Spring 5-8-2021

Clinical Consequences and Determinants of False Positive Blood Cultures in Adult Hospitalized Patients

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CLINICAL CONSEQUENCES AND DETERMINANTS OF FALSE POSITIVE BLOOD CULTURES IN ADULT HOSPITALIZED PATIENTS

by

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A DISSERTATION

Presented to the Faculty of
the University of Nebraska Graduate College
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy

Epidemiology
Graduate Program

Under the Supervision of Professor Lorena Baccaglini

University of Nebraska Medical Center
Omaha, Nebraska

March, 2021

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ACKNOWLEDGEMENT

I would like to acknowledge and thank my committee members for their constant support and encouragement throughout the process of this dissertation.

I would also like to acknowledge the team working at Nebraska Medicine Clinical Microbiology Laboratory for their expertise and support.

Finally, a very special thanks goes to my husband and my family for their continued understanding and sacrifice.

ABSTRACT

Blood cultures are the gold standard for detecting blood stream infections. However, in the US, 0.6-6% of all blood cultures get contaminated leading to adverse clinical outcomes such as unnecessarily prolonged hospital stay and antibiotic therapy. Using electronic medical records, we explored the clinical outcomes and patient-specific risk factors of contaminated blood cultures in an era where rapid blood culture testing was being utilized to provide blood culture results within hours. Rapid blood culture test results can help clinicians in early and more effective management of patients with contaminated blood cultures, thus improving clinical outcomes. We also studied the impact of rapid blood culture testing on clinical outcomes by comparing clinical outcomes before and after the implementation of rapid testing.

Results of the first study relate that contaminated blood cultures continue to have a significant effect on duration of hospital stay and antibiotic therapy. The second study indicated that patients with chronic obstructive pulmonary disease, and ICU stay during hospitalization, were at higher odds of experiencing blood culture contamination. The last study showed that rapid blood culture testing did not affect clinical outcomes in patients with contaminated blood cultures.

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US	United States
PCR	Polymerase chain reaction
BCID	Blood culture identification panel
CoNS	Coagulase-negative staphylococci
CHG	Chlorohexidine gluconate
VGS	Viridians group streptococci
BMI	Body mass index
ICD	International classification of diseases
COPD	Chronic obstructive pulmonary disease
CKD	Chronic kidney disease
LC	Liver cirrhosis
DM	Diabetes mellitus
ICU	Intensive care unit
ED	Emergency department
LOS	Length of stay
AIC	Akaike information criterion
SAS	Statistical analysis system
IQR	Interquartile range
SD	Standard deviation
Abx DOT	Antibiotic days of therapy
AOR	Adjusted odds ratio
OR	Odds ratio
ESRD	End-stage renal disease
PAD	Peripheral artery disease
IV	Intravenous
ASP	Antimicrobial stewardship program

INTRODUCTION

Background

Blood cultures are the gold standard for diagnosing bloodstream infections. It is important to detect bloodstream infections because they can lead to several serious complications, such as sepsis. The microorganisms causing blood infections produce toxins that can damage organs. These pathogens interfere with the body's normal defense system and prevent the immune system from responding adequately. Blood cultures can assist clinicians in determining which specific organism or bacteria is causing the blood infection and how best to treat it.

In the US, 0.6-6% of all blood cultures are false positive due to contamination.[1,2] Contaminated (false positive) blood cultures can interfere with the clinician's judgement and have a negative impact on patient management by exposing patients to unnecessary and inappropriate antibiotics, unnecessarily extending hospital stay, and requiring additional testing and consultation. As blood cultures can take up to 72 hours to provide results, a confirmatory test would further result in continued use of inappropriate antibiotics and extended hospital stay. For better antimicrobial stewardship, quick and accurate identification of micro-organisms is critical for differentiating between true and false positives to avoid unnecessary hospital stay and antibiotic prescription. Several technological advancements, such as polymerase chain reaction (PCR), that shorten duration of detecting blood pathogens have also been explored.[3-5] Results from these new techniques can be presented to physician within hours for early and more effective therapy. However, the clinical impact of these new interventions has not been fully explored in patients with contaminated blood cultures.

It is imperative to understand the process of how blood cultures are performed and how the results are used to diagnose blood stream infections. Briefly, the process includes collection of a

blood specimen, processing of specimen in the laboratory to detect the pathogens, generation of results, interpretation of result by the clinician, and finally appropriate clinical management.

Blood Cultures

Specimen collection

Specimen collection starts with confirming the identity of the patient and making sure that it matches the labels and bracelet. The phlebotomist wears non-sterile bedside gloves while the sample collection process is explained to the patient. The caps from the culture bottles are removed and bottle tops are wiped with alcohol prep pads. This is followed by locating a vein for venipuncture and disinfecting the skin using alcoholic chlorhexidine gluconate (CHG) which is a sponge applicator containing rapid-acting, broad-spectrum antiseptic formulation of 2% chlorhexidine gluconate and 70% isopropyl alcohol. Using a back-and-forth friction scrub, the skin is sterilized for at least 20-30 seconds, and then another 20-30 secs are allowed for the skin to dry before blood is drawn. Aerobic bottle is filled before the anaerobic bottle, and the amount of blood collected per culture bottle is 10 cc. Two sets of blood cultures are collected from two separate venipuncture sites.

Laboratory testing

After the specimen has been collected, it is sent to the microbiology laboratory for blood culture testing (

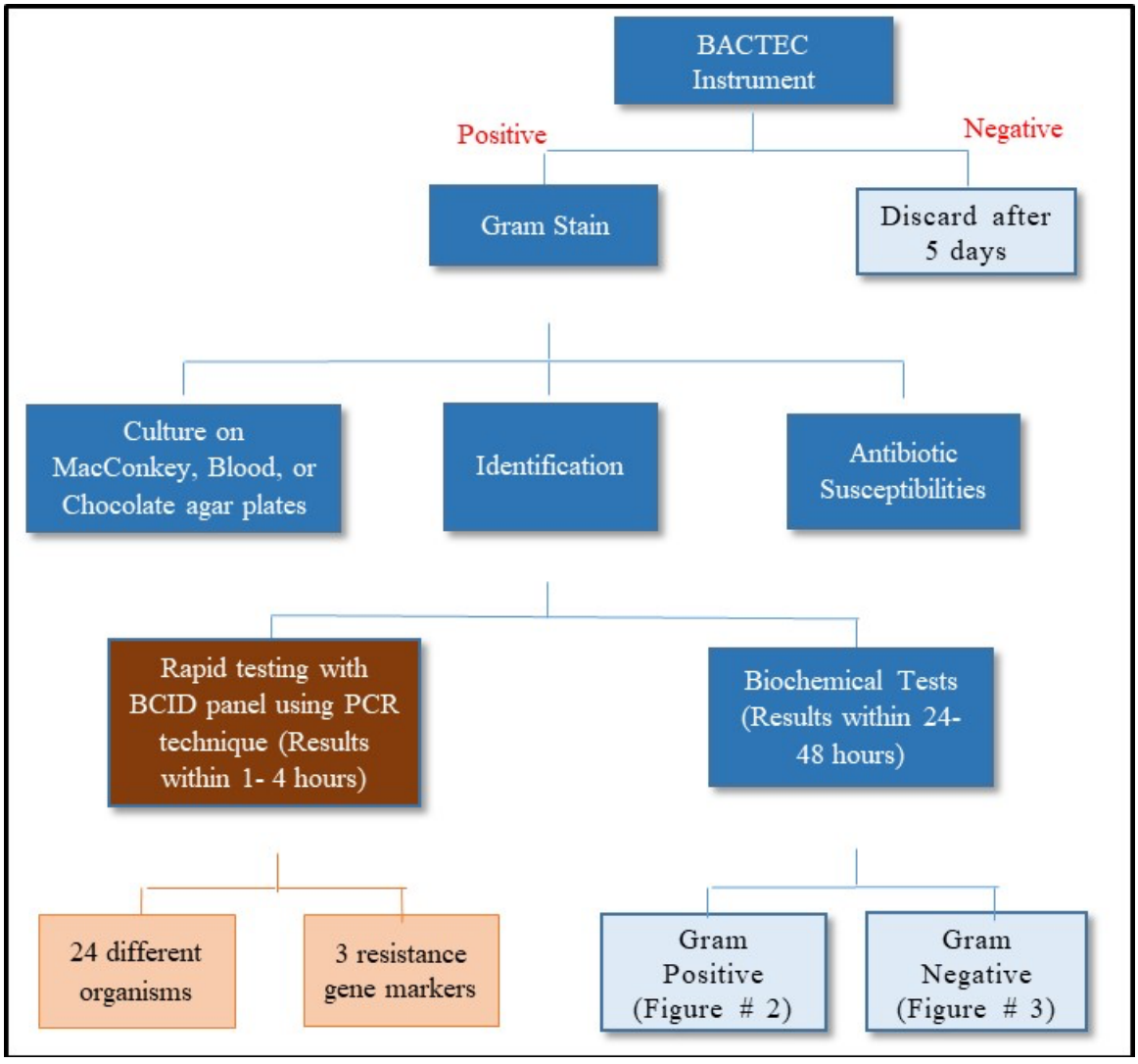
Figure *1*). The following paragraphs discuss the next steps as explained in the standard operating procedures manual adopted by the clinical laboratory at University of Nebraska Medical Center.[6] Once the bottles are received, they are incubated in the BACTEC 9240 instrument. When the instrument detects a bottle positive for an organism (usually within 1-2 days), it is removed from BACTEC 9240 instrument and the blood sample is Gram stained to provide preliminary results on whether bacteria is present and the general type, such as the shape and whether they are Gram-positive or Gram-negative. If the instrument does not detect any organism in a culture bottle for 5 days, the bottle is discarded.

The next three steps after Gram staining include identification of the organism using biochemical tests, sub-culturing of the blood sample, and running antibiotic susceptibilities. Biochemical tests help differentiate between various bacteria. Gram positive organisms are identified based on presence or absence of catalase and coagulase enzymes, and novobiocin, optochin and bacitracin sensitivities (Figure 2). Gram negative organisms are differentiated based on maltose utilization, lactose fermentation and oxidative activity (Figure 3). Simultaneously, sub-cultures are created on blood and chocolate agar plates, which are visually monitored by trained personnel every 24 hours, followed by determining susceptibility to various different antibiotics. The biochemical tests identify blood pathogens in 12-24 hours and the entire process after Gram staining takes 24-48 hours.

In recent years, a new and rapid approach has been adopted for identification of pathogens in blood. However, it does not replace sub-cultures and testing for antibiotic susceptibilities, which continue to be a part of blood culture testing process. After Gram-stain, instead of performing biochemical tests, the FilmArray Blood Culture Identification (BCID) Panel is used to identify the organism.[7] The FilmArray BCID pouch is a closed system disposable item that houses all the assays required to isolate, amplify and detect nucleic acid from multiple bloodstream pathogens from a single blood culture sample. It identifies 24 of the most common pathogens and organism

groups that cause bloodstream infections and three genetic markers that are known to confer antimicrobial resistance.

Figure 1: Flowchart for identification of blood culture organisms



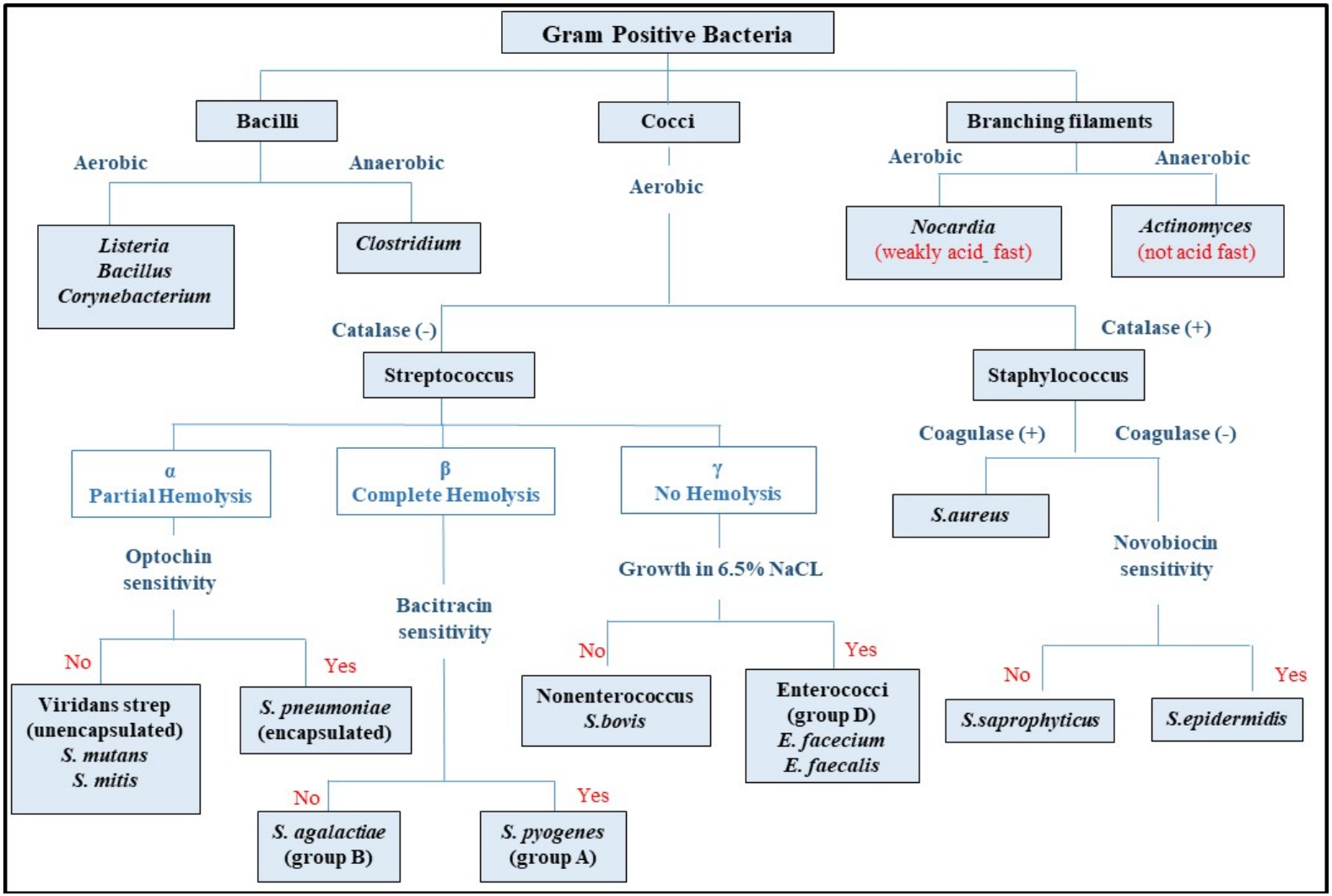
Reference: Adapted from 'Blood Cultures – Routine Aerobic and Anaerobic Blood Culture/Aerobic Blood Culture.' Laboratory Nebraska Medical Center (NMC). In: 2003 (Last edited: 2018).

The FilmArray Blood Culture Identification (BCID) Panel is a qualitative multiplexed nucleic acid-based in-vitro diagnostic test which uses polymerase chain reaction (PCR) technique to identify the pathogen. The test can be performed on blood culture bottles that are (1) flagged as positive by a continuously monitoring blood culture instrument and (2) positive by Gram stain examination. FilmArray BCID Panel results are usually available in one hour but can take 1-4 hours.

Selection of samples to be run on BCID panels is based on results of the Gram-staining. Samples are selected which are either Gram-positive cocci in pairs, chains or clusters, Gram-positive rods, Gram-negative bacilli or coccobacilli, Gram-negative cocci or diplococci, yeast, fungal elements with yeast present, or mixed Gram stain with two or more different kinds of organisms on Gram-staining. BCID panels are not used for any subsequent positive bottles within 5 days unless an organism with different Gram-stain characteristics is observed. They are also not used for acid-fast bacteria seen on Gram stain.

BCID panel is able to detect the following organisms: *enterococci, Listeria monocytogenes*, commonly encountered *staphylococci* (including specific differentiation of *Staphylococcus aureus)*, commonly encountered *streptococci* (with specific differentiation of *Streptococcus agalactiae*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*), *Acinetobacter baumannii*, commonly encountered *Enterobacteriaceae* (including specific differentiation of the *Enterobacter cloacae* complex, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus,* and *Serratia marcescens*), *Haemophilus influenzae*, *Neisseria meningitides* (encapsulated), *Pseudomonas aeruginosa*, *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, and *Candida tropicalis*.

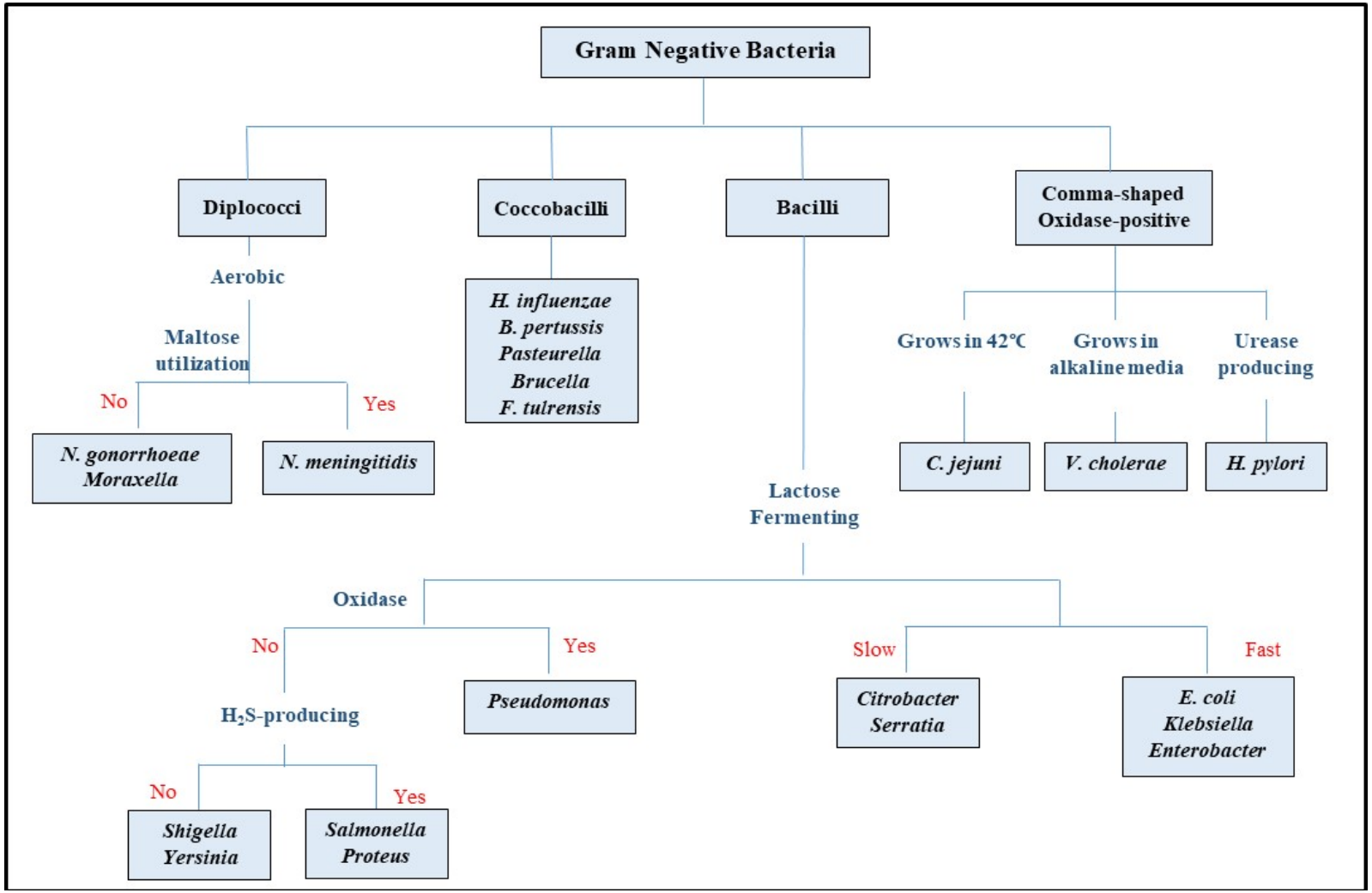
Figure 2: Flowchart for Gram positive bacteria



Reference: Adapted from 'Blood Cultures – Routine Aerobic and Anaerobic Blood Culture/Aerobic Blood Culture.' Laboratory Nebraska Medical Center (NMC). In: 2003 (Last edited: 2018).

The FilmArray BCID Panel also contains assays for the detection of genetic determinants of resistance to methicillin (*mecA*), vancomycin (*vanA* and *vanB*), and carbapenems (*bla*KPC) to aid in the identification of potentially antimicrobial resistant organisms in positive blood culture samples.

Figure 3: Flowchart for Gram negative bacteria



Reference: Adapted from 'Blood Cultures – Routine Aerobic and Anaerobic Blood Culture/Aerobic Blood Culture.' Laboratory Nebraska Medical Center (NMC). In: 2003 (Last edited: 2018).

Blood Culture Testing Algorithm

A single blood culture/phlebotomy event ideally results in 20 mL of blood draw which is split into two bottles (aerobic and anaerobic), referred to as a "set" of blood culture bottles (Figure 4). In most instances, when the first blood culture is ordered, it is ordered as a pair of two blood culture sets, meaning two separate phlebotomy events occur in close temporal relationship with each other (at the same time, usually one after another) to draw a total of 40 mL of blood (20 mL per venipuncture).

The reason why clinicians order 2 sets (or a pair of blood cultures) is to discern "true" bacteremia from contamination. If only one set of the pair of blood cultures/phlebotomy events is positive with an organism that is often found on the skin, it is regarded as a likely contaminant. If both blood cultures sets reveal skin flora, it is more likely to represent a true infection in the appropriate clinical setting (for example, presence of central vascular catheter, prosthetic device, etc) . In false-positive cultures due to contamination, the set positive for skin-residing organisms can be either set of the pair, and either (aerobic or anaerobic) or both bottles of the set (Table 1).

Figure 4: Blood culture testing algorithm

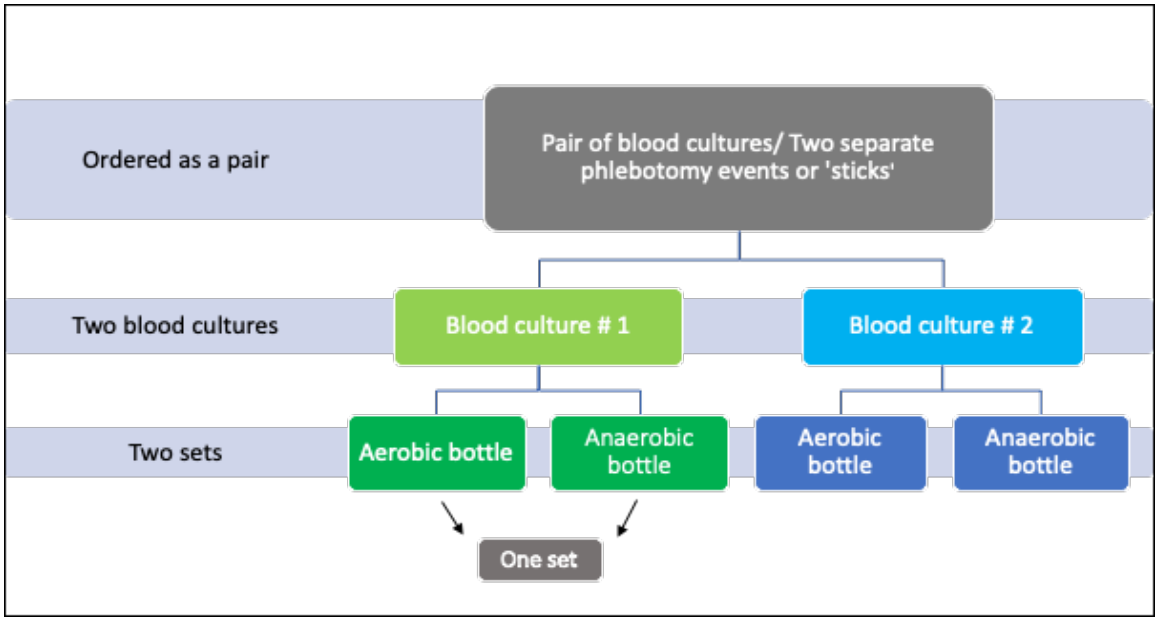


Table 1: Interpretation of blood culture results

No	PAIR OF BLOOD CULTURES				RESULT
	Set # 1		Set # 2		
	Aerobic	Anaerobic	Aerobic	Anaerobic	
1	+	+	+	+	**Positive**
2	+	+	+	-	
3	+	+	-	+	
4	+	-	+	+	
5	-	+	+	+	
6	+	-	+	-	
7	-	+	-	+	
8	-	+	+	-	
9	+	-	-	+	
10	-	-	-	-	**Negative**
11	+	+	-	-	**Contaminated**
12	-	-	+	+	
13	+	-	-	-	
14	-	+	-	-	
15	-	-	+	-	
16	-	-	-	+	

Blood Culture Contamination

A blood culture can get contaminated when skin-residing organisms get dislodged into the blood specimen. This can occur due to a breach in the anti-septic protocols during the process of blood draw, such as not wearing sterile gloves, inadequate disinfection of the site for blood draw, and inexperienced staff can lead to blood culture contamination.

Contaminated Blood Culture

A blood culture is considered contaminated if skin-residing organism(s) are identified in one of the two (or more) blood cultures sets. The skin-residing organisms are coagulase-negative staphylococci (CoNS), *Propionibacterium acnes*, *Micrococcus species*, viridians group streptococci, *Corynebacterium species*, and *Bacillus species*.

Contaminated Episode

For the research studies in the following chapters, an admission was categorized as a contaminated episode if any one set of the first pair of blood cultures was positive for contaminant organisms, and the second set of the pair was negative for any microorganisms. Additionally, any following blood culture(s) during the same admission had to be negative as well.

Prevention

There are several ways to limit blood culture contamination. A review of past literature shows that following blood specimen collection protocols can decrease blood culture contamination.

- Use of sterile gloves before initiating the process of blood specimen collection.
- Use of skin disinfectant to decontaminate skin before blood specimen collection.

- Following culture bottle disinfection protocols which include cleaning the opening of the blood culture bottle with disinfectant before transferring blood into the culture bottles.
- Utilization of blood specimen collection kits.
- Utilization of blood diversion devices to divert initial 1-2ml of blood close to skin surface (and potentially contaminated with skin residing organisms) before drawing blood for specimen collection.
- Having a trained team of phlebotomists dedicated to drawing blood specimens.
- Enforcing educational programs for medical staff employed to draw blood specimen when a trained phlebotomist is not available.

Blood collection guidelines indicate use of sterile gloves before performing a blood draw and it has shown to be effective in reducing contamination.[8] Several studies have demonstrated that using pre-packaged blood collection commercial kits reduces blood culture contamination from 4.3% to 1.7%.[9,10] However, recommendations for or against collection kits cannot be made based on a meta-analysis of only four studies.[11]

A handful of studies have shown promising results with the use of an initial specimen diversion device in reducing blood culture contamination rates by 30-50%.[12-14] However, the device remains to be tested in a large, randomized trial for further validation.

In another meta-analysis of six clinical trials, it was shown that alcoholic solutions are more effective in sterilizing skin for blood draw than non-alcoholic solutions, and 2% alcoholic CHG was the skin disinfectant of choice compared to other skin antiseptics.[15] A limitation of skin disinfectants is that they might not be able to reach 20% of the skin commensals that reside in sebaceous glands or are trapped between cells of superficial skin layers.[16] World Health Organization recommends antiseptic drying time of 30 secs.[17] However, another randomized trial demonstrated that choice of antiseptic did not matter if a trained phlebotomist was drawing blood.[18]

Equally important is disinfecting the opening of the blood culture bottles, and Centers of Disease Control and Prevention recommend cleaning them with 2% alcoholic CHG as well.[19] The medical staff not following recommended drying times for antiseptics to be fully effective is another limitation.

Studies conducted in the US have shown that phlebotomists collecting blood samples compared to other medical staff results in reduced contamination of blood cultures.[11,18] However, due to limited resources, it is not always possible to have phlebotomists available round the clock to draw blood culture specimens. Alternatively, educating nurses and other medical staff regarding contamination can be instituted to lower blood culture contamination.[20] A significant decline in contamination of blood cultures was demonstrated with implementing interventions that educate medical staff on devastating consequences of contamination, unnecessary workload and costs associated with contamination, proposing video demonstrations and offering simulation practices.[21-23]

Aims and Objectives

Only a handful of studies have explored the clinical consequences of contaminated blood cultures and PCR implementation.[4,5,24-27] Additionally, very little is known about patient-specific risk factors that might be contributing to blood culture contamination. There is a gap in evidence on patient-related risk factors and clinical impact of contamination and PCR implementation. The evidence could be used to educate clinicians and change their attitude towards more effective and appropriate management of patients with contaminated cultures, as well as to drive policy changes within health institutions to limit blood culture contamination.

To achieve our goals (Table 2), we used electronic medical records of patients who had blood cultures done at any time during an admission at Nebraska Medicine. We assessed the difference in length of stay and antibiotic use in patients with contaminated blood culture compared

to patients with negative blood cultures. We also determined patient-related risk factors that might have been making certain patients more susceptible to having a contaminated blood culture. Finally, looked at the clinical impact of PCR implementation on length of stay and antibiotic use in patients with contaminated blood cultures.

The first aim was to assess the clinical consequences of contaminated blood cultures in hospitalized patients at an institution using rapid identification system. We hypothesized that patients with contaminated blood cultures tended to be treated with antimicrobials unnecessarily and were admitted to the hospital for longer durations than needed.

The second aim was to determine patient-related factors that might be contributing to blood culture contamination. We hypothesized that patients with contaminated blood cultures had specific characteristics that made their cultures more likely to get contaminated.

The third aim was to investigate the impact of polymerase chain reaction on the clinical consequences of contaminated blood cultures. We compared hospital length of stay and days of antibiotic therapy in patients with contaminated blood cultures before and after the use of rapid PCR blood culture testing and hypothesized that implementation of a rapid identification system had an impact on clinical outcomes.

The overarching goal of the proposed work was to help identify the clinical impact of contaminated blood cultures and PCR on antibiotic use and length of stay, and to provide greater insight into strengthening antibiotic stewardship programs. Additionally, addressing aim 2 would provide information that could help create a profile of high-risk patients to ensure enhanced vigilance by healthcare workers (e.g., wearing sterile gloves, using antiseptic on skin) when drawing blood from these patients, as well as, considering the use of blood collection devices to reduce blood culture contamination.

Table 2: Summary of study design

	Aim I: To determine the impact of contaminated blood cultures on clinical outcomes of hospitalized patients	Aim II: To discover patient-related factors that contribute to contamination of blood cultures in hospitalized patients	Aim III: To assess the impact of PCR on clinical outcomes of contaminated blood cultures in hospitalized patients
Time period	06/01/14 – 12/31/16	06/01/14 – 12/31/16	Pre: 01/01/12 – 06/30/13 Post: 06/01/14 – 12/31/16
Data	Contaminated and negative blood culture episodes	Contaminated and negative blood culture episodes	Contaminated blood culture episodes only
Main Exposure(s)	Blood culture status	Risk factors	PCR status
Outcome(s)	- Days of hospital stay - Days of Abx therapy	Blood culture status	- Days of hospital stay - Days of Abx therapy

CHAPTER 1: CLINICAL CONSEQUENCES OF CONTAMINATED BLOOD CULTURES IN ADULT HOSPITALIZED PATIENTS AT AN INSTITUTION UTILIZING A RAPID BLOOD CULTURE IDENTIFICATION SYSTEM[1]

Abstract

Introduction: To assess the clinical impact of contaminated blood cultures in hospitalized patients during a period when rapid diagnostic testing using a FilmArray Blood Culture Identification (BCID) Panel was in use.

Methods: This was a retrospective cohort study conducted at a single academic medical center**.** Patients who had blood culture(s) performed during an admission between June 2014 and December 2016 were included in the study population. Length of hospital stay, and days of antibiotic therapy were assessed in relation to blood culture contamination using generalized linear models for univariable and multivariable analysis.

Results: Among 11,474 patients who had blood cultures performed, the adjusted mean length of hospital stay for patients with contaminated blood culture episodes (n= 464) was 12.3 days (95% CI: 11.4 to 13.2) as compared to 11.5 days (95% CI: 11.0 to 11.9) for patients (n=11,010) with negative blood culture episodes (p=0.032). The adjusted mean duration of antibiotic therapy for

[1] The material presented in this Chapter was previously published: Liaquat S, Baccaglini L, Haynatzki G, Medcalf SJ, Rupp ME. Clinical consequences of contaminated blood cultures in adult hospitalized patients at an institution utilizing a rapid blood-culture identification system. Infect Control Hosp Epidemiol. 2020 Dec 10:1-7. doi: 10.1017/ice.2020.1337. Epub ahead of print. PMID: 33298207.

patients with contaminated and negative blood culture episodes was 6.0 days (95% CI: 5.3 to 6.7) and 5.2 days (95% CI: 4.9 to 5.4), respectively (p=0.011).

Conclusion: Despite the use of molecular-based, rapid blood culture identification, contamination of blood cultures continues to result in prolonged hospital stay and unnecessary antibiotic therapy in hospitalized patients.

Introduction

Blood cultures are one of the most important methods of determining serious infection in hospitalized patients with suspected sepsis.[28] Traditionally, blood cultures take 3-5 days to provide results. A positive blood culture enables accurate diagnosis of an infection and allows for targeted antimicrobial therapy.[29] However, false positive blood cultures can arise if the blood specimen gets contaminated with organisms not present in the blood. Unfortunately, this is a frequently encountered clinical problem that results in extended hospital stay and unnecessary antimicrobial treatment.[24-26,30-32] Contaminated blood cultures are a challenge because, at times, it is difficult to differentiate true-positive from false-positive cultures.[28] Some of the most common contaminants, such as coagulase-negative staphylococci and viridians group streptococci, have increasingly been found as a cause of true bacteremia in patients with central venous catheters and prosthetic devices. If these organisms are considered contaminants and patients are left untreated, life-threatening conditions could develop.[33] However, unnecessary treatment is also problematic.[34,35] Inappropriate antibiotic use can result in antibiotic-related complications such as alteration of gut flora and increased risk of *Clostridioides difficile* infection, increase in colonization with multi-drug resistant organisms, as well as allergic reactions, side effects, toxicity, and increased cost.[36-39] Patients with contaminated blood cultures have an extended hospital stay which results in increased risk of developing hospital acquired infections and other conditions such as falls and pressure ulcers.[40,41]

The recent introduction of molecular-based, rapid diagnostic testing has greatly shortened the time needed to define pathogens in blood cultures. However, it is unclear whether this technologic advancement has influenced provider behavior when caring for patients with blood culture contamination. The objective of this study was to assess the impact of contaminated blood cultures on duration of hospital stay and antibiotic therapy among hospitalized patients at an institution where rapid blood culture identification was in use.

Methods

Study design

This was a retrospective cohort study involving secondary analysis of data extracted from hospital medical records. All patients who had blood culture(s) performed at any time during an admission during the study period were included in the study population.

Study Setting

Electronic medical records data from inpatients admitted between 1st June 2014 and 31st December 2016 at the University of Nebraska Medical Center were included in the study. Admissions that did not fit the study definitions of contaminated or negative blood culture episodes, and those of patients below 18 years of age were excluded. To maintain uniformity of data, only the first admission was included in the study sample if a patient had more than one eligible admission. Pregnant women, prisoners, decisionally-impaired persons, and other vulnerable persons were not excluded. Patients admitted to and discharged from the emergency department were not included; however, patients who were initially evaluated in the emergency department and subsequently admitted to the hospital were included. A molecular-based, rapid blood culture identification system (Biofire FilmArray Blood Culture Identification) was introduced at the study site in 2013.[7]

Study Definitions

Contaminated blood culture

A blood culture was considered contaminated if skin-residing organism(s) were identified in one of the two or more blood cultures sets. Skin-residing organisms were defined as coagulase-negative staphylococci (CoNS), *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*), *Micrococcus* species, viridians group streptococci (VGS), *Corynebacterium* species, and *Bacillus* species.

Contaminated episode

A patient admission was categorized as a contaminated episode if the first ordered blood culture was reported as contaminated (based on the aforementioned definition of contaminated blood culture) and any subsequent blood culture was negative during the same admission.

Negative episode

A patient admission was categorized as a negative episode if all blood cultures in that admission were negative for any microorganism.

Positive episode

If even one positive blood culture was reported during a hospital admission it was categorized as a positive episode.

Equivocal episode

Any combination of blood culture results during a patient admission that did not fall under contaminated, negative or positive episode were labelled as an equivocal episode.

Study size

The final analytical sample (n=11,474) consisted of 464 (4%) contaminated blood culture episodes and 11,010 (96%) negative blood culture episodes.

Variables

The primary independent variable was blood culture status. Admissions were categorized as contaminated or negative episodes based on blood culture status per study definitions. Socio-demographic variables included age, which was categorized based on quartiles (<50 years, 50-61 years, 62-73 years, >73 years), sex (male, female), race (White, Black, Other), body mass index (BMI; kg/m^2), smoking status (smoker/former smoker/current smoker, non-smoker), alcohol status (drinks alcohol/drinks alcohol daily/drinks alcohol occasionally, does not drink alcohol), marital status (married/partner/significant other, single/divorced), and medical insurance (insured, uninsured). Underlying diseases that have been shown to affect the association between blood culture contamination and increased hospitalization and antibiotic therapy were also included in the analysis. These co-morbidities were extracted from ICD-10 codes listed in the electronic medical record of each admission and included chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), liver cirrhosis (LC), and diabetes mellitus (DM). Additional variables included hospitalization-related factors such as stay in intensive care unit (ICU) during admission, admission from emergency department (ED), and location of blood drawn for blood culture (intravenous line, peripheral).

Outcomes

The primary outcome was length of hospital stay (in days) and the secondary outcome was duration of antibiotic therapy (in days). Patient admissions that included length of hospital stay and antibiotic therapy longer than 30 days were recorded as 30 days, assuming that treatment of patient with contaminated blood cultures, even if interpreted as a deep-seated infection, would not typically continue beyond 30 days. Data on antibiotic therapy included intravenous antibiotics and some of the highly bioavailable oral antibiotics that may appropriately be used to treat bacteremia. Only antibiotics prescribed within 72 hours of the blood culture draw were included, based on the assumption that antibiotics ordered in this timeframe were likely related to the blood culture event.

Antibiotic therapy was measured as the average maintenance dose of antibiotics required per day (i.e., daily defined dose).

A random subset of patient records was manually checked to ensure that electronic extraction of antibiotic administration and length of stay (LOS) data were correct.

Power calculation

Using an independent t-test with a two-sided α=0.05, a sample of 464 contaminated episodes and 11,010 negative episodes provided 80% power to detect a standardized difference of 0.132. G*Power software was used for power analysis.[42]

Statistical Analysis

For descriptive statistics, means and standard deviations were calculated for continuous variables, and counts and percentages for categorical variables. Chi-squared test and two-sample independent t-test were used to determine associations between main variables and covariates. Covariates found to be associated with both the primary dependent and independent variables based on alpha=0.1 in crude analyses were assessed further in the multivariable model. We used generalized linear models with a negative binomial distribution for univariable and multivariable analysis for both outcomes. A forward stepwise selection was utilized to create the final model, and the Akaike Information Criterion (AIC) value was used to assess model fit. All analyses were done in SAS (version 9.4 SAS Institute Inc., Cary, North Carolina).

Results

A total of 19,255 admissions that included blood culture testing were documented between June 1st, 2014 and December 31st, 2016 (Figure 5). After exclusions, 11,474 patients with 11,010 negative and 464 contaminated episodes were included in the final analytical sample. Socio-demographic characteristics were comparable between the two groups (Table 3). Approximately

half of the patients were male, and 80% were white. Among comorbidities, chronic obstructive pulmonary disease was present in 6% of patients with negative episodes, and in 10% of the contaminated group. Likewise, a slightly higher percentage (35.3%) of patients with contaminated blood culture episodes included ICU stay during the hospitalization, compared to 27.5% of patients with negative blood culture episodes. Some variables has missing data. Race, marital status and health insurance had less than 1% missing data, while body mass index, and location of blood draw had less than 5% missing data. Less than 10% of data was missing on smoking status, and 30% on alcohol status.

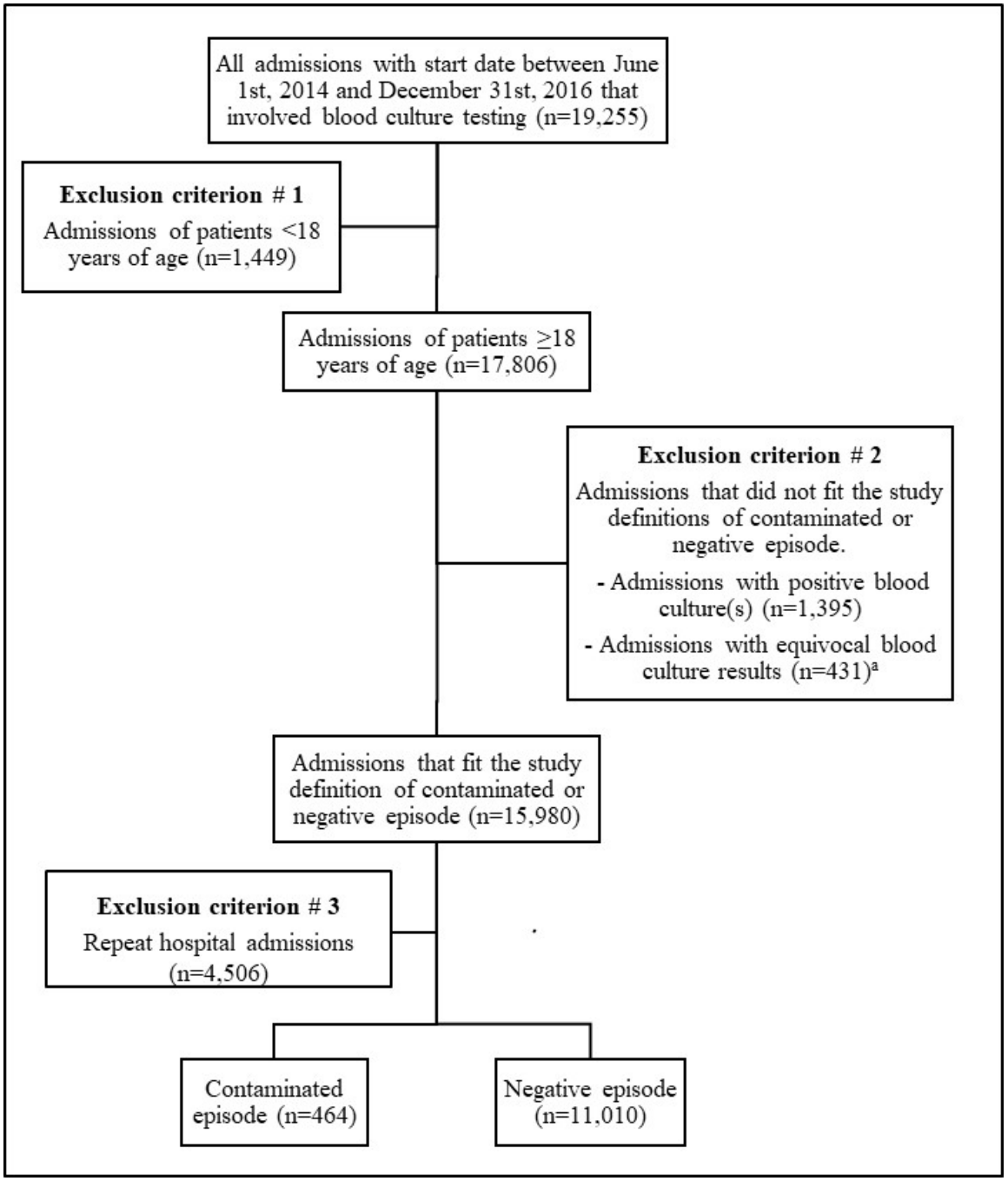
Duration of hospital stay

Secondary variables independently associated with duration of hospital stay on univariate analysis were included in multivariable analysis. After controlling for age, sex, race, BMI, marital status, health insurance status, location of blood draw, diabetes mellitus, admission from ED, and ICU stay, patients with contaminated episodes stayed in the hospital on average 0.8 days longer compared to those with negative episodes (p=0.032; Table 4).

Days of antibiotic therapy

Duration of antibiotic therapy for patients with contaminated blood culture episodes was also 0.8 days longer than antibiotic therapy for patients with negative blood culture episodes after controlling for age, sex, race, smoking status, BMI, location of blood draw, diabetes mellitus, admission from ED, and ICU stay (p =0.011; Table 5).

Figure 5: Flowchart of study participants



[a]Equivocal accounts for any combination of blood culture results that did not strictly fit into positive, negative, or contaminated category.

Table 3: Patients' clinical and socio-demographic characteristics by blood culture status

	Negative blood culture episode n = 11,010	**Contaminated blood culture episode n = 464**	**P-value[a]**
Variables	**No. (%)**	**No. (%)**	
Age			0.26
<50 years	2,916 (26.4)	108 (23.3)	
62-73 years	2,727 (24.8)	112 (24.1)	
50-61 years	2,659 (24.2)	128 (27.6)	
>73 years	2,708 (24.6)	116 (25.0)	
Sex			0.62
Male	5,730 (52.0)	236 (50.9)	
Female	5,280 (48.0)	228 (49.1)	
Race[b]			0.03
Black	1,106 (10.1)	61 (13.2)	
White	9,058 (82.7)	376 (81.6)	
Other[c]	791 (7.2)	24 (5.2)	
Alcohol status[d]			0.02
Drinks alcohol[e]	2,573 (32.8)	88 (26.5)	
Does not drink alcohol	5,280 (67.2)	244 (73.5)	
Smoking status[f]			0.04
Smoker[g]	5,941 (59.4)	273 (64.5)	
Non-smoker	4,058 (40.6)	150 (35.5)	
Marital status[b]			0.08
Single/Divorced/Widowed	5,890 (53.7)	267 (57.9)	
Married/Partner/Significant Other	5,071 (46.3)	194 (42.1)	
Health Insurance[b]			0.65
Yes	10,062 (92.1)	429 (92.7)	
No	866 (7.9)	34 (7.3)	
Body mass index (BMI)[h]			0.02[i]
Mean (SD), kg/m^2	29.5 (8.5)	30.6 (10.1)	
Location of blood draw[h]			0.67
Central or intravenous catheter	1,081 (10.2)	43 (9.6)	
Peripheral	9,529 (89.8)	406 (90.4)	

	Negative blood culture episode n = 11,010	Contaminated blood culture episode n = 464	p-value[a]
Variables	**No. (%)**	**No. (%)**	
Admission from ED			0.02
Yes	6,865 (62.4)	314 (67.7)	
No	4,145 (37.6)	150 (32.3)	
ICU stay			<0.001
Yes	3,030 (27.5)	164 (35.3)	
No	7,980 (72.5)	300 (64.7)	
Underlying Disease			
Chronic Obstructive Pulmonary Disease			<0.001
Yes	662 (6.0)	47 (10.1)	
No	10,348 (94.0)	417 (89.9)	
Chronic Kidney Disease			0.34[j]
Yes	9 (0.1)	1 (0.2)	
No	11,001 (99.9)	463 (99.8)	
Liver Cirrhosis			0.53[j]
Yes	146 (1.3)	4 (0.9)	
No	10,864 (98.7)	460 (99.1)	
Diabetes Mellitus			0.13
Yes	1,178 (10.7)	60 (12.9)	
No	9,832 (89.3)	404 (87.1)	

Note: ED=Emergency Department, ICU= Intensive Care Unit
[a]Chi-squared test
[b]Less than 1% missing data
[c]Other includes Asian, Hawaiian, Pacific Islander, Native American
[d]Less than 30% missing data
[e]Drinks alcohol includes drinks alcohol daily, drinks alcohol every other day, drinks alcohol occasionally
[f]Less than 10% missing data
[g]Smoker includes current smoker, former smoker, daily smoker
[h]Less than 5% missing data
[i]Two-sample independent T-test
[j]Fisher's exact test

Table 4: Final multivariable model for length of stay (LOS) after adjustment of co-variates.

Covariates	Adjusted mean LOS ratio (95% CI)[a]	p-value
Blood culture status		0.03
Contaminated	1.07 (1.01-1.14)	
Negative	1	
Age group		<0.001
>73	0.97 (0.93-1.00)	
62-73	1.05 (1.01-1.08)	
50 -61	1.03 (1.00-1.07)	
<50	1	
Sex		<0.001
Female	0.94 (0.92-0.96)	
Male	1	
Race		0.001
Other[b]	1.07 (1.00-1.14)	
White	0.97 (0.93-1.02)	
Black	1	
Body mass index (BMI)	1.00 (0.99-1.00)	<0.001
Health Insurance		0.03
Yes	1.06 (1.01-1.11)	
No	1	
Location of blood draw		<0.001
Central or intravenous catheter	1.30 (1.25-1.36)	
Peripheral	1	
Admission from ED		<0.001
Yes	0.69 (0.67-0.70)	
No	1	
ICU stay		<0.001
Yes	1.75 (1.70-1.80)	
No	1	
Diabetes mellitus		<0.001
Yes	1.08 (1.03-1.12)	
No	1	

Note: ED=Emergency Department, ICU= Intensive Care Unit

[a]Adjusted for age, sex, race, body mass index, health insurance, location of blood draw, admission from ED,
ICU stay, and presence of diabetes mellitus

[b]Other includes Asian, Hawaiian, Pacific Islander, Native American

Table 5: Final multivariable model for antibiotic days of therapy (Abx DOT) after adjustment of covariates

Covariates	Adjusted mean Abx DOT ratio (95% CI)[a]	p-value
Blood culture status		0.01
Contaminated	1.16 (1.03-1.29)	
Negative	1	
Age group		0.26
>73	0.95 (0.89-1.00)	
62-73	0.98 (0.92-1.04)	
50-61	1.00 (0.94-1.07)	
<50	1	
Sex		<0.001
Female	0.92 (0.88-0.96)	
Male	1	
Race		0.01
Other[b]	1.17 (1.05-1.31)	
White	1.08 (1.00-1.16)	
Black	1	
Location of blood draw		<0.001
Central or intravenous catheter	1.14 (1.06-1.23)	
Peripheral	1	
Admission from ED		0.002
Yes	0.92 (0.88-0.97)	
No	1	
ICU stay		<0.001
Yes	1.44 (1.37-1.51)	
No	1	
Body mass index (BMI)	1.00 (1.00-1.01)	<0.001
Smoking status		0.31
Smoker[c]	1.02 (0.98-1.07)	
Non-Smoker	1	

Note: ED=Emergency Department, ICU= Intensive Care Unit, Abx Dot = days of antibiotic therapy
[a]Adjusted for age, sex, race, basal metabolic index, location of blood draw, admission from ED, ICU stay and smoking status
[b]Other includes Asian, Hawaiian, Pacific Islander, Native American
[c]Smoker includes current smoker, former smoker, daily smoker

Table 6: Comparison of unadjusted mean number of days to mean number of days adjusted for covariates for each outcome

Clinical Outcomes	Unadjusted mean (95% CI)			Adjusted mean (95% CI)[a,b]		
	Negative episode	Contaminated episode	p-value	Negative episode	Contaminated episode	p-value
Days of hospital stay	8.9 (8.8-9.0)	9.5 (8.9-10.2)	0.04	11.5 (11.0-11.9)	12.3 (11.4-13.2)	0.03
Days of antibiotic therapy	4.5 (4.4-4.6)	5.1 (4.6-5.6)	0.03	5.2 (4.9-5.4)	6.0 (5.3-6.7)	0.01

[a]For days of hospital stay, mean was adjusted for age, sex, race, basal metabolic index, health insurance, location of blood draw, admission from ED, ICU stay, and presence of diabetes mellitus.
[b]For days of antibiotic therapy, mean was adjusted for age, sex, race, basal metabolic index, location of blood draw, admission from ED, ICU stay and smoking status.

Discussion

The study results indicate that despite the use of a molecular-based rapid blood culture identification system, contaminated blood cultures continue to have a significant effect on duration of hospital stay and antibiotic therapy. Patients with contaminated blood culture episodes were shown to have stayed an additional day (0.8 days) in the hospital compared to patients with negative blood culture episodes, even after adjusting for factors independently associated with duration of hospitalization (p=0.032). These results corroborate past studies in the pre-rapid blood culture identification era which observed an increased length of hospitalization in relation to contaminated blood cultures. In one study, median LOS was shown to increase by 3 days (IQR – 3 to 5) in patients with contaminated blood culture episodes compared to patients with negative blood cultures.[26] Meanwhile, in an another study, the mean increase in length was 2.35 days (p=0.008) for patients with contaminated blood culture episodes.[24] Thus, although we noted a decrease in the extended hospital stay documented in studies conducted prior to the widespread use of rapid blood culture identification systems, a significant increase in hospital stay associated with blood culture contamination remains. Similar to hospital stay, patients with contaminated blood culture episodes remained on antibiotic therapy for an additional day compared to patients with negative blood culture episodes (p=0.011). These results align with observations from a previous study showing that patients with contaminated blood culture episodes were maintained on antibiotic therapy for an additional 3 days.[26] In addition to longer hospital stay and use of antibiotic therapy (including vancomycin), other studies have shown that contaminated blood cultures also result in increased pharmacy cost and laboratory utilization.[31,43]

Our study is different from past studies in several ways. First, the rapid blood culture identification system was implemented at our institution in 2013, which shortens turnaround time for blood culture results by 24-48 hours, and allows for rapid differentiation between likely contaminants, such as coagulase-negative staphylococci, and likely pathogens, such as

Staphylococcus aureus as well as other targeted pathogens. Faster pathogen identification may allow clinicians to withhold, stop, or change antibiotics more quickly.

Additionally, to our knowledge, only one other study used multivariable analyses to control for confounders.[30] Univariate analysis that does not control for confounders can lead to over or under estimation of results. However, even though Bates *et al.* controlled for confounders, the authors used a 48-hour window to define a blood culture episode.[30] Subsequent positive blood cultures during the same hospitalization may have been missed, resulting in erroneous data. Our study definition of a contaminated episode only included admissions where the first blood culture was contaminated and any subsequent blood cultures were negative, thereby excluding the possibility of a true positive culture beyond the 48-hour initial culture window.

Results of our study might be a reflection of increasing awareness among clinicians about harms imposed by inappropriate use of antibiotics in patients with contaminated blood cultures, such as emergence of antibiotic resistance, unnecessarily extended hospital stay, and resultant increase in hospital acquired infections.[35,39] Our hospital has an antimicrobial stewardship program in place since 2004 that actively emphasizes the adverse effects resulting from inappropriate antimicrobial administration. Awareness of the above-mentioned factors might have contributed to reducing the gap between clinical outcomes of contaminated blood cultures and negative blood cultures that we observed compared to older studies. However, at the same time, our results provide sufficient evidence to support the claim that contaminated blood cultures continue to have an adverse effect on patient outcomes.

The current study had several limitations; some because of study design, and others because of the nature of the data that were used. First, it was not possible to track, measure, and account for all potential risk factors. For example, the increase in duration of hospital stay could have been due to other co-morbidities that we did not capture.[44,45] However, based on past literature we included four underlying diseases in the analysis that have been shown to affect the association

between contaminated blood cultures and duration of hospitalization. Additionally, another factor that has shown to play a role in blood culture contamination is mental well-being of the patient, due to difficulty in drawing blood from uncooperative patients.[30] For this study, a valid indicator of the mental well-being of the patient was not available. Individual physicians' management of patients with contaminated cultures can also influence a patient's hospital length of stay and duration of anti-microbial therapy, which we could not control for in this analysis. Finally, our retrospective cohort study was prone to information or misclassification bias because we were unable to fully ascertain the accuracy of the archived data in electronic medical records. However, we did perform manual review of a subset of records to check the accuracy of length of stay and antibiotic administration data, which demonstrated 100% concordance with the electronic data extraction.

We observed a significant difference in length of stay and antibiotic utilization associated with blood culture contamination. Although these findings are consistent with previous literature, the effect appears to be considerably smaller than observed by previous investigators and may reflect the influence of more rapid blood culture identification, or increased awareness of the ill effects of inappropriate antibiotic administration. Nonetheless, a significant adverse effect of blood culture contamination on clinical outcomes continues to exist despite diagnostic improvements. In this era of scarce medical resources, an extra day of hospitalization and an extra day of antibiotic administration is substantial and justifies additional efforts to prevent blood culture contamination.

CHAPTER 2: PATIENT-SPECIFIC FACTORS ASSOCIATED WITH BLOOD CULTURE CONTAMINATION

Abstract

Introduction: Contaminated blood cultures result in extended hospital stay and unnecessary antibiotic therapy. Patient-specific factors associated with blood culture contamination remain largely unexplored. Identifying patients at higher risk of blood culture contamination could alert healthcare providers to take extra precautionary measures to limit contamination in these patients, and thereby, prevent associated adverse outcomes. The objective of the study was to identify patient-related factors that contribute to blood culture contamination in hospitalized patients.

Methods: We conducted a secondary data analysis of a retrospective cohort study at a single institution. Participants included patients who had blood culture(s) performed during an admission between June 2014 and December 2016 (n=19,255). A total of 464 contaminated episodes, and 11,010 negative blood culture episodes were identified. Data were analyzed to evaluate risk factors for blood culture contamination using logistic regression.

Results: Chronic obstructive pulmonary disease (AOR:1.67, 95%:1.20-2.34) and ICU stay during an admission (AOR:1.41, 95% CI:1.14-1.74) were significantly associated with blood culture contamination. Similar results were seen on sub-group analyses of hospitalized patients admitted from the emergency department.

Conclusion: We identified patient-specific factors that increase the odds of false positive blood cultures. By introducing mitigation strategies to limit contamination in patients with these risk factors, we can potentially reduce the adverse clinical impact of blood culture contamination.

Introduction

In the US, 0.6-6% of all blood cultures are contaminated with skin-residing organisms resulting in increased hospital stay and unnecessary antibiotic therapy.[1,46-48] Blood culture contamination generally occurs prior to specimen processing in the laboratory during blood specimen collection and specimen handling.[49,50] It is during these steps that bacteria on skin fragments can dislodge into the specimen during venipuncture.[51] Using preventive measures during blood specimen collection and handling, such as antiseptic skin preparation, following appropriate venipuncture protocols, cleaning culture bottle tops, utilizing sterile gloves and blood culture collection kits, specimen diversion devices, double needle technique, and having a dedicated phlebotomist team have been found to decrease contamination of blood cultures.[9,26,52-55] Some studies have also shown that educating staff members on these preventative measures can help reduce blood culture contamination.[56]

In addition to specimen collection and handling, patient-specific factors such as age, body mass index, co-morbidities and patients' clinical status can also contribute to blood culture contamination. A study by Chang *et al.* showed that emergency department patients with contaminated blood cultures were more likely to be older (incidence risk ratio=1.02 per year), have end-stage renal disease (incidence risk ratio=2.05), and be in a critical condition (triage level I and II; incidence risk ratio=2.24) compared to patients with negative blood cultures.[57] In another study, mental status of the patient and the severity of underlying disease were found to be risk factors for contaminated culture in hospitalized patients.[30] The association between body weight (or body mass index; BMI), and blood culture contamination has not been studied in adults. However, a study of neonates showed that a weight less than 1,000 grams was associated with blood culture contamination.[58] To our knowledge, limited studies have systematically explored patient-related factors in hospitalized adult patients that might contribute to blood culture contamination.

Contaminated blood cultures can interfere with the clinician's judgement and have a negative impact on patient management by incurring treatment delays, exposing patients to unnecessary and inappropriate antibiotics, unnecessarily extending hospital stay and requiring additional testing and consultation.[25,30] The aim of this study was to determine patient-specific factors contributing to blood culture contamination in hospitalized patients. By defining these risk factors, a predictive scoring model could be devised to assist clinicians in identifying patients at higher risk for contamination and interpreting their blood culture results with caution to avoid treating them as true positives. Furthermore, additional preventive measures and resources can be focused on patients with these factors to decrease the risk of blood culture contamination and its clinical impact.

Methods

Study Design

This was a retrospective cohort study involving analyses of data stemming from patients with a hospital admission that included blood culture testing. All patients who had blood culture(s) performed at any time during an admission were included in the study population.

Study setting

Electronic medical records data from inpatients admitted between 1st June 2014 and 31st December 2016 at the University of Nebraska Medical Center were included in the study. Admissions that did not fit the study definitions of contaminated or negative blood culture episodes, and those of patients below 18 years of age were excluded. If a patient had more than one eligible admission, then only the first admission was included in the study sample. Patients discharged from the emergency department were excluded; however, patients who were initially treated in the emergency department and subsequently admitted to the hospital were included.

Study Definitions

Contaminated blood culture

A blood culture was considered contaminated if skin-residing organism(s) were identified in one of the two or more blood cultures sets. Skin-residing organisms were defined as coagulase-negative staphylococci (CoNS), *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*), *Micrococcus* species, viridians group streptococci (VGS), *Corynebacterium* species, and *Bacillus* species.

Contaminated episode

A patient admission was categorized as a contaminated episode if the first ordered blood culture was reported as contaminated (based on the aforementioned definition of contaminated blood culture) and any subsequent blood culture during that same admission was negative.

Negative episode

A patient admission was categorized as a negative episode if all blood cultures in that admission were negative for any organism.

Positive episode

If even one positive blood culture was reported during a hospital admission it was categorized as a positive episode.

Equivocal episode

Any combination of blood culture results during a patient admission that did not fall under contaminated, negative or positive episode were labelled as an equivocal episode.

Variables

Exposure variables included age, which was categorized based on quartiles (<50 years, 50-61 years, 62-73 years, >73 years), sex (male, female), race (white, black, other), BMI (kg/m^2), smoking status (smoker, non-smoker), alcohol status (drinks alcohol, does not drink alcohol), and medical insurance (insured, uninsured). Underlying diseases that have been shown to affect blood culture contamination were also included in the analysis. These co-morbidities were extracted from ICD-10 codes listed in the electronic medical record of each admission and included chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), liver cirrhosis (LC), and diabetes mellitus (DM). Additional variables included stay in intensive care unit (ICU) during admission, admission from emergency department, and anatomic location of blood drawn for first blood culture (central intravenous catheter or peripheral vein).

Outcome

The study outcome was blood culture episode categorized as contaminated or negative based on blood culture results obtained during the admission.

Power calculation

A sample of 11,010 negative blood culture episodes and 464 contaminated episodes provided 80% power to detect a standardized mean difference of 0.132. G*Power software was used for power analysis.[42]

Statistical Analysis

For descriptive statistics, means and standard deviations were calculated for continuous variables, and counts and percentages for categorical variables. Chi-squared tests and two-sample independent t-tests were used to determine associations between the outcome and the covariates. Covariates associated with the outcome variable in crude analyses at alpha=0.1 were included in a multivariable logistic regression model. Age and gender were maintained in the final model a-

priori. A forward stepwise selection at alpha 0.05 was utilized to create the final model, and the Akaike Information Criterion (AIC) value was used to assess model fit. Results were reported as crude odds ratios (OR) and adjusted odds ratios (AOR) with 95% confidence intervals. All analyses were done in SAS (version 9.4 SAS Institute Inc., Cary, North Carolina).

Results

We identified 19,255 admissions between June 1st, 2014 and December 31st, 2016. Variables such as race, marital status, health insurance and BMI had less than 5% missing data. Up to 10% of the data were missing for smoking status, and up to 30% for alcohol status. Complete data were available on all other variables.

After exclusions, the final analytical sample consisted of 11,474 patient admissions with 11,010 negative and 464 contaminated episodes. Overall, the two groups had comparable clinical and socio-demographic characteristics (Table 7). Nearly half of the patients in both groups were male, and 80% were white. 10% of patients in the contaminated group had chronic obstructive pulmonary disease, which was slightly more compared to 6% of patients with negative episodes. Likewise, a slightly higher percentage (35.3%) of patients with contaminated blood culture episodes included ICU stay at some point during the hospitalization, compared to 27.5 % of patients with negative blood culture episodes.

In the multivariable analysis (Table 8), the adjusted odds of blood contamination were higher for patients with an ICU stay versus no ICU stay during their hospitalization (AOR:1.41, 95% CI:1.14-1.74). Patients admitted from the ED had 1.20 higher adjusted odds of having their blood cultures contaminated than those not admitted from ED (AOR:1.20, 95% CI: 0.96-1.50). The adjusted odds of getting a false positive blood culture result in patients who had COPD was 1.67 (95% CI:1.20-2.34) higher compared to those who did not have COPD. Blacks had 1.35 higher adjusted odds of having a contaminated blood culture compared to whites (AOR: 1.32, 95%

CI:1.00-1.81). In our study, the adjusted odds of a contaminated blood culture result increased by 1.01 for every additional unit of BMI (AOR: 1.01, 95% CI:1.00-1.02).

A sub-group analysis of patients admitted to the hospital from ED showed similar results. The odds of contamination were higher in patients who were black, had COPD and unit change in BMI. Odds were also higher if the patients were admitted from the ED and the admission included ICU stay.

Table 7: Patients' clinical and socio-demographic characteristics by blood culture status

	Blood culture episode	
	Negative n = 11,010	**Contaminated n = 464**
Variables	**No. (%)**	**No. (%)**
Age		
<50 years	2,916 (26.4)	108 (23.3)
50-61 years	2,659 (24.2)	128 (27.6)
62-73 years	2,727 (24.8)	112 (24.1)
>73 years	2,708 (24.6)	116 (25.0)
Sex		
Male	5,730 (52.0)	236 (50.9)
Female	5,280 (48.0)	228 (49.1)
Race[a]		
Black	1,106 (10.1)	61 (13.2)
White	9,058 (82.7)	376 (81.6)
Other[b]	791 (7.2)	24 (5.2)
Body mass index (BMI)[c]		
Mean (SD)	29.5 (8.5)	30.6 (10.1)
Admission from ED		
Yes	6,865 (62.4)	314 (67.7)
No	4,145 (37.6)	150 (32.3)
ICU stay		
Yes	3,030 (27.5)	164 (35.3)
No	7,980 (72.5)	300 (64.7)
Health insurance[a]		
Yes	10,062 (92.1)	429 (92.7)
No	866 (7.9)	34 (7.3)
Location of blood draw[c]		
Central intravenous (IV) catheter	1,081 (10.2)	43 (9.6)
Peripheral vein	9,529 (89.8)	406 (90.4)

	Blood culture episode	
	Negative n = 11,010	**Contaminated n = 464**
Variables	**No. (%)**	**No. (%)**
Alcohol status[d]		
Drinks alcohol[e]	2,573 (32.8)	88 (26.5)
Does not drink alcohol	5,280 (67.2)	244 (73.5)
Smoking status[f]		
Smoker[g]	5,941 (59.4)	273 (64.5)
Non-smoker	4,058 (40.6)	150 (35.5)
Underlying disease		
Chronic obstructive pulmonary disease		
Yes	662 (6.0)	47 (10.1)
No	10,348 (94.0)	417 (89.9)
Chronic kidney disease		
Yes	9 (0.1)	1 (0.2)
No	11,001 (99.9)	463 (99.8)
Liver cirrhosis		
Yes	146 (1.3)	4 (0.9)
No	10,864 (98.7)	460 (99.1)
Diabetes mellitus		
Yes	1,178 (10.7)	60 (12.9)
No	9,832 (89.3)	404 (87.1)

Note: ED=Emergency Department, ICU= Intensive Care Unit
[a]Less than 1% missing data
[b]Other includes Asian, Hawaiian, Pacific Islander, Native American
[c]Less than 5% missing data
[d]Less than 30% missing data
[e]Drinks alcohol includes drinks alcohol daily, drinks alcohol every other day, drinks alcohol occasionally
[f]Less than 10% missing data
[g]Smoker includes current smoker, former smoker, daily smoker

Table 8: Crude and adjusted odds ratio for blood culture contamination

Variables	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Age group (years)		
<50	1	1
50-61	1.30 (1.00-1.69)	1.22 (0.92-1.61)
62-73	1.11 (0.85-1.45)	1.02 (0.76-1.37)
>73	1.16 (0.88-1.51)	1.00 (0.74-1.35)
Sex		
Male	1	1
Female	1.05 (0.87-1.26)	1.09 (0.89-1.34)
Race		
White	1	1
Black	1.33 (1.01-1.75)	1.35 (1.00-1.81)
Other[b]	0.73 (0.48-1.11)	0.83 (0.54-1.30)
ICU stay		
No	1	1
Yes	1.44 (1.18-1.75)	1.41 (1.14-1.74)
COPD		
No	1	1
Yes	1.76 (1.29-2.41)	1.67 (1.20-2.34)
Admission from ED		
No	1	1
Yes	1.26 (1.04-1.54)	1.20 (0.96-1.50)
Body mass index (BMI)	1.01 (1.00-1.03)	1.01 (1.00-1.02)
Smoking status		
No	1	1
Yes	1.24 (1.02-1.52)	1.18 (0.95-1.47)

Note: COPD= Chronic Obstructive Pulmonary Disease, ED= Emergency Department, ICU= Intensive Care Unit

[a]Adjusted for age, sex, race, body mass index, smoking status, presence of COPD, admission from ED, and ICU stay

[b]Others includes Asian, Hawaiian, Pacific Islander, Native American

Discussion

The results of our study showed that patients admitted from the emergency department were more likely to have contaminated blood cultures. This was echoed in the study by Chang *et al.* that looked at factors contributing to contamination of blood cultures, specifically in ED patients, based on the premise that patients in ED are more likely to have contaminated cultures.[57] Two studies found that patients in a critical condition were at higher risk of contaminated blood cultures, and our study reflected the same.[30,57] We used ICU stay during admission as a proxy for severity of clinical status and observed higher odds of blood contamination in patients with ICU stay. The higher odds of blood culture contamination in the ED or ICU could be in critically ill patients who often tend to be hypovolemic or hypotensive. This may lead to multiple needle sticks to draw blood from less prominent and fragile veins resulting in a contaminated blood culture.

We also saw a strong and direct association between chronic obstructive pulmonary disease and contamination of blood cultures (AOR=1.67, 95% CI=1.20-2.34). Chronic obstructive pulmonary disease (COPD) is strongly linked to Peripheral Artery Disease (PAD).[59] Patients with PAD have thin and weak peripheral veins which could result in multiple needle sticks to draw blood. As a result, patients with COPD might be prone to blood culture contamination. Additionally, COPD can result in higher frequency of visits to healthcare settings, as well as, frequent antibiotic treatments.[44,45] This can lead to an increased presence of microbiome on the skin making it more likely for bacteria to get dislodged into the blood culture sample and contaminate it.[60]

Chang *et al.* found old age and end-stage renal disease (ESRD) to be statistically significant risk factors of blood culture contamination.[57] We did not find a strong association between age and contaminated blood cultures. Additionally, we could not evaluate the association between ESRD

and blood culture contamination, since we did not have a sufficient number of participants with ESRD.

There are some limitations to the study. The current study was a retrospective review of electronic medical records and it was not feasible to verify the accuracy of archived data. Being a historical cohort, it was not possible to control for all possible confounders. Additionally, for patient admissions that included intensive care unit (ICU) stay, we were not able to ascertain if first blood culture was drawn during ICU stay, or at any other time during the hospitalization.

There is a gap in the current literature on patient-related factors contributing to contamination of blood cultures. Therefore, with this study, we have tried to fill that gap by determining patient specific factors that might put certain patients at higher risk of having contaminated blood cultures. Knowledge of these contributing factors can help hospitals identify these patients ahead of time and introduce additional measures to prevent contamination. Early identification of patients at greater risk of blood culture contamination can assist clinicians in better care of these patients by early recognition of blood culture contamination and avoidance of prolonged hospital stay and inappropriate antibiotic therapy. Furthermore, similar to predictive models to assist clinicians with the recognition of bacteremic patients,[61] with knowledge of specific patient factors associated with contamination, predictive equations can be formulated to identify patients with a higher likelihood of blood culture contamination

CHAPTER 3: RAPID BLOOD CULTURE IDENTIFICATION SYSTEM DOES NOT AFFECT CLINICAL OUTCOMES ASSOCIATED WITH BLOOD CULTURE CONTAMINATION

Abstract

Introduction: Contaminated blood cultures can result in extended hospital stay and duration of antibiotic therapy. Rapid blood culture testing can shorten hospital stay and duration of antimicrobial therapy by providing clinicians with results faster than conventional blood culture methods. The aim of this study is to determine the impact of rapid FilmArray Blood Culture Identification (BCID) Panel on clinical outcomes of contaminated blood cultures.

Methods: We conducted a retrospective cohort study involving secondary data analysis at a single institution. This was a pre-post study design where patients with contaminated blood cultures in the pre-PCR time period (n=305) were compared to patients with contaminated blood cultures during the post-PCR implementation time period (n=464). The primary exposure was rapid PCR blood culture testing status, and the main outcomes of the study were length of hospital stay and days of antibiotic therapy.

Results: Rapid blood culture identification system did not improve clinical outcomes in patients with contaminated blood cultures. We did not find a significant difference in adjusted mean length of hospital stay before (10.8 days, 95% CI: 9.8-11.9) and after (11.2 days, 95% CI: 10.2-12.3) the implementation of rapid PCR testing using BCID panel in patients with contaminated blood cultures (p=0.413). Likewise, adjusted mean days of antibiotic therapy between patients in pre-PCR group (5.1 days, 95% CI: 4.5-5.7) did not significantly differ from patients in post-PCR group (5.3 days, 95% CI: 4.8-5.9; p=0.543).

Conclusion: Use of rapid blood culture identification system did not affect clinical outcomes such as length of hospital stay and duration of antibiotic therapy in patients with contaminated blood cultures.

Introduction

Bloodstream infections are a leading cause of morbidity, mortality and increased healthcare costs.[62] Therefore, early recognition of the causative agent and appropriate antibiotic therapy are needed for adequate management of bloodstream infections.[62,63] However, 0.6-6% of all blood cultures in the United States are contaminated with skin-residing organisms.[1,2] Contamination of blood cultures often results in extended hospital stay and unnecessary use of broad spectrum antibiotics in patients with a suspected bloodstream infection until the causative organism has been identified.[64]

The conventional method of identifying the etiological organism in blood cultures and providing antimicrobial susceptibility information can take up to 48-72 hours.[65,66] In recent years, several new approaches have been explored for early identification of micro-organisms and detection of resistance genes in blood culture specimens which provide results to the clinicians within hours. Rapid comprehensive panel-based molecular assays using the polymerase chain reaction (PCR) technique such as the FilmArray Blood Culture Identification (BCID) Panel,[7] can detect many major bloodstream pathogens and selected antimicrobial resistance genes in positive blood cultures.[67-69] Since the clinicians receive PCR blood culture testing results within a few hours of a blood culture yielding microbial growth, there is some data to suggest that using rapid diagnostic testing can decrease length of hospital stay, duration of antibiotic therapy, as well as, the economic burden associated with bloodstream infections.[70,71]

However, there is very limited and conflicting evidence on the impact of PCR on clinical outcomes of false positive or contaminated blood cultures. Pardo and colleagues demonstrated that using PCR to detect blood pathogens lead to a statistically significant shorter duration of hospital stay (2.3 days) compared to the pre-PCR control group (2.9 days; p=0.008) in patients who were discharged within 6 days of a contaminated blood culture result. However, they reported that the duration of antibiotic therapy did not significantly differ between the two groups.[5] When comparing pre- and post-PCR time periods, MacVane et al. found the median length of hospital stay to be 8 days vs. 7 days (p=0.75) and antibiotic therapy with Vancomycin to be 1.3 vs. 1.7 days (p=0.28) in patients with contaminated blood cultures.[4] Another study by Cattoir et al. analyzing 154 episodes of contaminated blood cultures reported that 17% of those in PCR testing group were given unnecessary antibiotics compared to 10% patients in the conventional testing group (OR 1.77, 95% CI 0.62-5.12; p=0.237).[27]

There is insufficient and conflicting data available on the impact of rapid blood culture testing on clinical outcomes of patients with false positive blood cultures. Therefore, we aim to assess the impact of rapid blood culture testing on the length of hospital stay (LOS) and the duration of antibiotic therapy in patients with contaminated blood cultures.

Methods

Study setting

A retrospective cohort study involving secondary analysis of data extracted from hospital medical records at a single institution. The study population included all adult patients who had blood culture(s) collected during an admission. The FilmArray Blood Culture Identification (BCID) Panel using PCR technique was introduced at our institution in November 2013. Electronic medical records of patients with date of admission between 1st January 2012 and 30th June 2013

were included in pre-PCR group and patients with date of admission between 1st June 2014 and 31st December 2016 were included in the post-PCR group. Data were not available for July 2012 of the pre-PCR period.

Admissions of patients 18 years or above of age, and those that fit the study definition of contaminated blood culture episode, were included. Patients who were pregnant, prisoners, decisionally-impaired persons, and other vulnerable persons were also included. Participants who were discharged from the emergency department were not included; however, patients who were initially treated in the emergency department and subsequently admitted to the hospital, were included. Only the first admission was included in the study sample if a patient had more than one eligible admission during the study period.

Study definitions

Contaminated blood culture

A blood culture was considered contaminated if skin-residing organism(s) were identified in one of the two (or more) blood cultures sets. Skin-residing organisms include coagulase-negative staphylococci (CoNS), *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*), *Micrococcus* species, viridians group streptococci (VGS), *Corynebacterium* species, and *Bacillus* species.

Contaminated episode

A patient admission was categorized as a contaminated episode if the first ordered blood culture was reported as contaminated (based on the aforementioned definition of contaminated blood culture) and any subsequent blood culture was negative during the same admission.

Study size

The pre-PCR group with 305 contaminated blood culture episodes and post-PCR group with 464 contaminated blood culture episodes constituted the final analytical sample (n=769) of the study.

Variables

The primary independent variable was PCR status (pre, post) depending on whether PCR was used to detect pathogens in blood, or not. To assess the potential impact of socio-demographic variables on outcomes, certain variables were included in the analysis. These variables were age, categorized based on quartiles (<50 years, 50-61 years, 62-73 years, >73 years), sex (male, female), race (white, black, or other), body mass index (BMI; kg/m^2), smoking status (smoker, non-smoker), alcohol status (drinks alcohol, does not drink alcohol), marital status (single, married) and medical insurance (insured, uninsured). We also controlled for underlying diseases that have been shown to affect duration of hospitalization and antibiotic therapy in patients with contaminated blood cultures. These underlying diseases were extracted from ICD-10 codes listed in the electronic medical records of each patient admission and included chronic obstructive pulmonary disease (yes, no), chronic kidney disease (yes, no), liver cirrhosis (yes, no), diabetes mellitus (yes, no). Some hospitalization-related variables, such as stay in intensive care unit (ICU) during admission (yes, no), admission from emergency department (yes, no) were also included. Finally, to control for the impact of seasonal variation on study outcomes between the two time periods, we created a new variable reflecting the four seasons. Patients were assigned to this new variable based on date of admission and the effect of seasonality was tested against both outcomes during pre- and post-PCR time periods.

Outcomes

The study had two outcomes. The primary outcome was length of hospital stay (in days) and the secondary outcome was duration of antibiotic therapy (in days). Assuming that treatment

of patient with contaminated blood cultures would not typically continue beyond 30 days, both outcomes were censored at the 30-day mark. Antibiotic therapy included data on intravenous antibiotics and some of the highly bioavailable oral antibiotics that are sometimes used to treat bacteremia (e.g. fluoroquinolones) . Only antibiotics that were prescribed within 72 hours of the first blood culture draw were included, based on the assumption that antibiotics ordered within this timeframe would likely be related to the first blood culture event. Duration of antibiotic therapy was measured as the average maintenance dose of antibiotics prescribed per day (i.e., daily defined dose). To ensure the correctness of data on antibiotic administration and length of stay, a convenience subset of 50 patient admission records were checked manually.

Power calculation

An independent t-test with a two-sided α=0.05, a sample of 305 contaminated episodes in the pre-PCR time period, and 464 contaminated episodes in the post-PCR time period, provided 80% power to detect a standardized mean difference of 0.206. G*Power software was used for power analysis.[42]

Statistical analysis

For descriptive statistics, means and standard deviations were calculated for continuous variables, and counts and percentages for categorical variables. Chi-squared test and two-sample independent t-test were used to determine associations between main exposure variable and secondary exposure variables. Variables associated ($p<0.1$) with both the outcome variables in crude analyses were assessed further in the multivariable model. Generalized linear models with a negative binomial distribution were used for univariable and multivariable analysis of both outcomes. The final multivariable model was developed by adding secondary exposure variables in a forward stepwise selection process. We used Akaike Information Criterion (AIC) value to assess model fit.

A segmented regression analysis was performed to ascertain trends in outcomes before and after the introduction of the rapid blood culture ID system. Thus, we tested the primary exposure variable (PCR status), a time variable (in months) and a two-way interaction term between time and primary exposure variable against the outcome. If any significant associations were seen during segmented regression analysis (p-value < 0.05), the model would be used to create the final multivariable model by adding relevant covariates to it in a forward stepwise selection process. The model fit for the multivariable model would be based on the smallest AIC. Segmented regression analysis allowed for comparison of any difference in outcomes while controlling for the overall trend during the pre-PCR era that could carry over into the post-PCR era. The advantage of this analysis is that it allows and accounts for unintended consequences of interventions and policy changes that might have an impact on study outcomes. All analyses were done in SAS (version 9.4 SAS Institute Inc., Cary, North Carolina).

Results

A total of 26,303 admissions that included blood culture testing were identified between January 1st, 2012 and June 30th, 2013 (pre-PCR group; n=7,048) and between June 1st, 2014 and December 31st, 2016 (post-PCR group; n=19,255). After exclusions, a total of 769 patients with 305 contaminated episodes from the pre-PCR time period and 464 contaminated episodes from the post-PCR time period were included in the final analytical sample (Figure 6). Race, marital status and health insurance had some missing data (<1%). BMI had up to 5% missing data. Nearly 8% of data were missing information on patient's smoking status, and approximately 50% of the data were missing on patients' alcohol status.

A comparison of clinical and socio-demographic characteristics between the two groups has been presented (Table 9). Even though we were able to get data on underlying diseases relevant to the study outcomes, the numbers in each group were not sufficient for multivariable analysis.

Trend over time

The segmented regression analysis did not reveal an effect of time on the association between primary exposure (PCR status) and either study outcome i.e., length of hospital stay (Figure 7) and days of antibiotic therapy (Figure 8). The two-way interaction term between the time variable and primary exposure was not significant for both outcomes ($p \geq 0.05$), and therefore not included in the final multivariable models.

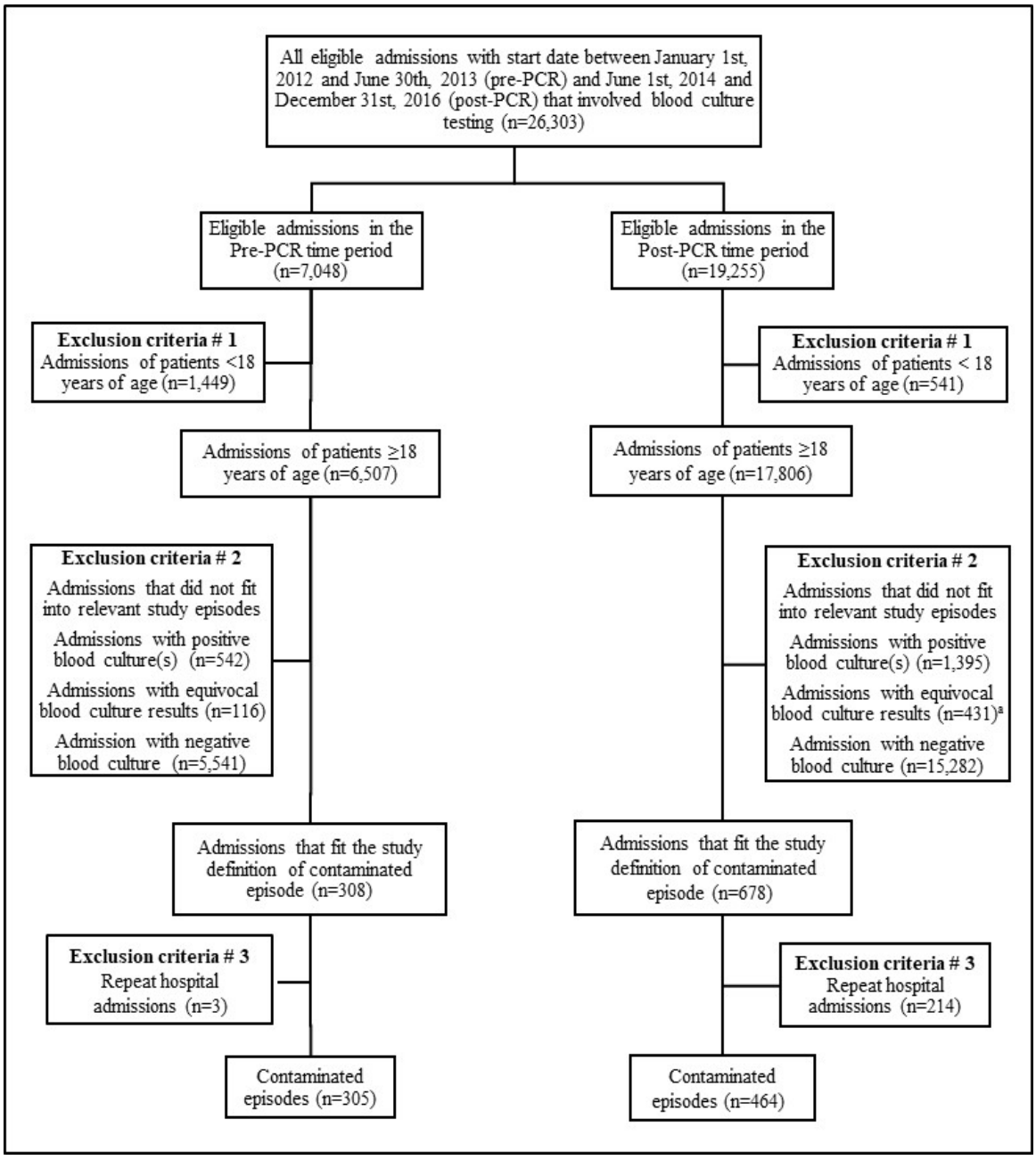
Duration of hospital stay

Rapid blood culture testing did not significantly change length of hospital stay (LOS) for patients with contaminated blood cultures (p=0.413; Table 10 and Table 12). The mean adjusted LOS for patients with contaminated blood cultures before the implementation of rapid identification system was 10.8 days (95% CI: 9.8-11.9) and for patients with contaminated cultures in the post-PCR implementation era was 11.2 days (95% CI: 10.2-12.3).

Days of antibiotic therapy

Similar to LOS, duration of antibiotic therapy for patients with contaminated blood culture before and after implementation of rapid PCR blood culture testing did not differ significantly (p=0.543; Table 11 and Table 12). In the pre-PCR period, patients were treated with antibiotics for an average of 5.1 days (95% CI: 4.5-5.7) and during the post-PCR period for 5.3 days (95% CI: 4.8-5.9), after controlling for ICU stay during hospitalization.

Figure 6: Flowchart of study participants



[a]Equivocal accounts for any combination of blood culture results that did not strictly fit into positive, negative, or contaminated category.

Figure 7: Length of Hospital Stay

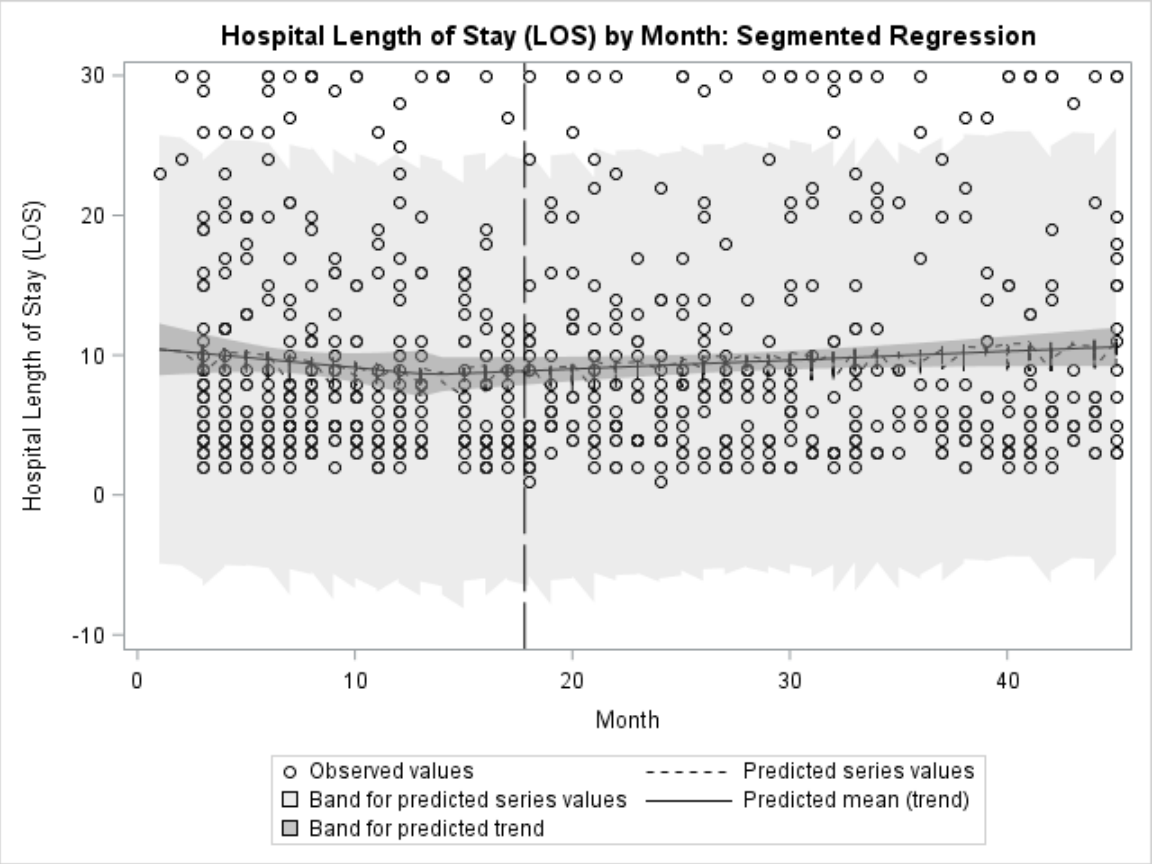


Figure 8: Days of Antibiotic Therapy

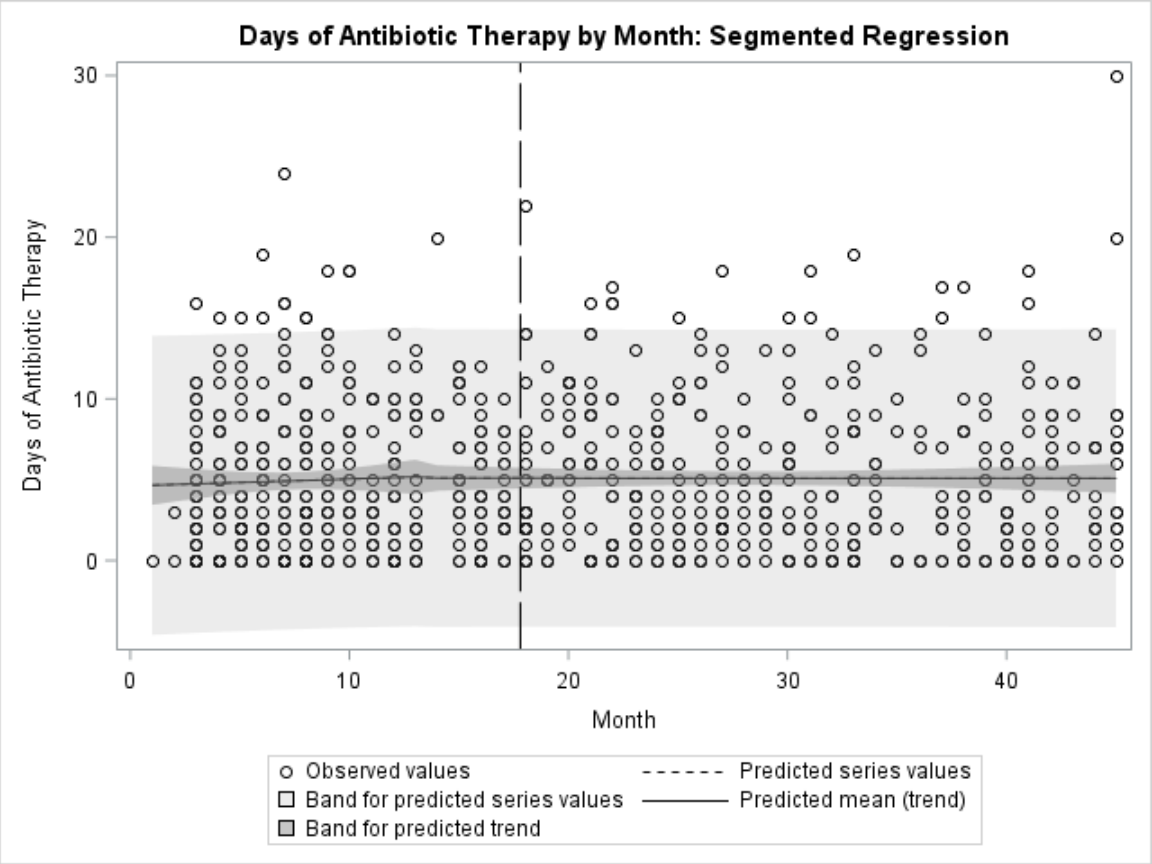


Table 9: Clinical and socio-demographic characteristics of study participants by PCR status

	Pre-PCR n = 305	**Post-PCR n = 464**	**p-value[a]**
Variables	**No. (%)**	**No. (%)**	
Age group (years)			0.751
<50 years	80 (26.2)	108 (23.3)	
50-61 years	76 (24.9)	128 (27.6)	
62-73 years	75 (24.6)	112 (24.1)	
>73 years	74 (24.3)	116 (25.0)	
Sex			0.586
Male	149 (48.9)	236 (50.9)	
Female	156 (51.1)	228 (49.1)	
Race[b]			0.658
Black	45 (14.8)	61 (13.2)	
White	240 (78.9)	376 (81.6)	
Other[c]	19 (6.3)	24 (5.2)	
Alcohol status[d]			0.543
Drinks alcohol[e]	49 (24.0)	88 (26.5)	
Does not drink alcohol	155 (76.0)	244 (73.5)	
Smoking status[f]			0.123
Smoker[g]	167 (58.8)	273 (64.5)	
Non-smoker	117 (41.2)	150 (35.5)	
Health insurance[b]			0.008
Yes	278 (97.2)	429 (92.7)	
No	8 (2.8)	34 (7.3)	
Body mass index (BMI)[h]			0.217[i]
Mean (SD)	29.7 (9.4)	30.6 (10.1)	
Admission from ED			0.208
Yes	193 (63.3)	314 (67.7)	
No	112 (36.7)	150 (32.3)	

	Pre-PCR n = 305	Post-PCR n = 464	p-value[a]
Variables	**No. (%)**	**No. (%)**	
ICU stay			0.697
Yes	112 (36.7)	164 (35.3)	
No	193 (63.3)	300 (64.7)	
Underlying disease			
Chronic obstructive pulmonary disease			<0.001[j]
Yes	2 (0.7)	47 (10.1)	
No	303 (99.3)	417 (89.9)	
Chronic kidney disease			1[j]
Yes	0 (0.0)	1 (0.2)	
No	305 (100.0)	463 (99.8)	
Liver cirrhosis			0.156[j]
Yes	0 (0.0)	4 (0.9)	
No	305 (100.0)	460 (99.1)	
Diabetes mellitus			0.460
Yes	34 (11.1)	60 (12.9)	
No	281 (88.9)	404 (87.1)	

Note: ED = Emergency Department, ICU = Intensive Care Unit, SD = Standard Deviation
[a]Chi-squared test
[b]Less than 1% missing data
[c]Other includes Asian, Hawaiin, Pacific Islander, Native American
[d]Less than 50% missing data
[e]Drinks alcohol includes drinks alcohol daily, drinks alcohol every other day, drinks alcohol occasionally
[f]Up to 8% missing data
[g]Smoker includes current smoker, former smoker, daily smoker
[h]Less than 5% missing data
[i]Two-sample independent T-test
[j]Fisher's exact test

Table 10: Final multivariable model for length of stay (LOS) after adjustment of co-variates

Covariates	Adjusted mean LOS ratio (95%CI)[a] (n=769)	p-value
PCR status		0.413
Pre-PCR	1	
Post-PCR	1.04 (0.95-1.14)	
Age group (years)		0.016
<50	1	
50-61	1.13 (0.99-1.29)	
62-73	1.18 (1.03-1.35)	
>73	0.98 (0.85-1.13)	
Race		0.065
Black	1	
White	0.99 (0.87-1.15)	
Other[b]	1.26 (1.00-1.59)	
Admission from ED		<0.001
No	1	
Yes	0.65 (0.59-0.72)	
ICU stay		<0.001
No	1	
Yes	1.83 (1.66-2.01)	

Note: ED = Emergency Department, ICU = Intensive Care Unit, CI = Confidence Interval
[a]Adjusted for age, race, admission from ED, ICU stay
[b]Other includes Asian, Hawaiian, Pacific Islander, Native American

Table 11: Final multivariable model for antibiotic days of therapy (Abx DOT) after adjustment of covariates

Covariates	Adjusted mean Abx DOT ratio (95% CI)[a] (n=769)	p-value
PCR status		0.543
Pre-PCR	1	
Post-PCR	1.05 (0.90-1.21)	
ICU stay		<0.001
No	1	
Yes	1.54 (1.32-1.79)	

Note: ED = Emergency Department, ICU = Intensive Care Unit, Abx DOT = Days of Antibiotic Therapy, CI = Confidence Interval

[a]Adjusted for ICU stay during admission

Table 12: Comparison of adjusted and unadjusted means for each outcome

Clinical Outcome	Unadjusted mean (95% CI) (n=769)			Adjusted mean (95% CI) [a,b] (n=769)		
	Pre-PCR (n=305)	Post-PCR (n=464)	p-value	Pre-PCR (n=305)	Post-PCR (n=464)	p-value
Days of hospital stay	9.5 (8.7-10.3)	9.5 (8.9-10.2)	0.888	10.8 (9.8-11.9)	11.2 (10.2-12.3)	0.413
Days of antibiotic therapy	4.9 (4.4-5.6)	5.1 (4.6-5.6)	0.680	5.1 (4.5-5.7)	5.3 (4.8-5.9)	0.543

[a]Mean LOS adjusted for age, race, admission from ED and ICU stay during hospitalization.
[b]Mean Abx days of therapy adjusted for ICU stay during hospitalization.

Discussion

Results of this study indicate that the use of a molecular-based rapid blood culture identification system did not affect clinical outcomes in patients with contaminated cultures. Similarly, past studies on contaminated blood culture have also largely shown an insignificant impact of PCR testing on clinical outcomes.[4,5,27]

There are few reasons that can be attributed to the lack of impact of PCR testing on clinical outcomes. First, clinicians continue to fear undertreating or missing real infections, and are thus quick to respond to any positive blood culture. For example, given the severity of rare, yet devastating consequences of an untreated infection with usual contaminants, such as coagulase-negative staphylococci, previous studies have shown that clinicians lean towards management of patients with contaminated blood cultures similar to true positive infections.[72,73] Secondly, many clinicians do not fully appreciate harms associated with blood culture contamination. For example, prolonged hospital stay associated with blood culture contamination can lead to hospital acquired infections, and unnecessary antimicrobial therapy that can result in antibiotic complications, such as the rise of anti-microbial resistance and *Clostridium difficile* infections.[74,75] These unwanted consequences of false positive cultures can lead to increased healthcare costs and financial burden on not only for the healthcare system, but also the patient. [76] Therefore, there is a need for increased awareness and education among clinicians regarding the negative and unnecessary impact of contaminated blood cultures.

To be most effective, it appears that rapid BCID systems should be coupled with an anti-microbial stewardship program (ASP) that can assist clinicians with interpretation and appropriate clinical response. Past studies have shown that a robust ASP, that monitors patient management and provides feedback in real-time, utilized in combination with rapid PCR testing significantly

reduced unwanted clinical consequences in patients with true bloodstream infections.[3,4,77] In fact, the influence of a strong ASP on patient outcomes is so critical that even conventional blood culture methods benefit from it.[77] This further highlights the relevance of using rapid blood culture identification system in combination with a vigorous ASP for improved clinical outcomes, specifically in patients with contaminated blood cultures.

A strength of our study was the larger sample size of patients with contaminated blood cultures in both pre-PCR and post-PCR groups than previous studies, thus allowing for greater precision around the estimates. There were also a few limitations in our study, such as potential information and misclassification bias which are inherent to retrospective study. Additionally, we did not have sufficient data to control for some underlying diseases, which might have resulted in confounding bias. One additional confounder that we were unable to control were clinicians, as each healthcare provider may manage patients with contaminated cultures differently. Finally, even though an antimicrobial stewardship program was in place to counteract the excessive use of antibiotics, we could not control for any potential effects of antimicrobial stewardship program on antibiotic prescription, and therefore on days on antibiotic therapy.

The rapid PCR technique can identify blood pathogens earlier than traditional blood culture methods. However, to see the clinical impact of the rapid PCR technique, there is a need to concurrently invest in continued and increased awareness and education among clinicians regarding the negative and unnecessary impact of contaminated blood cultures by further strengthening of the anti-microbial stewardship programs.

DISCUSSION & CONCLUSION

Summary of Current Research

This dissertation explored the determinants and clinical consequences of contaminated blood cultures in hospitalized patients. To answer the study aims we used a database extracted from electronic medical records between 2012 and 2016.

In Chapter 1 of the dissertation, we compared clinical outcomes in patients with contaminated blood cultures to those with negative blood cultures. The study was uniquely different from past studies as this study was conducted after implementation of a PCR based rapid blood pathogen identification system at our institution. Implementation of PCR based rapid blood pathogen identification was hypothesized to reduce hospital stay and antibiotic therapy due to blood culture contamination, however, we observed continued increase in hospital length of stay and antibiotic therapy among patients with contaminated blood cultures, similar to what has been observed in published studies conducted prior to PCR introduction.

In Chapter 2 of the dissertation, we focused on patient-specific risk factors that might contribute to blood culture contamination. We observed that patients with COPD and ICU stay during an admission had higher odds of blood culture contamination, compared to patients with negative blood culture results. These results were similar to past studies, where severity of patient condition was the strongest indicator of getting blood cultures contaminated with skin-residing organisms.

In Chapter 3, we explored the impact of rapid PCR blood culture testing on clinical outcomes of patients with contaminated blood cultures by comparing hospital length of stay and duration of antibiotic therapy before and after the implementation of rapid PCR testing using a pre-

post study design. Despite blood culture results being available to healthcare providers faster than conventional blood culture techniques, we did not find a clinically or statistically relevant difference between the two groups. These results were similar to previous studies which were also unable to observe difference in clinical outcomes after introduction of PCR in patients with contaminated blood cultures.

Implications of Current Research

In Chapter 1, our results indicate that despite the use of molecular-based, rapid blood culture identification, contamination of blood cultures still leads to prolonged hospital stay and unnecessary antibiotic therapy in hospitalized patients when compared to those with negative blood cultures. Although, the difference in outcomes appears to be considerably smaller than previous studies, possibly due to rapid turnaround time of culture results, or increased awareness of the unwanted effect of inappropriate antibiotic therapy, it remains significant. In an environment of scarce medical resources and ballooning costs, an additional day of hospitalization and antibiotic administration is considered substantial and warrants continued efforts to prevent blood culture contamination. Results from this study might inform healthcare professionals and anti-microbial stewards regarding unnecessary antibiotic use in patients with contaminated blood cultures. Furthermore, this information can be used to strengthen existing antimicrobial stewardship programs, in addition to implementing new policies, and introducing advanced blood culture testing technologies to reduce contamination.

In Chapter 2, we identified patient-specific risk factors that increase the odds of contaminated blood cultures. Knowledge of these contributing factors, and early identification of patients at higher odds of blood culture contamination, can facilitate hospitals in flagging these patients ahead of time to introduce additional measures to limit contamination. Secondly, similar to predictive models assisting clinicians in the recognition of bacteremic patients,[61] knowledge of

specific patient factors associated with contamination can aid in formulating predictive equations to identify patients with blood culture contamination. These innovations can inform and alert clinicians to possible contamination and route them to adequate management of these patients, thus avoiding prolonged hospital stay and unnecessary use of antibiotics.

In Chapter 3, we explored the impact of a rapid PCR based BCID panel on clinical outcomes before and after implementation. In our study, the utilization of the BCID panel did not significantly change the clinical outcomes in patients with contaminated blood cultures compared to pre-implementation era at our institution. Several studies have shown that a robust anti-microbial stewardship program (ASP) that provides feedback in real-time, coupled with rapid PCR testing, has shown to significantly reduce unwanted clinical consequences of contaminated blood cultures. Additionally, there is a need for increasing awareness and education among clinicians regarding the negative and unnecessary impact of contaminated blood cultures. In summary, further strengthening of current systems, including clinician awareness and robust anti-microbial stewardship program, are needed to be able to truly capitalize on the benefits of rapid blood culture testing.

Limitations and Future Direction

In addition to filling gaps in literature, this dissertation tried to build on past literature by improving study design, applying advanced statistical methods, and using larger sample sizes. However, our studies had some limitations. Based on these limitations and the implications of this dissertation, there still remain some outstanding questions.

One of the limitations of our study in Chapter 1 was that we could not control for outcomes by individual doctors, or their specialty, since clinicians working in various specialties and sub-specialties might differ in their approach to managing patients with contaminated cultures. Additionally, we were able to control for only four underlying diseases. We also did not have

information on comorbidity index or a severity index reflecting patient condition. Future studies controlling for confounding effect of attending physician, co-morbidities and severity of patient could further help determine true impact of contaminated blood cultures.

In Chapter 2, we studied patient-specific risk factors of blood culture contamination. This is an area of research that remains vastly unexplored. Since contamination is known to occur during blood culture specimen collection, anti-septic protocols during blood specimen collection, and education of staff involved in the process of drawing blood, has remained the focus of research. Despite our efforts to fill a research gap, we did not have all patient specific variables that might have contributed to blood culture contamination. For example, we could not control for altered mental state of the patient. If a patient is aggressive or agitated due to altered mental state when blood is being drawn for culture, it can lead to a breach in antiseptic protocol and contamination of the blood sample. Secondly, we did not have information on patients with skin diseases. Since blood contaminants are commonly skin commensals, if a patient has any skin disease, the organisms might get dislodged into the blood culture specimen and contaminate it. Therefore, further research is needed to control for the missing pieces as indicated above. Additionally, our sub-analysis on ED patients was restricted to hospitalized patients. Future research could focus on using a study population that is representative of all ED patients with contaminated blood culture results, irrespective of hospitalization status.

The Chapter 3 study was limited by several factors. Even though results were being provided sooner through rapid PCR based BCID panel, there is not sufficient data available in the electronic medical records to explore some factors that might be playing a role. Similar to our study in chapter 1, being able to account for individual clinicians, or clinicians in varying sub-specialties, who manage patients with contaminated blood cultures differently might provide some insight into the reason behind the non-significant results of the study. Additionally, even though an antimicrobial stewardship program (ASP) was in place to counteract the excessive use of

antibiotics, no information was available to control for the effects of antimicrobial stewardship program on antibiotic therapy and hospital stay. We propose a clinical trial in the future, where one arm of the cohort includes rapid PCR-based BCID panel along with current ASP practices, and the other with a an improved and interactive ASP combined with rapid PCR-based BCID panel, to gauge the full impact of rapid blood culture testing in patients with contaminated blood cultures.

Overall, our studies were restricted by the nature of retrospective design. Even though we manually cross-checked some of the data with electronic medical records, it was not feasible to check accuracy of every single data element due to large sample sizes. This makes our studies prone to information bias. Additionally, for the same reason, we could only demonstrate association, and not causation. Lastly, it was not possible to measure and control for all possible confounders due to a limited dataset. Conducting prospective studies, and even clinical trials where possible, should be considered for future research to further explore these areas.

Conclusion

With continued strengthening of the antimicrobial stewardship programs, knowledge of patient-specific factors, and increased education and awareness among healthcare providers regarding clinical consequences and implications of contaminated blood cultures, we hope the results of this dissertation can provide valuable insight to clinicians and hospital staff in reducing the burden of blood culture contamination.

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APPENDIX

Appendix A: Data Dictionary

DATA DICTIONARY			
Variable name	**Type**	**Variable name**	**Description**
Patient ID	categorical	pat_mrn_id	ID number
Admission ID	categorical	pat_enc_can_id	Encounter ID number
Blood culture status	categorical	status	Contaminated, All Negative
Length of hospital stay	counts	pat_los	Number of days in hospital
Antibiotic days of therapy	counts	pat_abx	Days of antibiotic therapy. Antibiotics started within 3 days of blood culture specimen taken date. Will be calculated as daily defined dose.
Age	categorical	agegroup	Based on quartiles: <50, 50-61, 62-73, >73
Sex	categorical	sex	Male, Female
Race	categorical	r_st	White, Black, Other (American Indian or Alaska Native, Asian, Hispanic, Multiracial, Native Hawaiian or other Pacific Islander)
Body mass index	continuous	bmi_at_encounter	Weight/Height (squared)
Smoking Status	categorical	s_st	Never, Smoker/Former Smoker
Alcohol Status	categorical	a_st	Yes (1), No (0)
Marital Status	categorical	m_st	Single/Divorced (0), Married/Partner/Significant other (1)
Insurance	categorical	i_st	Insured(1), Uninsured(0)
ICU admission	categorical	icu_yn	Yes, No
Emergency dept. admission	categorical	ed	Yes (1), No (0)
Underlying disease		icd10	Extracted specific underlying diseases from ICD-10 codes.
Chronic Pulmonary Obstructive Disease	categorical	copd	Yes (1), No (0)
Chronic Kidney Disease	categorical	ckd	Yes (1), No (0)
Liver Cirrhosis	categorical	lc	Yes (1), No (0)
Diabetes Mellitus	categorical	dm	Yes (1), No (0)

Appendix B: SAS Code

Formatting Covariates

Age

```
data test2;
set tmp1.first;
length agegroup $10;
if age le 49 then agegroup='<50';
else if 50<=age=<61 then agegroup='50-61';
else if 62<=age=<73 then agegroup='62-73';
else if age > 73 then agegroup='>73';
run;
```

Underlying diseases

```
data tempdiag2b;
set tempdiag2;
if CURRENT_ICD10_LIST='J44.9' /*COPD*/ then under_dis='COPD';
else if CURRENT_ICD10_LIST='E11.9' /*Diabetes*/ then under_dis='DM';
else if CURRENT_ICD10_LIST='K74.60' /*Liver Cirrhosis*/ then
under_dis='LC';
else if CURRENT_ICD10_LIST='I12.9' OR CURRENT_ICD10_LIST='I12.9, N18.4'
OR CURRENT_ICD10_LIST='I12.9, N18.3'/*CKD*/ then under_dis='CKD';
else under_dis='None';
run;

*now creating individual variables for underlying diseases*;

data tempdiag2bbb;
set tempdiag2bb;
if under_dis='CKD' then CKD=1;
else CKD=0;
run;

proc freq data=tempdiag2bbb;
table ckd;
run;

data tempdiag2bbb;
set tempdiag2bbb;
if under_dis='COPD' then COPD=1;
else COPD=0;
run;

proc freq data=tempdiag2bbb;
table ckd copd;
run;

data tempdiag2bbb;
set tempdiag2bbb;
if under_dis='LC' then LC=1;
```

```
else LC=0;
run;

proc freq data=tempdiag2bbb;
table ckd copd lc;
run;

data tempdiag2bbb;
set tempdiag2bbb;
if under_dis='DM' then DM=1;
else DM=0;
run;

proc freq data=tempdiag2bbb;
table ckd copd lc dm;
run;

*deleting extra rows per admissions to remove extra 0s from each new
underlying disease variable*;


proc sort data=tempdiag2bbb nodupkeys;
by pat_enc_csn_id;
run;
```

Race

```
data sid.new_2_r_new;
set sid.new_2_r;
if race='American Indian or Alaska Native' then r_st='Other'; else if
race='Asian' then r_st='Other';
else if race='Hispanic' then r_st='Other';
else if race='Multiracial' then r_st='Other'; else if  race='Native
Hawaiian or Other Pacific Islander' then r_st='Other';
else if race='Other' then r_st='Other';
else if race='Black or African American' then r_st = 'Black';
else if race = 'White or Caucasian' then r_st='White';
else call missing(r_st);
run;
```

Location of blood draw

```
data ddd;
set dd;
if ord_value='Arm' then draw='';
else if ord_value='Arm Left' then draw='';
else if ord_value='Blood' then draw='';
else if ord_value='Blood Venous' then draw='';
else if ord_value='0.511' then draw='';
else if ord_value='0.71' then draw='';
else if ord_value='0.74' then draw='';
else if ord_value='0.76' then draw='';
else if ord_value='0.82' then draw='';
else if ord_value='0.89' then draw='';
else if ord_value='0.92' then draw='';
```

```
else if ord_value='1.02' then draw='';
else if ord_value='1.9' then draw='';
else if ord_value='6.23' then draw='';
else if ord_value='<0.5' then draw='';
else if ord_value='>300.0' then draw='';
else if ord_value='>300.00' then draw='';
else if ord_value='Bone Marrow' then draw='';
else if ord_value='CSF Lumbar' then draw='';
else if ord_value='Buttock' then draw='';
else if ord_value='Leg Right' then draw='';
else if ord_value='Miscellaneous Source (See Comment)' then draw='';
else if ord_value='NULL' then draw='';
else if ord_value='No growth at 5 days' then draw='';
else if ord_value='Skin' then draw='';
else if ord_value='Blood, Line Draw' then draw='line';
else if ord_value='Blood, Line Draw ARTERIAL' then draw= 'line';
else if ord_value='Blood, Line Draw ARTERIAL LINE' then draw= 'line';
else if ord_value='Blood, Line Draw Arm Left' then draw='line';
else if ord_value='Blood, Line Draw Arm Right' then draw='line';
else if ord_value='Blood, Line Draw BLUE' then draw='line';
else if ord_value='Blood, Line Draw BROWN' then draw='line';
else if ord_value='Blood, Line Draw CENTRAL' then draw='line';
else if ord_value='Blood, Line Draw Hand Right' then draw='line';
else if ord_value='Blood, Line Draw LAC' then draw='line';
else if ord_value='Blood, Line Draw PORT' then draw='line';
else if ord_value='Blood, Line Draw PURPLE' then draw='line';
else if ord_value='Blood, Line Draw R HAND' then draw='line';
else if ord_value='Blood, Line Draw RAC' then draw='line';
else if ord_value='Blood, Line Draw RED' then draw='line';
else if ord_value='Blood, Line Draw RIGHT ARTERIAL LINE' then
draw='line';
else if ord_value='Blood, Line Draw Wrist Right' then draw='line';
else draw='peripheral';
run;
```

Marital status

```
data marital;
set marital;
if marital_status='Married' then marital_status='Married/Significant
Other';
else if marital_status='Significant Other/Life Partner' then
marital_status='Married/Significant Other';
else if marital_status='Divorced' then
marital_status='Single/Separated';
else if marital_status='Legally Separated' then
marital_status='Single/Separated';
else if marital_status='Single' then marital_status='Single/Separated';
else if marital_status='Widowed' then
marital_status='Single/Separated';
else call missing(marital);
run;
```

Insurance

```
data well2;
set well2;
if Payor='PENDING' then Insurance='Unknown';
else if payor='NOT INSURED' then Insurance='Uninsured';
else Insurance='Insured';
run;
/*change unknown to missing later*/
```

Alcohol status

```
data alcohol;
set marital;
if alcohol_status='NULL' then alcohol_status='Not Asked';
run;
```

Smoking status

```
data well2;
set alcohol;
if smoking_status='Current Every Day Smoker' then smoking_status='Yes';
else if smoking_status='Current Some Day Smoker' then
smoking_status='Yes';
else if smoking_status='Former Smoker' then smoking_status='Yes';
else if smoking_status='Smoker, Current Status Unknown' then
smoking_status='Yes';
else if smoking_status='Never Smoker' then smoking_status='No';
else if smoking_status='Passive Smoke Exposure - Never Smoker' then
smoking_status='No';
else call missing(smoking_status);
run;
```

Chapter 1

Table 3

```
/*--Clinical and socio-demographic factors by main exposure (blood
culture status)--*/

proc freq data=data19;
tables sex*status agegroup*status r_st*status i_st*status a_st*status
s_st*status m_st*status draw*status ed*status icu_yn*status copd*status
ckd*status lc*status dm*status/chisq fisher exact;
run;

proc ttest data= data19;
class status;
```

```
var bmi_at_encounter;
run;
```

Table 4

```
/*---Final model for outcome # 1: Length of stay ---*/

ods output parameterestimates=los;

proc glimmix data= data19;
class status (ref='ALL NEGATIVE') agegroup(ref='<50') sex (ref='Male')
r_st(ref='Black') i_st (ref='0') draw ed(ref='0') icu_yn(ref='N')
dm(ref='0');
model pat_los= status agegroup sex r_st bmi_at_encounter i_st draw ed
icu_yn dm/ dist=negbin link=log solution cl;
LSMEANS status/ilink diff cl;
*random intercept/ subject=pat_mrn_id;
run;

data los_negbin;
set los;
count=exp(estimate);
lower=exp(lower);
upper=exp(upper);
run;
```

Table 5

```
/*---Final model for outcome # 2: Antibiotic days of therapy ---*/

ods output parameterestimates=abx;

proc glimmix data= data19;
class  status (ref='ALL NEGATIVE') agegroup(ref='<50') sex (ref='Male')
r_st(ref='Black') draw ed(ref='0') icu_yn(ref='N') s_st(ref='0');
model pat_abxdot= status agegroup sex r_st draw ed icu_yn
bmi_at_encounter s_st/ dist=negbin link=log solution cl;
LSMEANS status/ilink diff cl;
*random intercept/ subject=pat_mrn_id;
run;

data abx_negbin;
set abx;
count=exp(estimate);
lower=exp(lower);
upper=exp(upper);
run;
```

Table 6

```
/*-------Unadjusted means for outcome # 1: Length of stay ---------*/
```

```
ods output parameterestimates=los_unadj;

proc glimmix data= data19;
class status (ref='ALL NEGATIVE') ;
model pat_los= status / dist=negbin link=log solution cl;
LSMEANS status/ilink diff cl;
*random intercept/ subject=pat_mrn_id;
run;

data los_unadj_negbin;
set los_unadj;
count=exp(estimate);
lower=exp(lower);
upper=exp(upper);
run;


/*--------Adjusted means for Outcome # 1: Length of stay---------*/


ods output parameterestimates=los;

proc glimmix data= data19;
class status (ref='ALL NEGATIVE') agegroup(ref='<50') sex (ref='Male')
r_st(ref='Black') i_st (ref='0') draw ed(ref='0') icu_yn(ref='N')
dm(ref='0');
model pat_los= status agegroup sex r_st bmi_at_encounter i_st draw ed
icu_yn dm/ dist=negbin link=log solution cl;
LSMEANS status/ilink diff cl;
*random intercept/ subject=pat_mrn_id;
run;

data los_negbin;
set los;
count=exp(estimate);
lower=exp(lower);
upper=exp(upper);
run;


/*--Unadjusted means for outcome # 2: Antibiotic days of therapy --*/

ods output parameterestimates=abx_unadj;

proc glimmix data= data19;
class  status (ref='ALL NEGATIVE');
model pat_abxdot= status / dist=negbin link=log solution cl;
LSMEANS status/ilink diff cl;
*random intercept/ subject=pat_mrn_id;
run;

data abx_unadj_negbin;
set abx_unadj;
count=exp(estimate);
lower=exp(lower);
```

```
upper=exp(upper);
run;

/*----Adjusted means for Outcome # 2: Antibiotic days of therapy----*/

ods output parameterestimates=abx;

proc glimmix data= data19;
class  status (ref='ALL NEGATIVE') agegroup(ref='<50') sex (ref='Male')
r_st(ref='Black') draw ed(ref='0') icu_yn(ref='N') s_st(ref='0');
model pat_abxdot= status agegroup sex r_st draw ed icu_yn
bmi_at_encounter s_st/ dist=negbin link=log solution cl;
*random intercept/ subject=pat_mrn_id;
LSMEANS status/ilink diff cl;
run;

data abx_negbin;
set abx;
count=exp(estimate);
lower=exp(lower);
upper=exp(upper);
run;
```

Chapter 2

Table 7

```
/*--Clinical and socio-demographic factors by main exposure (blood
culture status)--*/


proc freq data=data19;
tables sex*status agegroup*status r_st*status i_st*status a_st*status
s_st*status draw*status ed*status icu_yn*status copd*status ckd*status
lc*status dm*status/chisq fisher exact;
run;

proc ttest data=data19;
class status;
var bmi_at_encounter;
run;
```

Table 8

```
/*--Crude ORs for risk factors ------- run once for each variable --*/

proc logistic data=data19;
class status (ref='ALL NEGATIVE') agegroup(ref='<50');
model status= agegroup/ link=logit cl;
```

```
run;

/*--Adjusted ORs for risk factors--*/

proc logistic data=data19;
class status (ref='ALL NEGATIVE') agegroup(ref='<50') sex (ref='Male')
r_st (ref='Black') icu_yn (ref='N') copd (ref='0') ed(ref='0') s_st
(ref='0');
model status= agegroup sex r_st icu_yn copd ed bmi_at_encounter s_st/
link=logit cl;
run;
```

Chapter 3

Table 9

```
/*--Clinical and socio-demographic factors by main exposure (PCR
status)--*/

proc freq data=pre_post;
tables sex*PCR agegroup*PCR r_st*PCR i_st*PCR a_st*PCR s_st*PCR
draw*PCR ed*PCR icu_yn*PCR copd*PCR ckd*PCR lc*PCR dm*PCR/chisq fisher
exact;
run;

proc ttest data=pre_post;
class PCR;
var bmi_at_encounter;
run;
```

Table 10

```
/*---Final model for outcome # 1: Length of stay ---*/


ods output parameterestimates=los;

proc glimmix data=pre_post;
class PCR (ref='0') agegroup(ref='<50') r_st(ref='Black') ed(ref='0')
icu_yn(ref='N');
model pat_los= PCR agegroup r_st ed icu_yn/ dist=negbin link=log
solution cl;
LSMEANS PCR/ilink diff cl;
run;

data los_negbin;
set los;
count=exp(estimate);
lower=exp(lower);
upper=exp(upper);
run;
```

Table 11

```
/*---Final model for outcome # 2: Antibiotic days of therapy ---*/

ods output parameterestimates=abx;

proc glimmix data=pre_post;
class  PCR (ref='0') icu_yn(ref='N');
model pat_abxdot= PCR icu_yn/ dist=negbin link=log solution cl;
LSMEANS status/ilink diff cl;
run;

data abx_negbin;
set abx;
count=exp(estimate);
lower=exp(lower);
upper=exp(upper);
run;
```

Table 12

```
/*-------Unadjusted means for outcome # 1: Length of stay ---------*/


ods output parameterestimates=los_unadj;


proc glimmix data=pre_post;
class PCR (ref='0') ;
model pat_los= PCR / dist=negbin link=log solution cl;
LSMEANS PCR/ilink diff cl;
run;

data los_unadj_negbin;
set los_unadj;
count=exp(estimate);
lower=exp(lower);
upper=exp(upper);
run;


/*--------Adjusted means for Outcome # 1: Length of stay---------*/


ods output parameterestimates=los;

proc glimmix data=pre_post;
class PCR (ref='0') agegroup(ref='<50') r_st(ref='Black') ed(ref='0')
icu_yn(ref='N');
model pat_los = PCR agegroup r_st ed icu_yn/ dist=negbin link=log
solution cl;
LSMEANS PCR/ilink diff cl;
```

```
run;

data los_negbin;
set los;
count=exp(estimate);
lower=exp(lower);
upper=exp(upper);
run;


/*--Unadjusted means for outcome # 2: Antibiotic days of therapy --*/

ods output parameterestimates=abx_unadj;

proc glimmix data= pre_post;
class PCR(ref='0');
model pat_abxdot= PCR / dist=negbin link=log solution cl;
LSMEANS PCR/ilink diff cl;
run;

data abx_unadj_negbin;
set abx_unadj;
count=exp(estimate);
lower=exp(lower);
upper=exp(upper);
run;


/*----Adjusted means for Outcome # 2: Antibiotic days of therapy----*/

ods output parameterestimates=abx;

proc glimmix data=pre_post;
class  PCR (ref='0') icu_yn(ref='N');
model pat_abxdot= PCR icu_yn / dist=negbin link=log solution cl;
LSMEANS PCR/ilink diff cl;
run;

data abx_negbin;
set abx;
count=exp(estimate);
lower=exp(lower);
upper=exp(upper);
run;
```

Appendix C: Supporting tables

Chapter 1

Supplementary Table 1: Bivariate Analysis between primary outcome (LOS) and covariates

Variable	p-value
Sex	<0.0001
Age	0.0011
Age-Group	<0.0001
Race	<0.0001
Alcohol Status	0.0874
Smoking Status	0.5758
Marital Status	0.0134
Insurance Status	<0.0001
BMI	<0.0001
BMI-Group	<0.0001
Draw	<0.0001
ED Admission	<0.0001
ICU Admission	<0.0001
Chronic Obstructive Pulmonary Disease	0.6155
Chronic Kidney Disease	0.7016
Liver Cirrhosis	<0.0001
Diabetes Mellitus	0.0189

Supplementary Table 2: Bivariate Analysis between secondary outcome (Abx DOT) and covariates

Variable	p-value
Sex	<0.0001
Age	0.0128
Age-group	0.001
Race	0.0039
Alcohol Status	0.4187
Smoking Status	0.046
Marital Status	0.5167
Insurance Status	0.3394
BMI	0.0028
BMI-group	0.0322
Draw	<0.0001
ED Admission	<0.0001
ICU Admission	<0.0001
Chronic Obstructive Pulmonary Disease	0.1225
Chronic Kidney Disease	0.6708
Liver Cirrhosis	0.4693
Diabetes Mellitus	0.0858

Chapter 3

Supplementary Table 3: Bivariate Analysis between primary outcome (LOS) and covariates

Variables	p-value
Sex	0.0164
Age-group	<0.0001
Race	0.0161
Alcohol Status	0.9232
Smoking Status	0.3397
Marital Status	0.2054
Insurance Status	0.6669
BMI	0.7992
ED Admission	<0.0001
ICU Stay	<0.0001
Seasons	0.4420

Supplementary Table 4: Bivariate Analysis between secondary outcome (Abx DOT) and covariates

Variables	p-value
Sex	0.7168
Age-group	0.4663
Race	0.5410
Alcohol Status	0.9232
Smoking Status	0.7544
Marital Status	0.6563
Insurance Status	0.8183
BMI	0.1417
ED Admission	0.1811
ICU Stay	<0.0001
Seasons	0.9856

Supplementary Table 5: Time series analysis for primary outcome (LOS)

Type III Tests of Fixed Effects (LOS)				
Effect	**Num DF**	**Den DF**	**F Value**	**p-value**
pcr	1	765	3.71	0.0543
time	1	765	0.54	0.4636
time*pcr	1	765	2.78	0.096

Supplementary Table 6: Time series analysis for secondary outcome (Abx DOT)

Type III Tests of Fixed Effects (Abx DOT)				
Effect	**Num DF**	**Den DF**	**F Value**	**p-value**
pcr	1	765	0.22	0.6417
time	1	765	0.2	0.6522
time*pcr	1	765	0.21	0.6476