Bloodstream Infections Caused by Contaminants: Epidemiology and Risk Factors: A 10-Year Surveillance

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ABSTRACT: **Background:** Skin colonization of microorganisms in blood cultures (BCs) are generally considered clinically non-significant and can be the source of a true infection, particularly in immunosuppressed patients.

Objectives: To study the epidemiology and risk factors for bacteremia caused by contaminants.

Methods: This retrospective, descriptive study is based on adult BCs collected (2004–2013) and categorized as positive (True bacteremia [TrueB] or contamination) or negative. Clinical, demographic, and laboratory characteristics of BCs positive for the six most common potential contaminant pathogens (PCPs) that can cause TrueB and contamination (*Coagulase-negative Staphylococcus* [CoNS], *Streptococcus viridans*, *Propionibacterium acnes*, *Corynebacterium* spp., *Bacillus* spp., *Clostridium* spp.) were assessed. Ninety-two TrueB were identified vs. 196 contaminations (1:2 ratio).

Results: From 74,014 BCs, PCPs were found in 3735 samples, of which 3643 (97.5%) were contaminations and 92 (2.5%) were TrueB. The overall rate of BC contamination decreased during the study period from 6.7% to 3.8%. CoNS was the most common PCP. *Bacillus* spp. were only contaminants. *Clostridium* spp. and *Streptococcus viridans* were more often TrueB. In a multivariate model, predictors of TrueB included high creatinine levels, *Streptococcus viridans* in BC, and multiple positive BCs. A single culture of CoNS was strongly predictive of contamination.

Conclusions: Ten years of data on BCs, focusing on six PCPs, demonstrates a significant, yet insufficient reduction in the rate of contamination. High creatinine level, isolation of *Streptococcus viridans*, and multiple positive BCs were predictors of TrueB, while growth of CoNS was strongly predictive of contamination. This model could assist in diagnostic and therapeutic decision making.

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KEY WORDS: bloodstream infection, *Coagulase-negative Staphylococcus* (CoNS), contamination, contaminant pathogens, true bacteremia (TrueB)

Fever, as a manifestation of infection, and sepsis are common causes of hospitalization. Such infections are associated with high rates of morbidity and mortality [1]. Blood cultures (BCs) are part of the routine initial investigation to identify the source of infection and causative pathogen [2]. Guidelines recommend evaluating two sets of BCs prior to antibiotic therapy to ensure appropriate early antibiotic treatment, which is known to reduce mortality [3-6].

BCs with a growth of skin colonization microorganisms, generally not considered clinically significant, are called contaminations [2,7,8]. Under certain circumstances, these bacteria can be the source of a true infection, particularly in immunosuppressed patients or in the presence of foreign bodies (prosthetic valve, pacemaker, joint implant), and often require additional BCs and antibiotics, which incur increased length and cost of hospitalization [2,7,9,10].

Standards of the American Society for Microbiology [7] and the Clinical and Laboratory Standards Institute [11] state that an acceptable BC contamination rate should not exceed 3% of all BCs. Still, reviews indicated that the rate of contamination exceeds 6% of BCs, including at academic hospitals [12].

Previous studies evaluating hospital wards identified associations of high work load, low staff/patient ratio, high rate of staff turnover, resuscitation procedures, and urgent need of antibiotic treatment in critical conditions with high BC contamination rate [1,2,13-15].

Many variables were found to affect BC contamination rates in hospital settings, including techniques for drawing BCs (hand hygiene, skin disinfection, aseptic technique) [1,3,8,10], phlebotomy team [3,9,12,14], ward where BCs were taken (high rates in emergency department [ED] due to a high work load) [2,13-17], time to bacterial growth (contaminants usually grow slowly and have an incubation period of > 72 hours), number of culture bottles [11,18], site from which the BCs are taken (peripheral vein versus central line) [8,9,16-18], and patient-related parameters such as age, high body mass index, smoking history, drug or alcohol use, presence of foreign bodies, co-morbidity (diabetes, immunosuppression), recurrent hospitalizations, or residence in a long-term care facility [6,7,19-21].

Microorganisms generally considered contaminants include: *Coagulase-negative Staphylococcus* (CoNS), *Streptococcus viridans*, *Propionibacterium acnes*, *Corynebacterium* spp., *Bacillus* spp., and *Clostridium* spp. [2,7,10,15], and are referred to as potential contaminant pathogens (PCPs).

In light of the clinical, institutional, and economic significance of BCs defined as contaminated, and the significant number of these specimens, we examined the scope of the phenomenon of contamination in our institution.

The objectives of this study were to define the epidemiology of BCs with PCPs between 2004 and 2013 at our medical center, to determine which were classified as true bacteremia (TrueB) versus contamination, and to identify risk factors associated with contamination. This study was conducted in order to develop a model to predict TrueB versus contamination, which could then assist medical teams to make decisions regarding further investigation or treatment.

The study was approved by the institutional ethics committee.

PATIENTS AND METHODS

We performed a retrospective case-control study at Emek Medical Center, a university-affiliated hospital with 550 beds serving approximately 500,000 residents in northeast Israel, during a 10 year period (2004–2013). For the past 15 years, a prospective survey has been conducted of all bacteremia events in real time. The infectious disease specialist performs a clinical assessment and classifies cultures as TrueB or contaminant. Instructions are then given in accordance with classification for further investigation and treatment of the patient. Criteria for decisions include clinical signs of infection (temperature > 38°C or < 35°C, pulse rate > 100 beats per minute, > 30 breaths per minute, systolic blood pressure below 90 mmHg), presence of an active focus of infection, white blood cell (WBC) count > 11,000 or < 4000/cells/μl, and presence of a foreign body.

BC data were obtained from the laboratory information system (AutoLims, AutoReports, and AutoGenerator; NeTLIMS, Ridgefield Park, NJ, USA) and records of hospitalized adult patients. BCs were collected from patients diagnosed as suspected bacteremia. All specimens were collected as routine practice. Venipuncture sites were disinfected with 0.5% chlorhexidine in 70% ethanol and allowed to dry for at least 15 seconds. BD BACTEC Plus Aerobic/F and BACTEC Plus Anaerobic/F (Becton, Dickinson and Co., Sparks, MD, USA) blood culture vials were inoculated with 5–10 ml of blood. After the vials were received in the laboratory, they were placed into the BACTEC FX BD instrument (Becton, Dickinson and Co.) and incubated until a sign for positive for growth was identified or a maximum of 6 days had passed. Signal positive bottles were handled according to standard laboratory procedures for identification of microorganisms and susceptibility testing. Positive BC broths were gram stained and inoculated on Trypticase soy agar plates supplemented with 5% sheep blood, chocolate agar, and sheep blood supplemented with CNA Columbia agar (Hy Laboratories, Rehovot, Israel) and incubated at 35°C in 5% CO2 for up to 48 hours. In parallel, a MacConkey agar plate (Hy Laboratories) was incubated in ambient air for the same time period and two anaerobic blood agar plates (one supplemented with gentamicin) were incubated in an anaerobic atmosphere. Bacterial identification was performed with the VITEK® 2 ID cards in a VITEK 2 instrument (BioMerieux, Marci-l'Etoile, France) instrument.

Cultures found to be positive for any of the six PCPs were included and categorized as either TrueB or contaminant. This distinction was possible based on the continual survey of bacteremia, as previously described.

To build a predictive model for contamination, BC data were compared for 92 BCs with TrueB and 196 randomly selected BCs with contaminants (1:2 ratio). The sample was representative of the contamination group in all aspects, including distribution of bacteria.

INCLUSION CRITERIA

Patients aged > 18 years who were hospitalized at Emek Medical Center between 2004 and 2013 with positive BCs with a growth of bacteria from the PCP group were included in the study.

EXCLUSION CRITERIA

Patients with a positive BC who were not hospitalized or who were transferred to a different hospital immediately after BCs were taken were excluded from the study. BCs with more than one bacteria (even if one was PCP) or an incomplete medical record at the time of data collection were also excluded.

Data including patient demographic and clinical characteristics, co-morbidities, and the presence of a foreign body, such as long-term urinary and vascular catheters, were obtained from medical records. We examined laboratory findings from the day of BC draw and the next 2 days. Information was collected on the use of chronic steroid therapy, chemotherapy, or other immunosuppressive therapy at the time of hospitalization or during the 3 months preceding BCs as well as previous hospitalizations (previous 3 months) and residence in a long-term care facility.

We recorded the number of BCs that tested positive for the same bacteria, the hospital division where the culture was taken (ED, intensive care unit, surgical division, or internal medicine division), and the site from which the BCs were drawn (peripheral vein or central line). In addition, outcome was recorded: cure, death during hospitalization, or death within 90 days of discharge.

STATISTICAL ANALYSIS

For categorical variables, proportions were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were analyzed with Student's *t*-test. A two-tailed *P* value < 0.05 was considered significant. Multivariate analysis was performed using logistic regression, with a significance level of 0.05. The statistical analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Of 74,014 BCs drawn, bacterial growth was identified in 9349 cultures (12.6%). Of these, PCP growth was identified in 3735 BCs (5.04% of all BCs and 39.9% of all positive BCs). A total of 3643 of PCP-positive BCs were defined as contamination and 92 as TrueB (97.5% and 2.5% of all PCPs, and 4.9% and 0.12% of all BCs, respectively). The average percentage of contamination showed a downward trend during the study, from 6.7% to 3.8% between 2004 and 2013 ($P < 0.0001$) [Figure 1]. This trend was observed in the ED, internal medicine division, and surgical division. Mean patient age was 68.7 ± 15.1 years (median 70.5) in the TrueB group, and 67.4 ± 18.6 years (median 73) in the contamination group (N.S.). Mean body mass index (BMI) was 26.9 ± 7.7 kg/m^2 (median 26) in the TrueB group and 27.8 ± 8 kg/m^2 (median 26.8) in contamination group (N.S.). The most common PCP bacterium was CoNS, which, together with *Corynebacterium* spp. and *Propionibacterium acnes* were mainly observed in the contamination group. *Bacillus* spp. only grew as a contaminant, yet *Clostridium* spp. only grew as TrueB and *Streptococcus viridans* was mainly seen in TrueB cases ($P < 0.0001$) [Table 1].

Time to positivity was 40:15 hours in TrueB isolates (n=92) vs. 50:15 hours in contamination isolates (n=173). Data were missing for 23.

In univariate analysis, risk factors for TrueB included: fever at the time of taking BCs and three co-morbidities: chronic anemia, chronic renal failure, and active malignant disease. Additional variables showing a trend toward association with TrueB episodes, but which did not reach statistical significance, included preserved cognitive state and hospitalizations during the 3 months preceding the hospitalization with bacteremia [Table 2].

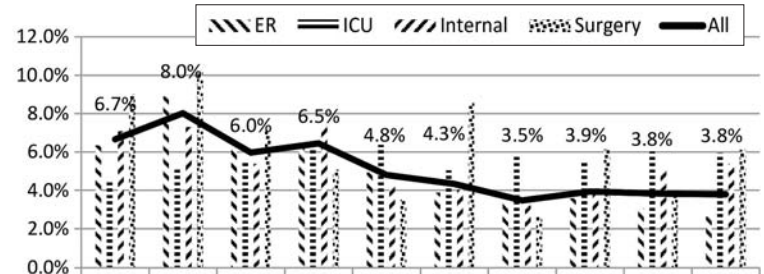
Mortality during hospitalization was higher in patients with TrueB but without statistical significance ($P = 0.0931$) [Table 2]. No association was found between the type of bacteria grown in culture and mortality in either of the study groups.

Continuous variables found to increase risk for TrueB included a high serum creatinine level ($P = 0.0009$), a high number of BC bottles ($P < 0.0001$), and a high number of positive BCs ($P < 0.0001$). None of the other variables we assessed were found to increase the risk for TrueB events [Table 2].

The presence of a foreign body or catheter was more common in the group of patients with contamination (35 with contamination vs. 16 with TrueB); however, foreign bodies were not found to be a significant risk factor for TrueB in univariate or multivariate analysis [Table 2].

The multivariate regression analysis found that elevated creatinine (odds ratio [OR] 1.4), each additional BC bottle (OR 4.5), each additional positive BC bottle (OR 3.9), and growth of *Streptococcus viridans* (OR 5.1) increased the risk for TrueB. In contrast, growth of CoNS reduced the risk for TrueB (OR 0.1), in other words, a ninefold increased risk for contamination [Table 3].

Figure 1. The percentage of contamination at Emek Medical Center between 2004 and 2013 (average and at each location separately)



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
ER	6.3%	8.9%	6.3%	6.2%	4.9%	3.9%	3.4%	3.6%	3.0%	2.6%
ICU	4.5%	5.1%	5.6%	6.6%	6.4%	5.0%	5.9%	5.5%	6.0%	6.0%
Internal	7.1%	7.3%	5.4%	7.3%	4.2%	4.0%	3.2%	4.1%	5.1%	5.4%
Surgery	9.0%	10.2%	7.1%	5.1%	3.5%	8.6%	2.7%	6.1%	3.7%	6.1%
All	6.7%	8.0%	6.0%	6.5%	4.8%	4.3%	3.5%	3.9%	3.8%	3.8%

ER = emergency department, ICU = intensive care unit

Table 1. Distribution of types of bacteria in the two arms: TrueB and contamination

Pathogen	Total n=288	Contamination n=196	TrueB n=92
Bacillus spp.	23	23 (100%)	0 (0%)
Clostridium spp.	18	0 (0%)	18 (100%)
CoNS	191	147 (76.9%)	44 (23.1%)
Streptococcus viridans	34	6 (17.6%)	28 (82.4%)
Others	22	20 (90.9%)	2 (9.1%)
		$P < 0.0001$ (for all pathogens)	

CoNS = *Coagulase-negative Staphylococcus*, Others = *Corynebacterium* spp., *Propionibacterium acnes*, TrueB = true bacteremia

DISCUSSION

This study assessed the incidence of BCs with six PCPs at Emek Medical Center. We found PCPs in 5.04% of all of the BCs and 39.9% of all positive BCs. The average percentage of contamination was 4.9% and showed a downward trend during the study, from 6.7% to 3.8% between 2004 and 2013 [Figure 1]. The accepted recommendation in the literature is for contaminants in < 3% of BCs [3,7]; however, reports range between 0.6% and 6% [3]. Factors affecting the percentage of contaminations include improper disinfection of skin, incorrect phlebotomy technique, inadequate proficiency for drawing BCs, and high work load [1]. The ED was identified with a particularly high rate of BC contamination; even so, we found a significant decrease in contamination rate in the ED (6.3% to 2.6%). A decrease was also documented in the internal medicine (7.1% to 5.4%) and surgical divisions (9.0% to 6.1%). These findings are within the range reported in literature, but still higher than the 3% recommended by the U.S. Centers for Disease

Table 2. Demographic, clinical, and laboratory characteristics of patients with TrueB versus those with contamination on univariate analysis

Clinical condition	Contamination n=196	TrueB n=92	*P* value
Gender, Male/Female	117 (59.7%)/79 (40.3%)	48 (52.2%)/44 (47.8%)	NS
Fever, No/Yes	135 (70.3%)/57 (29.7%)	15 (16.3%)/77 (83.7%)	0.0247
Smoking status, No/Yes	176 (89.8%)/16 (8.2%)	85 (92.4%)/7 (7.6%)	NS
Chronic renal failure, No/Yes	153 (78.1%)/43 (21.9%)	59 (64.1%)/33 (35.9%)	0.0124
Diabetes mellitus, No/Yes	116 (59.2%)/80 (40.8%)	48 (52.2%)/44 (47.8%)	NS
Chronic anemia, No/Yes	146 (74.5%)/50 (25.5%)	55 (59.8%)/37 (40.2%)	0.0113
Cirrhosis, No/Yes	192 (98%)/4 (2%)	89 (96.7%)/3 (3.3%)	NS
Normal cognitive function/dementia, No/Yes	159 (81.1%)/37 (18.9%)	82 (89.1%)/10 (10.9%)	0.0864
Normal body weight/morbid obesity (BMI ≥ 35)	142 (72.5%)/54 (27.5%)	69 (75.0%)/23 (25.0%)	NS
No steroid treatment/chronic steroid treatment	191 (97.4%)/5 (2.6%)	89 (96.7%)/3 (3.3%)	NS
Chemotherapy and immunosuppression therapy, No/Yes	185 (94.4%)/11 (5.6%)	85 (92.4%)/7 (7.6%)	NS
Malignancy in the past, No/Yes	176 (89.8%)/20 (10.2%)	78 (84.8%)/14 (15.2%)	NS
Current malignant disease, No/Yes	180 (91.8%)/16 (8.2%)	77 (83.7%)/15 (16.3%)	0.0377
Hematologic malignancy in the past, No/Yes	194 (99%)/2 (1%)	90 (97.8%)/2 (2.2%)	NS
Current hematologic malignancy, No/Yes	189 (96.4%)/7 (3.6%)	87 (94.6%)/5 (5.4%)	NS
Nursing home, No/Yes	171 (87.2%)/25 (12.8%)	82 (89.1%)/10 (10.9%)	NS
Hospital admissions in the last 3 months, No/Yes	131 (66.8%)/65 (33.2%)	52 (56.5%)/40 (43.5%)	0.0899
Mortality in hospital/90 day post-discharge	27 (13.8%)/28 (14.3%)	21 (22.8%)/8 (8.7%)	0.0931

BMI = body mass index, NS = not significant, TrueB = true bacteremia

Table 3. Variables found to be significant in the multivariate analysis

Significant variable in multivariable analysis	OR	95%CI	*P* value
Streptococcus viridans vs. other pathogens	5.1	1.35–19.506	0.0164
CoNS vs. other pathogens	0.1	0.034–0.347	0.0002
High creatinine level	1.4	1.073–1.895	0.0145
Number of bottles taken	4.5	2.58–8.134	< 0.0001
Number of bottles positive on culture	3.9	1.526–10.435	0.0048

95%CI = 95% confidence interval, CoNS = *Coagulase-negative Staphylococcus*, OR = odds ratio

Control and Prevention. Self et al. [2] succeeded in reducing contamination rates from 4.3% to 1.7% of all cultures drawn after transitioning to a sterile culture-taking technique and by using a phlebotomy team. Since our study was retrospective we could not determine which intervention caused improvement: introduction of a Vacutainer blood collection tube, initiation of skin disinfection using a sterile pad, or guidance and training of staff for correct procedures.

Bacillus spp. grew only as a contaminant, similar to that found by MacGregor and Beaty [22]. Furthermore, frequency of CoNS, *Corynebacterium* spp. and *Propionibacterium acnes* was particularly high in cases of contamination. In our study 76.9% of CoNS were classified as contaminations, similar to that reported in the literature [6,21]. Gander and colleagues [14] found that 20% of CoNS cases were defined as TrueB, which is consistent with our findings of 23.1%.

Multiple positive BC bottles indicated TrueB (75.2% with two positive sets, compared to 27.8% contamination in cases in which there was only one positive set) [3].

In addition to the number of positive BC bottles and the type of bacteria that grow, other parameters can help to distinguish contamination from TrueB, such as the time for a BC to become positive for growth (time to positivity) and the site from which the culture was taken (a peripheral vein or central line) [3]. Tonnesen and colleagues [23] found no elevated risk for contamination between taking BCs from a central line or a peripheral vein.

The recommendation to take two sets of BCs facilitates differentiation of contamination from TrueB [6]. For example, growth of CoNS in one, two, three, or four cultures is associated with an increase in risk for TrueB by 2%, 9%, 13%, and 27%, respectively [24].

Our results are consistent with the literature: each additional BC bottle drawn and each additional positive BC bottle increased risk of TrueB 4.5-fold and 3.9-fold, respectively.

In the case of a positive BC taken from a central catheter, it is unclear whether the finding represents TrueB, contamination, or colonization of the catheter [3,25]. In our study, nine events of contamination were recorded in patients with a central catheter versus no events of TrueB in those patients. Although the numerical difference was clear, it was unlikely to be statistically significant due to the small number of cases.

It is noteworthy that of 74,014 blood cultures taken over 10 years, 87% were negative and 13% were positive. Of cultures in which the six PCP bacteria included in the study grew, 3643 (97.5%) were defined as contamination and only 92 (2.5%) were defined as TrueB. This finding indicates that risk for a TrueB event is only 2.5% when bacteria from the PCP group were identified.

In some studies, higher mortality was reported for patients with TrueB than for those with contamination [6]. In our study, in-hospital mortality was elevated for patients with TrueB with PCPs, but without statistical significance.

A multivariate analysis of our data showed that elevated serum creatinine level, isolation of *Streptococcus viridans*, multiple BC bottles drawn, and multiple positive BC bottles significantly increased the risk for true positive blood culture. These parameters can assist the physicians in their clinical decision workup. In contrast, isolation of CoNS showed a ninefold increased risk for contamination.

The strengths of this study were prospective collection of bacteremia events over the study period, ensuring accuracy of categorization of events as either TrueB or contamination, and

a long follow-up period, which allowed decreased trends in contamination rate to be identified.

The shorter time to positivity in isolates of TrueB vs. contamination that we found correlates with the findings in the literature [25]. Yet, since our study is retrospective, some data were missing; hence, no major conclusions were drawn.

Limitations of our study include the retrospective collection of data from hospitalization records; inability to recover missing parameters such as alcohol consumption, drug use, blood sedimentation rate, and C-reactive protein; and the small number of patients with foreign bodies.

Presence of a foreign body was also identified in the literature as a factor that can increase the risk of TrueB from bacteria in the PCP group. In the current study, no statistically significant difference was found between patients with TrueB compared to contamination. The small number of foreign bodies may preclude differentiation among the groups.

CONCLUSIONS

At Emek Medical Center, the percentage of contamination in BCs decreased during the 10 year study period, but was still above the recommended level. Since we have no control of patient-related parameters, we should keep implementing an intensive and continuous program of team training and surveillance to maintain constant awareness of the risk of contaminating BCs.

Based on the model we have described, when bacteria from the PCP group grow on a culture, the medical team should be alerted to the presence of variables predicting TrueB, including high creatinine level, isolation of *Streptococcus viridans*, and high number of BCs, specifically positive BCs. In contrast, growth of CoNS, particularly one single culture that was found to be a strong predictor for contamination, should be addressed and treated accordingly. This model could help medical staff with diagnostic workup and therapeutic decision making.

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"If all men knew what others say of them, there would not be four friends in the world"

Blaise Pascal, (1623–1662), philosopher and mathematician