Blood Cultures Positive for Coagulase-Negative Staphylococci: Antisepsis, Pseudobacteremia, and Therapy of Patients†

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Received 26 January 1998/Returned for modification 12 March 1998/Accepted 7 April 1998

A blood culture cohort study investigating issues related to isolation of coagulase-negative staphylococci (CoNS) and other skin microflora is reported. Data were collected over 12 weeks to determine the incidence of significant CoNS bacteremia versus that of pseudobacteremia (contaminants) and to evaluate drug therapy in patients with cultures positive for CoNS. In addition, the effectiveness of 0.2% chlorine peroxide as a bactericidal disinfectant was compared to that of 10% providone iodine. A total of 3,276 cultures of blood from 1,433 patients were evaluated in the study. Eighty-nine cultures were positive for skin flora, with 81 of 89 (91%) involving CoNS. The incidence of significant CoNS bacteremia was 20 of 81 (24.7%), that of indeterminate bacteremia was 10 of 81 (12.3%), and that of contamination was 59 of 81 (72.8%). The incidence of significant bacteremia involving CoNS was double the 10 to 12% rate based on previous estimations at our institutions. In tests with the two bactericidal disinfectants, 22 of 1,639 cultures (1.3%) in the chlorine peroxide group versus 37 of 1,637 (2.3%) in the providone iodine group were considered contaminated (P = 0.065). Rates of contamination for venipuncture versus catheter collection were not significantly different (P = 0.46). The overall contamination rate was 59 of 3,276 (1.8%), which is consistent with the lower end of published quality assurance benchmark standards. The low rate was believed to be due to the professional phlebotomy staff in our institutions. There was excellent agreement between retrospective analysis by reviewers, when formal criteria were used, and the attending physicians’ intuitive clinical impressions in the classification of significant bloodstream infections (100% agreement) or contamination (95% agreement). However, physicians still used antimicrobial agents to treat nearly one-half of the patients with contaminated blood cultures, with vancomycin being misused in 34% of patients. In addition, 10% of patients with significant bacteremia were treated with inappropriate agents. There were no significant adverse events or prolonged hospital stays due to the unnecessary use of vancomycin; however, the additional costs of treating patients whose cultures contained CoNS contaminants was estimated to be $1,000 per patient. Measures to limit the unnecessary use of vancomycin (and other agents) are important.

Coagulase-negative staphylococci (CoNS), the most frequent blood culture isolates, are predominately blood culture contaminants but they are also a significant cause of bacteremia (2–5, 7, 9, 13). Institution-specific contamination rates vary from 2 to more than 6% (3, 5, 23, 26, 27). In the past 5 years, estimated contamination rates at our hospitals ranged from 2.5 to 3.5%. During this period, CoNS accounted for 45 to 60% of total blood isolates, and we estimated, using laboratory criteria, that 10 to 12% of CoNS isolates from blood were implicated in significant bloodstream infections. A relatively large proportion of the patient population with presumed false-positive blood cultures due to contaminants (pseudobacteremia) were treated with antimicrobial agents, in particular, vancomycin.

Clinical and microbiologic guidelines for the differentiation of true bacteremia from pseudobacteremia or contamination have been published (5, 13, 15). Suggested laboratory criteria for true bacteremia include growth within 48 h and multiple blood cultures positive for the same organism. In contrast, increased duration of time before positivity, polymicrobial growth of skin organisms, or growth during antibiotic treatment suggest contamination. Others recommended that the addition of clinical guidelines is essential for the appropriate classification of bacteremia (4, 8, 9, 15, 18).

We conducted a cohort study to evaluate clinical and laboratory data for adult patients with blood cultures positive for CoNS. The study was done at two tertiary-care teaching centers, Deaconess Medical Center (DMC) and Sacred Heart Medical Center (SHMC), with a combined capacity of 900 beds. We examined problems associated with false-positive bacteremia and determined the incidence of significant bacteremia. Our goal was to make recommendations to improve clinicians’ ability to recognize the significance of potentially contaminating organisms and to evaluate treatment given to patients with CoNS-positive blood cultures. To attempt to minimize contamination, we evaluated the nontoxic, antiseptic and disinfectant chlorine peroxide in comparison to a standard disinfectant.

(This work was previously presented in abstract form at the...
MATERIALS AND METHODS

Data collection and standards. Over a period of 3 months in 1995, phlebotomists and nursing staff obtained for culture blood samples from veins or catheters, respectively. Members of a multidisciplinary infectious disease service collected the data. The laboratory and pharmacy data acquired with computer assistance included demographics, organisms isolated, time to culture positivity, total number of positive cultures, susceptibility test results, critical laboratory values, and the therapeutic agents used. Members of the Spokane Internal Medicine Program in conjunction with the infectious disease service conducted chart reviews to assess patient risk factors and the clinical significance of blood CoNS isolates and other skin microflora. By using a combination of previously published criteria (4, 5, 8, 13, 15, 18, 28), patients were assigned to one of three categories: significant bacteremia, indeterminate bacteremia, and contamination. Essential clinical criteria for classification of true bacteremia included one or more of the following: prolonged temperature (≥38°C), hypotension (<90 mm Hg), leukocytosis or neutropenia with a left shift differential, or disseminated intravascular coagulopathy. In addition, a major risk factor for potential infection caused by skin flora was required; this included long-term intravenous catheterization, which is used for such patients as patients on critical care units, immunosuppressed patients with central lines, peritoneal dialysis or hemodialysis patients, and patients with extensive postsurgical infections with CoNS. Indeter-
minate bacteremia were considered in patients who had a major risk factor but who had minimal or transitory clinical symptoms (such patients may also be considered to have insignificant or transient bacteremia not necessarily requiring therapy). Blood cultures were considered to be contaminated for patients who (i) experienced an insignificant febrile episode and were without significant risk factors; (ii) had significant risk factors but were shown by prior, concurrent, or subsequent blood cultures to have a septic episode with an unequivocal patho-
gen; or (iii) had infectious or noninfectious shock-like complications associated with an inconsistent CoNS etiology (e.g., aspiration pneumonia or acute respi-
atory distress syndrome, respectively). The culture criteria examined but not necessarily used to categorize patients included: (i) isolation of an identical organism (same antibiogram) from another infected site; (ii) semiquantitative, culture-positive isolation from a catheter tip and an organism with an identical antibiogram (16); and (iii) multiple (two or more) positive blood culture sets. The reviewers also assessed primary clinicians’ initial and final clinical impres-
sions, therapy, and outcome. Patient costs for drugs and monitoring tests were evalua-
ted for the contaminant group.

Blood collection and disinfectant study. Phlebotomists who had been enrolled in an initial educational program with annual in-service training performed all venipunctures. Catheter blood collections on critical care units were done by nursing staff. Skin antiseptics or catheter disinfection was done by initial appli-
ation of 70% isopropyl alcohol (Kendall Healthier Products Co., Mansfield, Mass.), followed by application of either 10% povidone iodine-saturated sponges (Swab Aid, Betadine Solution; Purdue Frederick Co., Norwalk, Conn.) or 2-by-
2-in. gauze sponges (Kendall Healthier Products Co.) saturated with 0.2% chlo-
rine peroxide (Bioglobe, Inc., Spokane, Wash.). Blood was obtained approxi-
ately 1 min after application of the povidone iodine or chlorine peroxide. Chlorhexidine gluconate provided by Bioglobe Inc., in 1-gal, opaque containers and was transferred to 8-oz. automatic dispensing bottles (Baxter Diagnostics Inc., McGraw Park, Ill.). Chlorine peroxide was replenished every 72 h or when depleted.

Study design. At SHMC, chlorine peroxide was used exclusively for 6 weeks. At DMC, chlorine peroxide or povi-
done iodine was used on alternating days during the 12-week study. Because the two disinfectants were packaged differently and the chlorine peroxide had a distinctive odor, the study was not blinded. To minimize disinfectant bias, phle-
botomists and nursing staff were instructed to use identical procedures, and in-service training was done at 3-week intervals during the 12-week investigation.

Blood culture procedures. Following skin or catheter preparation, 20 ml of blood was collected with a syringe and at SHMC was distributed at the bedside in 10-ml aliquots into standard aerobic and anaerobic bottles (Bact/Alert; Org-
anon Technica, Durham, N.C.). At DMC, 15 ml of blood was collected in a similar fashion and was inoculated at the bedside as follows: 10 ml was inoculated into an aerobic bottle and 5 ml was inoculated into an anaerobic bottle (BACTEC 6A and 7A, respectively; Becton Dickinson, Cockeysville, Md.). Cul-
tures were incubated at 37°C in either a continuous monitoring system (Bact/Alert) at SHMC or a semiautomated monitoring system (BACTEC 620) at DMC. The bottles were monitored for 5 days and were discarded on day 6 without terminal subculture. Since the BACTEC 620 system was not a continu-
ous monitoring system, only SHMC data were used to monitor time to culture positivity. Culture sets were considered to be contaminated if blood cultures occurred within a 24-h period. The number of positive culture sets per patient and the total number of culture-positive bottles (aerobic and anaerobic) within sets were determined.

Organisms. The species of CoNS (defined as catalase-positive, coagulase-
negative staphylococci [gram-positive cocci]) were not determined in this study. When gram-
positive cocci (or other organisms) were identified by Gram staining of signal-
positive culture bottles, direct disk diffusion tests were done. When growth was obtained on isolation plates, repeat disk susceptibility testing was done according to established guidelines (20). A latex coagulase test (Staphaurex; Murex Biotech Limited, Dartford, United Kingdom) was performed for all gram-positive coagulase-
negative staphylococci. Equivocal latex test results were confirmed by a tube coagulate test (Difco Laboratories, Detroit, Mich.). Catalase tests were done with 3% H2O2.

Statistical methods. Most variables were categorical, and statistical tests of the null hypothesis (no difference in categorical proportions between groups) were chi-square tests of independence. Time to positive culture detection was calcu-
lated for each patient by averaging the times for all positive cultures; the distri-
bution of these averages was compared between groups by the Mann-Whitney (Wilcoxon rank sum) test. All tests were two tailed. P values of less than 0.05 were regarded as significant.

RESULTS

During the study, 3,276 blood samples for culture were obtained from 1,433 adult patients (average, 2.3 cultures per patient). The average patient age was 56 years; 58% were male and 42% were female. A total of 95 potentially contaminating isolates were obtained from 89 culture-positive episodes. The organisms isolated were CoNS (n = 81), coagulase-negative micrococci (n = 2), coryneforms (n = 8), Bacillus spp. (n = 2), and viridans group streptococci (n = 2). For six patients one additional organism was concurrently isolated with CoNS (two micrococci, one coryneform, one Corynebacterium jeikeium iso-
late, one Bacillus isolate, and one viridans group streptococcus). Five Propionibacterium acnes isolates were isolated on day 5 of incubation (the patients’ medical records contained no notation of culture positivity by attending physicians, nor were any of these patients treated with antibiotics). Other single-organism cultures yielded a coryneform, a Bacillus, and a viri-
dans group streptococcus, each of which was considered by the reviewers to be a contaminant.

Bacteremic classification. Of the 89 patients with cultures positive for skin flora, CoNS were isolated from 81 patients (91% of the patients with cultures positive for skin flora). Following chart review, we classified patients into the final clinical categories: significant bacteremia (n = 20), indetermi-
inate bacteremia (n = 10), and pseudobacteremia or contami-
nation (n = 59). When the retrospective reviewers’ assessment was compared to the initial impression of the attending clini-
cians, we found 100% agreement for the significant bacteremia category and 95% agreement for the contamination category. The indeterminate group was not evaluated, except that we noted that 5 of the 10 patients were not treated with antibiot-
ics.

Antimicrobial therapy and cost. Antibiotic therapy and out-
come were further reviewed for patients in the categories of significant bacteremia and contamination. Among the 20 pa-
tients with significant CoNS bacteremia, vancomycin was used 18 times, nafcillin was used once, and ciprofloxacin was used once. Among the 59 patients in the contamination category, 24 patients (41%) were treated with antimicrobial agents. Cefa-
zolin was used twice, imipenem was used once, and metroni-
dazole was used once; vancomycin was administered to 20 patients (34%). The average length of vancomycin therapy was 6.5 days for patients in the contamination category, with an average cost per patient for pharmacokinetic monitoring as-
says and drug of $645. No adverse event attributable to van-
comycin was found among these 20 patients, and prolonged length of stay was not evident.

Comparison of povidone iodine and chlorine peroxide. The combined contamination rate for all contaminating organisms in both the povidone iodine and the chlorine peroxide groups was 1.8% for cultures considered to be contaminated (59 con-
taminants in 3,276 collections). In the povidone iodine disinfec-
tant group, 37 of 1,637 cultures (2.3%) were contaminated, and in the chlorine peroxide group, 22 of 1,639 cultures (1.3%).
were contaminated \( (P = 0.065) \). The contamination rates for venipuncture collection (46 contaminants in 2,682 collections) versus catheter collection (12 contaminants in 594 collections) were 1.7 and 2.0\%, respectively \( (P = 0.46) \).

**Laboratory analysis.** The proportions of patients in the true bacteremia, indeterminate, and contaminant groups with multiple culture sets positive for CoNS were 65, 18, and 12\%, respectively. There was a significant difference in these proportions \( (P < 0.0001) \) both when the true bacteremia group was compared to the other two groups combined and when the true bacteremia group was compared to the contaminant group only. A similarly significant difference was found when the numbers of positive culture bottles within a set were compared between the two groups (data not shown). For CoNS-positive cultures, there was no significant difference between the contaminant group and the true bacteremia group in the time to detection of a positive culture (median times, 28 and 25 h, respectively) \( (P = 0.2) \).

During the study, only two catheter tips were sent for culture, one from a patient considered by the clinician and reviewer to be a member of the contamination group and the other from a patient with true bacteremia.

**DISCUSSION**

CoNS and other skin microflora are isolated at variable rates; contamination rates are typically institution specific and are related to phlebotomist expertise and the efficacies of skin-degerming agents \( (23, 26, 27) \). Contamination rates of 2 to 3\% are recommended as benchmarks \( (5, 23, 26) \). Gram-positive organisms predominate among contaminants and tend to be multidrug resistant, with many being susceptible only to vancomycin. In patients predisposed to nosocomial or iatrogenic infection, reflexive use of vancomycin following reports of gram-positive cocci in blood cultures is common. During the era of vancomycin-resistant enterococci, prudent use of vancomycin is imperative and many institutions have implemented programs aimed at reduced vancomycin use \( (10) \). Congruently, the incidence of significant CoNS bacteremia requiring vancomycin therapy is also increasing \( (9, 17) \). In this investigation, the rate of incidence of significant CoNS bacteremia \( (24.7\%) \) was about double our previously estimated rate of 10 to 12\%. This rate approximates the quantitative blood culture rate of 26.4\% and the lowest stratified rate of 21.1\% for CoNS bacteremia found by Herwaldt and colleagues \( (9) \).

Chlorine peroxide, a chlorite-chlorate derivative (also known as chlorine dioxide), is a potent oxidizing agent and is rapidly bactericidal \( (1) \). The agent was shown to be nontoxic to skin and mucous membranes in an animal model in which the concentrations of chlorine peroxide were 8- to 16-fold higher than those that we used in this investigation \( (4b) \). Although the compound is bactericidal over a wide \( p\text{H} \) range, activity is enhanced at low \( p\text{H} \). Moreover, chlorine peroxide is unstable, being slowly inactivated in the presence of light. On the basis of stabilization and activation procedures, the agent was shown to have activity that is equal to or that exceeds that of the tincture of iodine \( (4a) \), a disinfectant that was twofold more effective than povidone iodine in reducing blood culture contamination \( (26) \). In this study, we found a reduced contamination rate with chlorine peroxide \( (1.3\%) \) compared with that with povidone iodine \( (2.3\%) \), a difference that approached but that did not achieve statistical significance \( (P = 0.065) \). However, a significant disadvantage of chlorine peroxide is the absence of a commercial preparation similar to that for isopropyl alcohol, povidone iodine, or tincture of iodine. The preparation and quality control costs of a noncommercial degemming system may exceed any financial benefits of contamination reduction. If a commercial preparation becomes available, chlorine peroxide merits further investigation.

The rate of true contaminants for both disinfectants combined \( (59\) patients) was 1.8\%, or 2.1\% if the 10 patients in the indeterminate category were included in the contamination category. These rates were lower than our previously projected contamination rates, possibly due to current study bias or underestimation of significant bacteremia from our prior unpublished epidemiological surveys. The low contamination rates, which are consistent with benchmark standards, may also be attributed to the professional, highly motivated phlebotomy staffs, which have operated in our institutions for more than 20 years. The employment of professional blood collection teams may be the most important aspect in contaminant reduction because centers that use a variety of health care professionals for blood collection typically have contamination rates that exceed 6\% \( (4, 26, 27) \).

Bacteremia classification models include laboratory elements \( (2–4, 9, 16, 22) \), with some models based solely on laboratory findings \( (11–13, 22, 24) \). Although such models may be useful for the ultimate classification of bloodstream infections, our study does not support the utility of a rapid laboratory information-based system. Clinical reports on the relevance of laboratory information conflict. For example, two traditional laboratory criteria for determining significance, i.e., time to positivity and the presence of multiple positive blood culture sets, have been challenged \( (9, 17, 24) \). Other laboratory techniques such as species determination, antibiogram or phage typing, and molecular profiling can assist in the appropriate categorization, but all require extended testing times. Given the disparate procedures outlined in previous studies \( (6, 9, 11, 14, 17, 19, 21, 22, 24, 25) \), controversy is inevitable. Major confounding issues include phlebotomist expertise, the volumes of blood collected, the number of culture sets, the culture media used, the culture systems used (manual, semiautomated, automated), and the availability of multiple identification schema and kits. In this investigation, use of automated blood culture did not result in an appreciable difference in time to culture positivity (median times, 25 and 28 h, respectively, for cultures indicating true bacteremia and CoNS-contaminated cultures, respectively; \( P = 0.2 \)). We found highly significant differences \( (P < 0.0001) \) for multiple positive culture sets between patients with contamination and true bacteremia; however, 12\% of patients in the contamination category had two or more positive culture sets, and for 35\% of samples from patients with significant bacteremia, only a single culture set was positive. Exclusive use of these laboratory data for rapid predictions would lead to substantial miscategorization of both true bacteremia and pseudobacteremia.

Although our institutions do not use a formal, statistically driven model for the classification of bacteremia, our retrospective review indicated excellent agreement between attending physicians and reviewers in categorizing patients with bacteremia or pseudobacteremia. For the 20 patients with significant bacteremia, there was complete agreement in classification; however, therapy was sometimes inappropriate. In the contamination group \( (59\) patients), clinicians recorded organisms as probable contaminants for 95\% of the treated patients. We did not extensively review the medical records of the 10 patients with indeterminate bacteremia but noted that 50\% of them were not treated. We assumed that the physicians considered the cultures to be contaminated or assumed that the patients had insignificant (transient) bacteremia that did not merit therapy.

Two patients with significant bacteremia \( (10%) \) were treated with inadequate agents. One patient had two CoNS-positive...
blood cultures and one patient had CoNS isolated from an empyema drainage tube (all isolates were oxacillin resistant and had identical antibiograms). Nafcillin was initiated “for staph coverage” when the culture results were posted; the patient died 12 days later. The other patient received monotherapy with ciprofloxacin and survived; however, this agent was considered suboptimal therapy for CoNS.

We further analyzed the data for the 24 patients in the contamination group who were treated with antimicrobial agents. Three patients were treated with inappropriate anti-CoNS agents (cefazolin and imipenem), and one patient with a Bacillus contaminant received metronidazole therapy. Among the 20 patients with CoNS contaminants treated with vancomycin, isolates from 19 patients were recognized as nonsignificant on the first note on the patients’ charts following the return of the culture results; in the other patient the CoNS was recorded as a contaminant 48 h after reporting the positive culture result. We believe that this discordance in the treatment of assumed contaminants represents defensive medicine.

In two frequently cited studies, the costs attributed to the unwarranted use of vancomycin exceeded $4,000 per patient (2), and costs of more than $5,000 per patient were found for general inappropriate use of antimicrobial agents in bacteremic patients (6). Although we did not conduct a comprehensive cost analysis, we examined two elements (adverse drug reactions and length of stay) which led to significant excess costs in the studies of Bates et al. (2) and Dunagan et al. (6). We found neither factor to be significant in our study, and costs attributable to vancomycin misuse appear to be considerably less in our community. Accordingly, we estimate our institutional costs for excessive therapy for patients with pseudobacteremia to be about $1,000 per patient. With our current contamination rate, we project that a substantial reduction in unneeded therapy could result in cost savings of up to $200,000 per year.

In conclusion, CoNS continue to be frequently isolated in blood cultures and represent the most common cause of pseudobacteremia in our institutions. Physicians typically recognized contamination in our study but continued to use vancomycin inappropriately in this setting. We believe that vancomycin use should be monitored and that practitioners should be made aware of the danger of progressive antibiotic resistance caused by unwarranted vancomycin therapy. We have recently implemented an antibiotic review team composed of microbiologists, pharmacists, and infectious disease physicians to continue to address these issues. Further study of skin decontamination and blood collection may also lead to reductions in the misuse of antimicrobial agents due to contamination.

ACKNOWLEDGMENTS

This work was supported in part by grants from Bioglobe, Inc., and the SHMC Research Foundation. We thank the phlebotomy, microbiology, and nursing staffs (oncology and critical care services) at SHMC and DMC for assistance with the study. We are indebted to Andrew Pavia and Larry Reimer for critical review of and suggested revisions to the manuscript.

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