performance liquid chromatography (HPLC) to determine if residual antimicrobial concentrations could be detected after 5 days of incubation in the laboratory [11].

Data Analysis
Categorical data were evaluated using χ^2 test. Discordance in species isolation was compared across groups using McNemar test. Other nonparametric data, such as time to detection and fill volumes, were compared across groups using Wilcoxon

matched-pairs signed-rank tests (for within-group matched-pair data) and Mann-Whitney tests (for independent group comparisons). Number of septic events was compared using an unpaired t test. Comparison of prior antimicrobial dosing was calculated using logistic regression with results reported as odds ratios (ORs) and 95% confidence intervals. P values were considered significant at <.05 and were calculated as 2-tailed.

RESULTS

A total of 9395 BCs were evaluated during the study period, resulting in 1219 (13.0%) positive cultures, of which 831 met inclusion criteria (Supplementary Methods and Supplementary Figure 1). A total of 924 microorganisms were isolated from the 831 positive cultures, representing 59 distinct bacterial species/groupings (Supplementary Table 1).

Overall, Class, and Species Isolation
Media comparisons were based on the percentage that each contributed to the number of total positive cultures (Table 1). Of the 831 total organisms recovered, 474 (57%) showed discordance between the media. Among the 524 pathogens detected, growth was detected in BACTEC in 182 (34.7%) cultures compared with 72 (13.7%) in BacT/Alert ($P < .0001$); 270 organisms grew in both blood culture media (Table 1).

Overall, 452 of 524 (86.2%) pathogens isolated grew in BACTEC media compared with 342 of 524 (65.3%) in BacT/Alert media ($P < .001$; Table 1).

The BACTEC media isolated more pathogenic gram-negative rods ($P < .0153$) and gram-positive cocci ($P < .0001$) than did BacT/Alert. The BACTEC media isolated more *Staphylococcus aureus*, *Enterococcus faecalis/faecium*, and *Klebsiella pneumoniae* (Figure 1A). Both media were equivalent for yeast recovery.

In an attempt to eliminate BC fill volumes as a possible confounder in the study, the fill volume of each BC bottle was recorded by the laboratory. Differences in volume did not explain the differences in isolation rates between the 2 media (Supplementary Data [Bottle Fill Volumes] and Supplementary Figures 3 and 4).

Time to Detection
BACTEC isolated organisms an average of 1.77 hours faster than did BacT/Alert ($P < .005$; Figure 1A). For cases in which concordant growth (growth in both media resulting from a single venipuncture) was observed, TTD was 4.55 hours faster in the BACTEC media ($P < .0001$). When evaluating cultures with concordant growth, TTD with BACTEC was 4 hours faster if both bottles had equal fill volumes ($P < .0001$) and 4.36 hours faster if the organism isolated was a pathogen

Table 1. Isolation by Blood Culture Media

Organism category	Growth in BACTEC	Growth in BacT/Alert	Growth in Both	Total No.	P Value*
Contaminants[a]	112 (40.4)	92 (33.2)	73 (26.4)	277	.016
Indeterminates[a]	13 (43.3)	3 (10)	14 (46.7)	30	.024
Pathogens[a]	182 (34.7)	72 (13.7)	270 (51.5)	524	<.0001
Total	307 (36.9)	167 (20.1)	357 (43)	831	<.0001
Bacterial grouping					
All GPCs[b]	136 (39.4)	39 (11.3)	170 (49.3)	345	<.0001
All GNRs[c]	48 (27.4)	27 (15.4)	100 (57.1)	175	.0153
Staphylococcus aureus					
MSSA	74 (53.2)	15 (10.8)	50 (36)	139	<.0001
MRSA	27 (48.2)	7 (12.5)	22 (39.3)	56	.0006
Bacterial species					
Enterococcus faecalis/faecium	13 (26)	5 (17)	32 (64)	50	.0593
Escherichia coli	20 (29)	12 (17.4)	37 (53.6)	69	.157
Klebsiella pneumoniae	11 (29)	4 (10.5)	23 (60.5)	38	.0707
Pseudomonas aeruginosa	7 (35)	2 (10)	11 (55)	20	.0956
Yeast/mold[d]	5 (14.7)	11 (32.4)	18 (52.9)	34	.1336

Data are presented as No. (%) unless otherwise specified.

Abbreviations: GNR, gram-negative rod; GPC, gram-positive cocci; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

[a] For determination of organism classification, see the "Clinical Assessment" section of the Methods.

[b] Gram-positive cocci: 68.5% of overall organism burden.

[c] Gram-negative rods: 20.1% of overall organism burden.

[d] A single mold species representing *Scedosporium* was isolated from a single blood culture bottle during the evaluation.
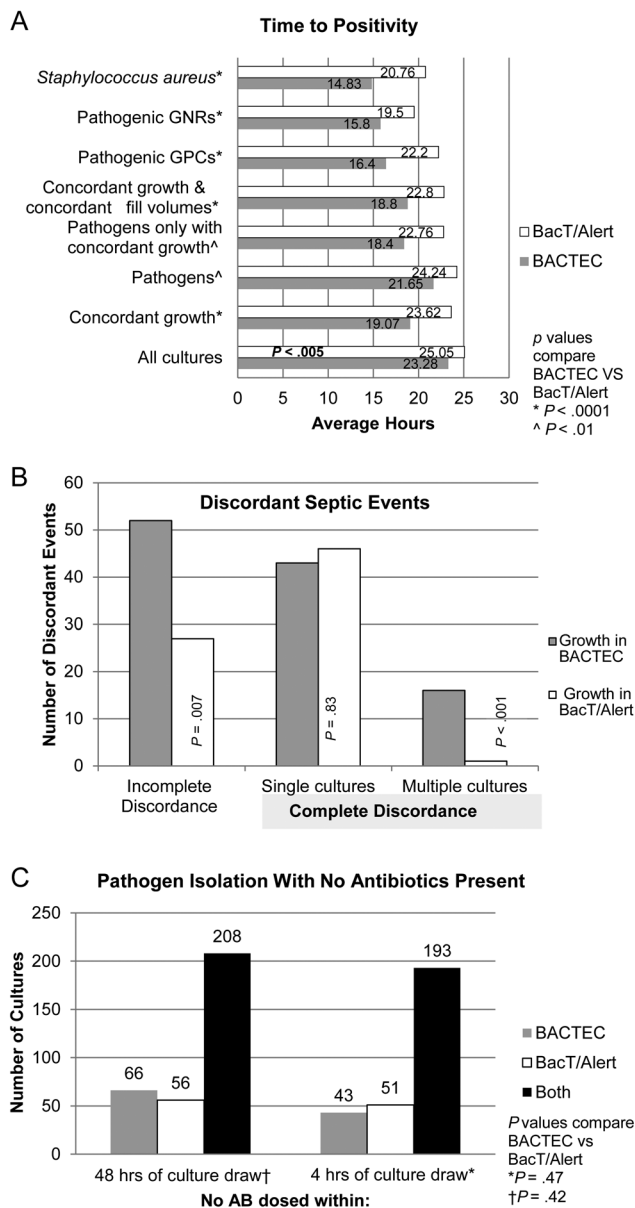
*P values compare BACTEC vs BacT/Alert.

Figure 1. Blood culture metrics. Abbreviations: AB, antibiotic; GNR, gram-negative rod; GPC, gram-positive cocci.

($P < .01$). For *S. aureus*, TTD was 5.93 hours faster in the BACTEC media ($P < .0001$; Figure 1*A*).

Septic Events

The number of septic events attributed to each individual patient varied, allowing the authors to stratify organism recovery between BC media based on complete or incomplete discordance. A completely discordant septic event was defined when one medium failed to identify all organisms from all serial blood collections pertaining to that event. An incompletely discordant event was identified when some of the

cultures pertaining to that event were identified by one media and some by the comparator media or both media. Of 185 septic events, 106 (57.3%) were completely discordant between the 2 BC media (Figure 1*B*). Of these 106, 59 (55.7%) events were isolated from the BACTEC media and 47 (44.3%) from the BacT/Alert media ($P = .0036$; Figure 1*B*). Throughout the 241-day study period, the 59 septic events identified only from the BACTEC media resulted in a missed septic event by the BacT/Alert media every 4.1 days. Similarly, every 5.1 days a septic event was detected only by BacT/Alert and missed by BACTEC.

When incompletely discordant septic events were analyzed, 52 of 81 (64.2%) events favored the BACTEC media compared to 27 of 81 (33.3%) favoring the BacT/Alert media ($P = .009$; Figure 1*B*). These longitudinal differences in positivity identified in our study have not been adequately addressed in prior BC studies.

Antimicrobial Exposure

Administration of an antimicrobial PCC was common. The likelihood that an antimicrobial was dosed within 4–48 or 0–4 hours PCC was 46% and 51%, respectively, on the general wards, but rose to 74% and 82%, respectively, in the medical ICU. The average number of antimicrobials administered within 48 hours and 4 hours PCC was 2.2 and 1.89, respectively, across all wards, but 2.5 and 2.2, respectively, in the medical ICU. Antimicrobials dosed most frequently were vancomycin and piperacillin-tazobactam.

Table 2 demonstrates isolation differences based on prior antimicrobial exposure. Differences in isolation rates between BC media were observed across all time points when an antimicrobial was administered PCC. In instances where antimicrobial administration occurred 0–4 hours, 4–8 hours, and 8–12 hours PCC, the likelihood was 4.77, 4.02, and 3.37 times higher, respectively, that the microorganism involved in sepsis was isolated in the BACTEC media (Table 2). The effectiveness of yeast recovery with prior antifungal exposure could not be determined, because only 7 of 35 (20%) of the cases in which yeast species were isolated had an antifungal dosed within 48 hours PCC.

When the spectrum of antimicrobial activity was compared to the microorganism(s) recovered, additional differences in isolation rates were noted. Across all time points, BACTEC outperformed BacT/Alert and was significantly more likely to isolate a microorganism in cases where an active antimicrobial had been administered, but noted particularly between 4–8 hours (OR = 6.85) and 8–12 hours (OR = 5.55) PCC (Table 2). Bacterial isolation rates were equivalent when antimicrobials were deemed inactive or had not been administered PCC (Figure 1*C*), suggesting that antimicrobial removal systems by BC media are important.

Table 2. Isolation by Prior Antimicrobial Dosing

Antibiotic Present in Patient Between	Media Isolation			OR[a]	95% CI[c]
	BACTEC Only	BacT/Alert Only	Both		
0–4 h of culture draw					
Pathogen	149	35	120	4.77	2.63–8.61
Active AB[b]	139	21	77	4.78	2.7–8.45
4–8 h of culture draw					
Pathogen	127	26	97	4.02	2.27–7.10
Active AB[b]	112	13	56	6.58	3.33–13.02
8–12 h of culture draw					
Pathogen	119	26	89	3.37	1.92–5.92
Active AB[b]	101	13	50	5.55	2.8–11.0
12–24 h of culture draw					
Pathogen	112	26	88	2.78	1.59–4.87
Active AB[b]	94	13	44	4.53	2.21–9.29
24–48 h of culture draw					
Pathogen	100	24	71	2.39	1.36–4.2[d]
Active AB[b]	85	10	31	4.88	2.32–10.26
4–48 h of culture draw					
Pathogen	130	28	106	3.88	2.2–6.84
Active AB[b]	116	16	62	5.15	2.64–10.0

Abbreviations: AB, antibiotic; CI, confidence interval; OR, odds ratio.

[a] Comparison between BACTEC and BacT/Alert.

[b] Pathogens and indeterminates used for calculation.

[c] P values for all data <.0001 except where noted.

[d] P = .002.

Detection of Piperacillin Concentrations by HPLC

Antimicrobials present in patients' blood at the time of BC collection have been suggested as one explanation for differences in positivity between the BACTEC and BacT/Alert media. In an effort to demonstrate that residual antimicrobial remains in BC media after 5 days of incubation, BC media containing patients' blood were tested by HPLC for residual piperacillin levels in 9 discordant cases isolated from the BACTEC media and 1 discordant case isolated from the BacT/Alert media. Piperacillin was chosen as a representative antimicrobial on the basis of its stability and high utilization within our hospital. Discordant cases were chosen on the basis of predictable drug kinetics in patients and well-documented administration times of piperacillin monotherapy. Using these criteria, 4 cases were identified in which trough concentrations were likely to be present at the time of collection, 4 cases with midlevel concentrations, and 2 with peak serum concentrations.

Piperacillin levels were not detected in either media from cases with estimated trough levels. However, in 3 of 9 (33.3%) cases in which a microorganism was preferentially recovered from the BACTEC media, residual piperacillin concentrations above the minimum inhibitory concentration of the microorganism isolated were detected in the BacT/Alert media (Figure 2A).

To validate these clinical findings, BACTEC and BacT/Alert media were inoculated in vitro with 8–10 mL of whole blood and simulated peak, mid and trough levels of piperacillin. After 5 days of laboratory incubation, the BC media was removed and tested by HPLC. Piperacillin concentrations were detected in the BacT/Alert media for all triplicate series containing simulated peak and midlevel piperacillin doses. Residual piperacillin concentrations could not be detected in BacT/Alert media containing simulated trough levels. No concentrations of piperacillin could be identified in any BACTEC bottle. These findings suggest that removal of antimicrobials in BacT/Alert BC media may be dose dependent (Figure 2B).

DISCUSSION

In the diagnosis and treatment of sepsis, time is of the essence. Delays in initiation of effective antimicrobials can increase mortality rates by 7.6% [12]; therefore, timely administration of antimicrobial therapy has been incorporated into
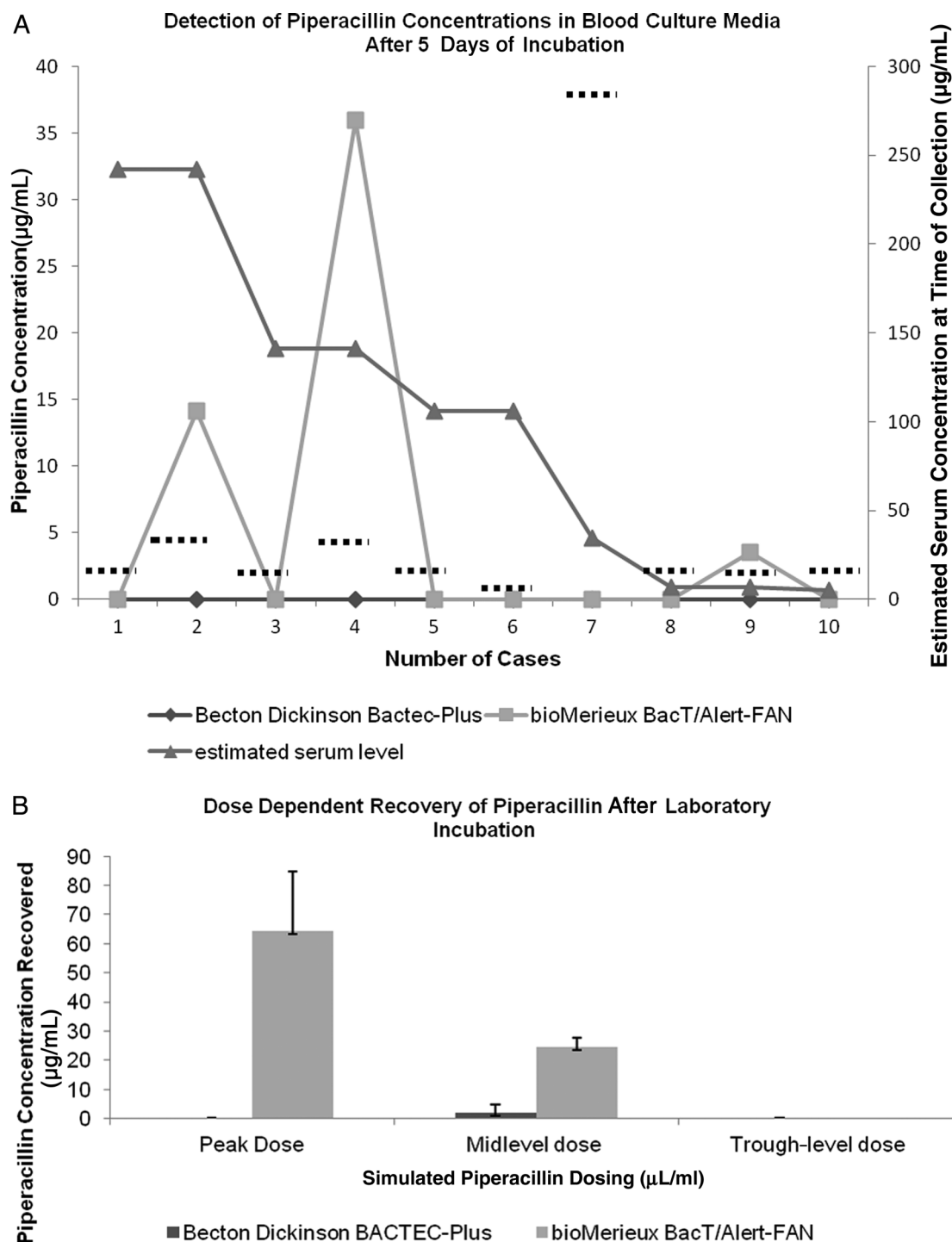
Figure 2. *A*, Ten clinical samples containing aliquots of blood culture (BC) media with patients' blood were tested by high-performance liquid chromatography (HPLC). Microorganisms were preferentially recovered from BACTEC media for all cases except case 7. Triangles represent detection of piperacillin concentrations from BACTEC media (Becton Dickinson) after 5 days of incubation in the laboratory. Squares represent detection of piperacillin concentrations from BacT/Alert (bioMérieux) media after 5 days of incubation in the laboratory. Triangles represent estimated patient piperacillin concentrations present at the time of BC collection. Dashed lines represent the piperacillin minimum inhibitory concentration of the microorganism isolated in the case. Lower limit of piperacillin detection was 2.0 µg/mL. *Patient 4 received a 4.5-g dose of piperacillin and had received a total of 7 doses prior to BC collection. The time differential between piperacillin administration and collection of BC was on average 1 hour 40 minutes. *B*, Simulated peak, mid-, and trough-level doses of piperacillin were administered in vitro in triplicate into BACTEC and BacT/Alert aerobic BC bottles and incubated for 5 days in the laboratory prior to HPLC testing. Error bars indicate standard deviation between triplicate testing. Lower limit of piperacillin detection was 2.0 µg/mL.

early goal–directed therapy protocols. In 2008, guidelines for the management of septic shock recommend that appropriate antimicrobials be started in the emergency department within 1 hour of recognition of sepsis [4, 12]. Physicians are faced with competing demands of balancing the need for early initiation of appropriate empiric antimicrobial therapy with concerns over coverage for multidrug-resistant organisms, medication side effects, and the limited availability of novel antimicrobials. Thus, diagnostic tools that detect pathogenic organisms more rapidly are critically important and may facilitate this decision making. Our study highlights the importance of antimicrobial removal systems in contemporary BC media and represents one of a few studies specifically designed to examine how prompt antimicrobial prescribing affects the microbiological detection of sepsis. The reality of this paradoxical relationship between rapid treatment initiation and potential impact on diagnostics is exemplified in our study, as 50% and 82% of patients seen in our wards and ICU environments, respectively, had a an antimicrobial administered PCC.

It was of interest to the authors that each medium failed to isolate organisms even with ideal growth conditions in the absence of antimicrobials. Of 287 cultures where no or inactive antimicrobial(s) were present, 51 of 287 (17.8%) grew only in the BacT/Alert media and 43 of 287 (14.9%) grew only in the BACTEC media, demonstrating that differences in yield of bacterial recovery between media may be as high as 17% in any direct BC comparison. Such differences may be attributable to differences in media composition, level of bacteremia, or pathogen fitness.

Previous studies designed to compare contemporary BC media within hospital settings failed to reveal differences. Why our findings differ so dramatically from those of previously published series is unclear. However, of the previously published studies, only that of Jorgensen et al [8] referenced antimicrobial utilization, but they offered no details on the agents used, proportion of cultures tested, timing of antimicrobial administration, or impact on species recovery. We hypothesize that the trend of early empiric dosing of multiple antimicrobials, increased recognition of the impact of early antimicrobial intervention in new sepsis pathways, changes in national bacterial resistance patterns, and/or changes in media formulation or manufacturing processes over the past 15 years are all variables that could explain the differences observed in our study. However, the most likely explanation for our findings is that antimicrobials are not being readily removed from the blood/broth solution in the BacT/Alert media, thereby allowing antimicrobials to exert a persistent inhibitory effect. Both media were equivalent when no antimicrobial was present, offering further support for this hypothesis. Furthermore, HPLC data suggest that antimicrobial removal may be dose dependent within the BacT/Alert media, possibly via a "saturation" effect on the antibiotic removal system.

The present study is representative of an inner-city hospital population, with an overall BC positivity rate (13%) and sex distribution similar to other studies [3, 13, 14]. The distribution of organisms with a preponderance of S. aureus is also typical [7, 13]. However, differences in the recovery and TTD for S. aureus is a key finding in our study that has not been previously described. Barenfanger et al demonstrated that decreases in mortality of up to 9% occur when a positive Gram stain result from a BC is reported within 1 hour of TTD [2]. Thus, differences in detection of S. aureus between the 2 BC media are likely to be clinically significant.

The potential clinical implications of discordant septic events is a metric not easily captured in BC studies but is a key clinical decision point. Both media were equivalent when septic events consisted of a single BC collection, but strongly favored BACTEC when multiple cultures were positive. We frequently noted that a patient would not receive antimicrobials prior to initial BC collection but empiric antimicrobials were rapidly initiated afterward, likely explaining why all subsequent BC cultures were positive from only BACTEC media (Figure 1B). Differences in the detection of persistently positive cultures could affect the decision to terminate antimicrobial therapy, as frequently the time of the first negative BC determines overall duration of therapy. In several cases, patients were bacteremic for up to 10 days without detection by the BacT/Alert media beyond the initial positive BC. In these patients, if the BacT/Alert media alone had been used, antimicrobial therapy may have been stopped earlier under the erroneous impression that the patients were no longer bacteremic.

Microorganisms had a 4 times greater likelihood of growing in the BACTEC media if active antimicrobials were present PCC, and were 6.58 and 5.55 times more likely to be isolated between the time points of 4–8 hours and 8–12 hours when an active antimicrobial was present PCC (Table 2). These time points are critical, as this is when the peak blood levels of many commonly prescribed antimicrobials occur. In cases where the antimicrobial half-life was prolonged (eg, in dialysis patients), the potential therapeutic drug effect of antimicrobials dosed prior to 48 hours of BC collection was considered and is likely to have a greater effect on differences in BC recovery.

BACTEC media exhibited statistically increased bacterial recovery and faster TTD compared to BacT/Alert media in the following parameters: overall bacterial recovery, overall pathogen recovery, gram-negative rod and gram-positive cocci recovery, S. aureus recovery, and detection of septic events. Experts agree that collection of BCs prior to initiation of antimicrobial therapy should be a goal; we also recognize that initiation of antimicrobial therapy in patients with suspected sepsis is a competing goal and one that will continue to challenge the laboratory.

Type I statistical error is always a possibility given the number of comparisons present in this study; however, given

the consistency of the results throughout the study, it is unlikely that chance alone explains the findings. The present study demonstrates differences in recovery of bacterial organisms involved in sepsis between 2 contemporary BC media widely used in hospital laboratories. These differences have not been previously recognized. It is important for both physicians and laboratorians to understand the limitations and realities of how contemporary prescribing practices affects the microbiologic diagnosis of sepsis, and to further recognize the limitations of BC systems. As such, the diagnosis of sepsis remains both a clinical and laboratory diagnosis.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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