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Multiplex Polymerase Chain Reaction Pathogen Detection in Trauma, Emergency, and Burn Surgery Patients with Suspected Septicemia

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Abstract

Background—The goal of this study is to determine the clinical value of multiplex PCR for enhancing pathogen detection in trauma, emergency, and burn surgery patients with suspected septicemia. PCR-based pathogen detection quickly reveals occult bloodstream infections in these high-risk patients and may accelerate initiation of targeted antimicrobial therapy.

Methods—We conducted a prospective observational study comparing results for 30 trauma and emergency surgery patients to 20 burn patients. Whole-blood samples collected with routine blood cultures (BC) were tested using a new multiplex PCR-based pathogen detection system. PCR results were compared to culture data.

Results—PCR rapidly detected more pathogens than culture methods. Acute Physiology and Chronic Health Evaluation II (APACHE, $P = 0.019$), Sequential Organ Failure Assessment (SOFA, $P = 0.011$), and Multiple Organ Dysfunction (MODS, $P = 0.033$) scores were significantly higher in PCR positive versus PCR negative trauma and emergency surgery patients. Negative PCR results (OR 0.194; 95% CI, 0.045 – 0.840, $P = 0.028$) acted as an independent predictor of survival for the combined surgical patient population.

Conclusions—PCR detected the presence of pathogens more frequently than blood culture. These PCR results were reported faster than blood culture results. Severity scores were significantly higher in PCR-positive trauma and emergency surgery patients. The lack of pathogen DNA as determined by PCR served as a significant predictor of survival in the combined patient population. PCR testing independent of traditional prompts for culturing may have clinical value in burn patients. These results warrant further investigation through interventional trials.

Keywords

Antimicrobial therapy; blood culture; nucleic acid recognition; sepsis; serial testing; turnaround time

INTRODUCTION

The goal of this study is to determine the clinical value of multiplex polymerase chain reaction (PCR)-based pathogen detection in high-risk trauma, emergency, and burn surgery patients with suspected septicemia. Studies report blood culture (BC) pathogen detection turnaround times ranging from 24 to 48 hours and exhibiting reduced analytical sensitivity in the presence of antimicrobial drugs.^{1,2} Alternately, PCR represents a faster and more sensitive method.^{3–10}

Trauma, emergency, and burn surgery patients are at risk for sepsis due to post-surgical and -trauma related immunosuppression.^{11,12} Burn patients have lost their primary barrier to microorganism invasion—leading to extremely high infection rates.^{13–16} The persistent hypermetabolic and pro-inflammatory state following burn injury diminishes the utility of the systemic inflammatory response syndrome criteria and traditional sepsis definitions.^{13–17} We hypothesize that PCR-based pathogen detection could quickly reveal occult bloodstream infections within these high-risk surgery patients in order to augment clinical decision-making when traditional indicators of sepsis are unreliable.

MATERIALS AND METHODS

We enrolled 30 adult (≥ 18 years) trauma and emergency surgery, and 20 adult burn ($\geq 20\%$ total body surface area) surgery patients from the University of California, Davis, Medical Center. This prospective observational study was approved by the University of California, Davis, Institutional Review Board (IRB#200311747).

PCR Sample Collection

PCR samples were simultaneously collected with physician-ordered BC (BacT/Alert, Bioré, Durham, NC) samples in patients presenting with the signs and symptoms of sepsis.^{13–17} Blood culture media did not contain antimicrobial drug inactivating charcoal or resins. Each blood sample was drawn in a 12 mL syringe by venipuncture or through existing arterial or central venous catheters. In addition to the routine 10 mL BC blood sample volume, an extra 2 mL was drawn into the same syringe. The BC bottles were dosed (10 mL/bottle) first and sent to the microbiology laboratory for routine testing. The remaining 2 mL of whole-blood was dosed into an ethylenediaminetetraacetic acid Vacutainer (Becton Dickinson, Franklin Lakes, NJ) for PCR testing. Paired samples were defined as PCR and BC whole-blood samples collected in the same syringe or when other cultures (OC: urine, tracheal aspirate, sputum, tissue, stool, wound samples) were collected during the same time interval. Initial samples were defined as the first paired PCR, BC, and/or OC samples collected after enrollment. Samples collected after the initial set following enrollment are classified as serial samples.

PCR Testing

Pathogen DNA extraction was performed immediately following blood sample collection using the M-Grade SeptiFast Blood Extraction Kit (Roche Diagnostics, Indianapolis, IN) and tested on the SeptiFast PCR system. Initial PCR samples were tested immediately. Serial PCR samples were stored at -25°C post-DNA extraction for batch testing within 5 days.

SeptiFast targets conserved bacterial/fungal internal transcribed spacer regions between the ribosomal DNA genes as reported previously⁵ to simultaneously detect up to 25 different bacterial and fungal pathogens in about 6 hours. The test panel includes: *Acinetobacter baumannii*, *Aspergillus fumigatus*, *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, *Candida tropicalis*, Coagulase negative *Staphylococcus* species,

Enterobacter aerogenes, *Enterobacter cloacae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, and *Streptococcus* Viridans-Group.^{4,5} PCR samples positive for *Staphylococcus aureus* were differentiated with the M-Grade SeptiFast *mecA* gene kit to identify methicillin resistant *Staphylococcus aureus* (MRSA). PCR results were compared to paired BC results and evaluated using an arbitrated case review process to determine clinical significance.

Data Collection

Patient demographics, type of trauma and/or burn size were collected at admission. Acute Physiology and Chronic Health Evaluation (APACHE) II, Sequential Organ Failure Assessment (SOFA) and the Multiple Organ Dysfunction (MOD) scores were calculated on the same day of blood sample collection. Length of stay and mortality was also determined. Blood culture, PCR, and OC detection events were recorded. Pathogen detection events are defined as discrete time points when culture or the PCR test identified a pathogen. Culture speciation, antimicrobial sensitivity results, and turnaround times (i.e., time from sampling to result reporting) for initial paired PCR and BC samples were recorded for comparison.

Arbitrated Case Review

Arbitrated case review was performed by a medical intensivist, 3 trauma surgeons, 3 burn surgeons, 1 microbiologist, and an infectious disease physician to determine antimicrobial adequacy based on paired PCR/BC results. The arbitrated case review process is adapted from our previous study.⁵ Physicians were first presented cases with only BC results. Cases were then represented with PCR results included. Physicians were asked to classify the antimicrobial therapy as either adequate or inadequate based on PCR and BC results. Adequate therapy is defined as antimicrobial therapy that correctly targets the identified pathogen suspected of causing the septic episode. Inadequate therapy is defined as antimicrobial therapy that incorrectly targets the identified pathogen due to intrinsic antimicrobial resistance, incorrect antimicrobial drug selection, or improper antimicrobial dosing.

Statistics

Concordance between PCR versus culture methods was determined by Cohen's κ -analysis, where $0 \leq \kappa \leq 1$, with 1 meaning complete agreement and 0, poor agreement. Mean $\pm$ SD were calculated. The Student's 2-Sample *t*-test and one-way analysis of variance (ANOVA) analyzed (SPSS 17, SPSS Inc., Chicago, IL) continuous variables when applicable. The parametric Tukey's pair-wise analysis was performed on significant ANOVA results. The Fischer's Exact test evaluated relationships between categorical variables. Multivariate logistic regression was performed to determine independent risk factors for hospital mortality. We report adjusted odds ratios (OR) and 95% confidence intervals (CI).

RESULTS

Seventy-six patients were consented. Twenty-six patients expired before PCR samples could be collected or were deemed as screening failures by not manifesting signs or symptoms of sepsis. Thirty (60%) trauma and emergency surgery and 20 (40%) burn patients were enrolled and had PCR samples collected. Forty-two (42/50) patients consented during the first 24-hours of hospital admission did not have any prior cultures drawn or antimicrobials administered. The remaining 8 patients had at least one BC set collected and were on antimicrobial therapy at the time of enrollment.

PCR and Blood Culture Turnaround Times

PCR turnaround times were significantly faster (5.85 vs. 25.3 hours, $P < 0.0001$) than BC speciation times. The PCR turnaround times ranged from 5.42 to 6.46 hours. In contrast, blood culture speciation turnaround times ranged from 11.4 to 31.9 hours. Blood culture antimicrobial sensitivity reporting occurring 31.6 to 102.8 hours after sample collection. Aseptic blood culture samples were finalized after 120 hours of incubation.

Antimicrobial Therapy

As determined by arbitrated case review, antimicrobial therapy was inadequate relative to PCR results in 7/24 (29.2%) PCR+ patients. Five of these patients came from the trauma and emergency surgery group. In one notable emergency surgery patient, BC failed to identify *Klebsiella* species and *Enterobacter* species on two separate occasions (day 4 and 6 following admission) while on inadequate empiric antimicrobial therapy. PCR identified these organisms on both occasions in 5.67 and 5.83 hours respectively. As a result of worsening signs of sepsis (fever $> 39^{\circ}\text{C}$, mean arterial pressure < 65 mmHg), and without knowledge of the PCR results, treatment was changed empirically to enhance coverage for Gram negative bacteria including *Klebsiella* and *Enterobacter* species. The patient's status improved over the next 5 days and was discharged from the intensive care unit by day 17.

Two other inadequately treated patients came from the burn patient group. One patient was PCR+/BC- and wound culture positive for methicillin sensitive *Staphylococcus aureus*. The other patient was PCR+/BC+ and respiratory culture positive for multi-drug resistant (based on *in vitro* culture sensitivity testing) *Escherichia coli*.

When PCR was not included in the case review, antimicrobial therapy was inadequate in 3 out of 16 BC+ patient cases. These three inadequately treated cases involved resistant strains of *Candida albicans*, *Chryseobacterium meningoseptium*, and the before mentioned multi-drug resistant *Escherichia coli*.

Outcomes

There was a significant relationship between PCR results and mortality for the entire patient population ($P = 0.047$) and for the trauma and emergency surgery group ($P = 0.049$) (Table 1). APACHE II scores differed significantly between PCR+ and PCR- patients within the trauma and emergency surgery group (17.0 vs. 13.82, $P = 0.019$). Both SOFA and MOD scores were significantly higher in PCR+ trauma and emergency surgery patients (SOFA: 8.38 vs. 6.82, $P = 0.011$; MODS: 9.85 vs. 8.65, $P = 0.033$). Multivariate analysis of the entire study population revealed the absence of pathogen DNA as determined by PCR to be an independent predictor of survival (OR 0.194; 95% CI, 0.045 – 0.840, $P = 0.028$).

When comparing BC positivity versus mortality, only the trauma and emergency surgery patient group exhibited a significant relationship ($P = 0.0027$). APACHE II (20.9 vs. 14.0, $P = 0.002$) and SOFA (9.0 vs. 6.0, $P = 0.019$) scores were significantly higher in BC+ burn patients. However, only SOFA scores (8.25 vs. 6.88, $P = 0.017$) were significantly higher in the BC+ trauma and emergency patient group. Blood culture results in the trauma, emergency and burn surgery populations were not significant predictors of mortality.

Pathogen Detection Events

There were significantly more PCR detection events (28) versus BC (7) and OC (8) events in the trauma and emergency surgery group ($P < 0.001$) (Table 2). For the burn group, PCR (13) had equivalent success of pathogen detection versus BC (13) ($P = 0.564$). With both study groups combined, there were significantly ($P = 0.006$) more pathogen detection events by PCR (41) than BC (22) and OC (18) ($P = 0.006$).

Concordance Between Initial PCR and Blood Culture Results

Figure 2 illustrates the concordance between paired initial PCR and BC samples. Sixteen patients (32%) had BC+ results. Twenty-four out of the 50 patients (48%) had PCR+ results, of which, 10 paired PCR/BC results were positive for the same pathogen. Three patient cases were PCR-/BC+. Pathogens missed by PCR were: *Acinetobacter baumannii*, *Bacillus non-anthraxis* species, *Candida albicans*, *Chryseobacterium meningiosepticum*, coagulase negative *Staphylococcus*, and *Proteus mirabilis*. *Bacillus* (non-anthraxis) species and *Chryseobacterium meningiosepticum* are not detectable by our PCR test panel. Eleven PCR+/BC- cases were observed where PCR detected pathogens missed by BC. These PCR+/BC- cases revealed *Klebsiella* species and *Enterobacter* species, *Enterococcus faecalis/faecium*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans* and *Candida tropicalis*.

The magnitude of concordance between paired initial PCR versus culture-based methods was determined by Cohen's κ -analysis on PCR, BC, and both BC and OC results combined. When PCR served as the reference for both BC and OC results, the κ -coefficient was 0.69. With BC as the reference, the κ -coefficient was 0.10. Kappa increased to 0.42 when both BC and OC results served as the reference for PCR.

Concordance Between Serial PCR and Blood Culture Results

Among the 24 PCR+ patients, 5 had serial PCR samples collected and tested. These 5 patients were on concurrent antimicrobial therapy at the time of PCR sample collection. We found serial PCR agreeing with paired BC 28.6% (10/35) of the time and 20% (7/35) of the time with OC results. Pathogens detected by serial PCR samples included: coagulase negative *Staphylococcus*, *Enterobacter* species, *Enterococcus faecalis*, *Klebsiella* species, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus* species.

DISCUSSION

The clinical utility of multiplex whole-blood PCR-based pathogen detection has been studied in several patient populations except for trauma, emergency, and burn surgery patients (Table 3).^{3,5,6-10} These trauma, emergency, and burn surgery patients represent unique populations where rapid multiplex pathogen nucleic acid recognition techniques exhibit clinical value.

PCR provided pathogen speciation and negative results 21.5 and 125.85 median hours faster than BC+ versus BC- results respectively. In two patient cases, despite unproductive BCs, rapid PCR results would have facilitated adequate antimicrobial therapy at least 24 hours earlier. These inadequate antimicrobial therapy events occurred when BC did not detect *Klebsiella* species and *Enterobacter* species, and *Staphylococcus aureus* respectively.

During antimicrobial therapy, serial PCR testing identified clinically significant pathogens missed by BC and exhibited clinical value for monitoring antimicrobial therapy as suggested by previous literature.^{18,19} The rapid PCR-based determination of pathogen DNA free whole-blood samples served as an independent predictor of survival in the combined trauma, emergency, and burn surgery population. Adjust odds ratios suggested patients with negative PCR results were more likely to survive compared to those having a single positive PCR result.

Severity scores were significantly higher in PCR+ trauma and emergency surgery patients. Alternately, lack of severity score significance between PCR+ versus PCR- burn patients may due to the inability of existing scoring systems to account for complex pathologies found in this population—as previously suggested by Greenhalgh et al.¹⁴ Blood culture

positive burn patients showed significantly higher APACHE II and SOFA scores. Higher severity scores associated with BC+ results were expected in the burn population due to the use of late-stage signs (e.g., temperature $>39.5^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, thrombocytopenia, hypotension) of sepsis for initiating routine BC sample collection.⁹

Failure of PCR to detect BC-confirmed pathogens in three patient cases may be related to genetic polymorphisms, presence of rare organisms undetectable by the SeptiFast assay (e.g., *Chryseobacterium meningiosepticum*), or whole-blood sample matrix effects. Limitations of this study include small patient population sizes, the PCR system not being FDA-licensed for interventional therapy in the United States, the inherent inability for PCR techniques to determine *in vitro* minimum inhibitory antimicrobial concentration, and BC not being a “gold standard” for comparison.

CONCLUSIONS

Post-surgical, -burn, and -trauma related immunosuppression increases the prevalence of bloodstream infections and mortality. Our study showed multiplex whole-blood PCR providing a rapid and highly sensitive pathogen detection method compared to BC. Serial testing was unaffected by concurrent antimicrobial therapy and helped identify persistent occult bloodstream infections. The absence of pathogen DNA as determined by PCR was a significant predictor of patient survival in the overall study population. We recommend the use of PCR methods in trauma, emergency, and burn surgery patients to quickly identify the presence of high-risk pathogens and initiate targeted antimicrobial therapy. However, late stage indicators of burn sepsis including high fever ($>39.5^{\circ}\text{C}$), thrombocytopenia, and hypotension, limits the utility of both PCR and culture methods. Further investigations are warranted to address the incidence of PCR detection events independent of traditional prompts for blood culturing, especially in burn patients, and to determine the merit of PCR-driven antimicrobial therapy for managing sepsis.

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Figure 1. Paired Initial PCR and Blood Culture Timing Events

The figure shows the descriptive statistics and a histogram of paired initial PCR and blood culture (BC) detection events ($N = 50$). PCR reported results within a 5.42 to 6.46 hour window following sample collection. Blood culture Gram's Stain results were reported around 8.7 to 18.5 hours after sample collection. Speciation results were reported 11.4 to 31.9 hours after sample collection. Antimicrobial sensitivity results were reported 31.6 to 102.8 hours after sample collection. Negative results were finalized after 120 hours of incubation as shown with the open bar on the right. PCR results were significantly ($P < 0.001$) faster than blood culture speciation times.

Figure 2. Paired Initial Patient PCR and Blood Culture Sample Results

The Venn diagram illustrates the number patients with initial PCR-positive (PCR+), PCR-negative (PCR-), blood culture positive (BC+), and blood culture negative (BC-) results. The left circle shows the number of patients with PCR+ (N=24) results. The right circle shows the number of patients with BC+ (N=16) results. The overlapping region identifies patients with matching paired PCR+ and BC+ results. Trauma and emergency, and burn patients are stratified within the Venn. The box in the upper left corner identifies patients with PCR-/BC- paired results (N=23).

Table 1
Demographics, Disease Severity and Outcomes Results for PCR Positive and PCR Negative Patients

Variable	Mean Values (SD)		Proportions		P-value
	PCR+	PCR-	PCR+	PCR-	
Age (years) [*]					
<i>All Patients</i>	47.0 (19.6)	36.1 (15.1)	24/50	26/50	0.036
<i>Trauma Patients</i> [†]	53.9 (22.6)	38.4 (16.9)	13/30	17/30	NS
<i>Burn Patients</i>	38.0 (10.1)	32.3 (11.1)	11/20	9/20	NS
Gender [†]			24/50	26/50	NS
<i>Male</i>	NA	NA	20/50	21/50	
<i>Female</i>	“	“	4/50	5/50	
ICU Length-of-Stay (days) [†]					
<i>All Patients</i>	33.3 (32.8)	40.4 (32.6)	24/50	26/50	NS
<i>Trauma Patients</i> [†]	17.8 (13.7)	39.3 (38.4)	13/30	17/30	0.045
<i>Burn Patients</i>	53.3 (39.9)	42.2 (21.1)	11/20	9/20	NS
APACHE II Score ^{‡,§}					
<i>All Patients</i>	17.8 (3.8)	14.6 (4.7)	“	“	0.010
<i>Trauma Patients</i> [†]	17.0 (3.8)	13.8 (2.8)	“	“	0.019
<i>Burn Patients</i>	18.9 (3.8)	15.9 (6.9)	“	“	NS
MODS ^{‡,§}					
<i>All Patients</i>	9.4 (1.5)	7.0 (4.7)	“	“	NS
<i>Trauma Patients</i> [†]	9.8 (1.5)	8.6 (1.3)	“	“	0.033
<i>Burn Patients</i>	8.8 (1.4)	8.5 (1.9)	“	“	NS
SOFA Score ^{‡,§}					
<i>All Patients</i>	8.0 (1.8)	7.0 (2.4)	“	“	NS
<i>Trauma Patients</i> [†]	8.4 (1.7)	6.8 (2.8)	“	“	0.011
<i>Burn Patients</i>	7.4 (1.8)	7.4 (3.5)	“	“	NS
PCR as an independent predictor of mortality//	NA	NA	“	“	0.028, OR 0.195 (95% CI 0.045 – 0.840)
Relationship of PCR and and mortality (all patients) [‡]	NA	NA	23/50	27/50	0.047

Variable	Mean Values (SD)		Proportions		P-value
	PCR+	PCR-	PCR+	PCR-	
Survivors	"	"	14/50	24/50	
Non-survivors	"	"	9/50	3/50	
Relationship of PCR and mortality (Trauma) ^{†,‡}	NA	NA	14/30	16/30	0.049
Survivors	"	"	7/30	15/30	
Non-survivors	"	"	6/30	2/30	
Relationship of PCR and mortality (Burns) [‡]	NA	NA	10/20	10/20	NS
Survivors	"	"	8/20	8/20	
Non-survivors	"	"	3/20	1/20	

Footnotes:

^{*} Student's 2-sample t-test;

[†] "Trauma" includes trauma and emergency surgery patients;

[‡] Fischer's Exact Test;

[§] calculated for variables at the time of sample collection; and

// multivariate logistic regression.

Abbreviations: APACHE, acute physiology and chronic health evaluation; BC, blood culture; CI, confidence interval; ICU, intensive care unit; MODS, multiple organ dysfunction score; NA, not applicable; NS, not significant; OR, adjusted odds ratio; PCR, polymyrase chain reaction; SOFA, sequential organ failure assessment.

Table 2

Frequency of Pathogens Detection Events for PCR and Culture-Based Methods

TRAUMA AND EMERGENCY SURGERY (N = 30 Patients)

<u>Pathogen</u>	<u>PCR</u>	<u>BC</u>	<u>OC</u>
<i>Candida albicans</i>	5	2	2
<i>Enterococcus faecalis</i>	4	1	0
<i>Staphylococcus aureus</i>	4	1	3
Coagulase negative <i>Staphylococcus</i>	3	1	1
<i>Enterobacter</i> species	3	1	1
<i>Klebsiella</i> species	2	0	0
MRSA	2	1	1
<i>Candida krusei</i>	1	0	0
<i>Candida tropicalis</i>	1	0	0
<i>Enterococcus faecium</i>	1	0	0
<i>Pseudomonas aeruginosa</i>	1	0	0
<i>Streptococcus</i> species	1	0	0
Subtotal:	28	7	8

$P < 0.001$

BURN SURGERY (N = 20 Patients)

<u>Pathogen</u>	<u>PCR</u>	<u>BC</u>	<u>OC</u>
MRSA	3	2	2
<i>Staphylococcus aureus</i>	3	2	2
Coagulase negative <i>Staphylococcus</i>	2	2	0
<i>Enterobacter</i> species	2	1	2
<i>Enterococcus faecalis</i>	1	1	0
<i>Escherichia coli</i>	1	1	1
<i>Pseudomonas aeruginosa</i>	1	1	0
<i>Acinetobacter baumannii</i>	0	1	1
<i>Aspergillus fumigatus</i>	0	0	1
<i>Candida albicans</i>	0	1	0
<i>Proteus mirabilis</i>	0	1	0
<i>Bacillus</i> (non-anthraxis) species*	0	1	0
<i>Chryseobacter meningiosepticum</i> *	0	1	1
Subtotal:	13	15	10

NS

COMBINED POPULATION: TRAUMA, EMERGENCY, AND BURN SURGERY PATIENTS (N=50)

TOTAL:	41	22	18
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$P = 0.006$

Note:

* Pathogens not detectable by PCR. Statistically significant pair-wise comparisons determined by ANOVA and Tukey's post-hoc analysis identified by arrows and brackets.

Abbreviations: ANOVA, analysis of variance; MRSA, methicillin resistant *Staphylococcus aureus*; NS, not significant; OC, other cultures (wound swabs, respiratory aspirates, urine); and PCR, polymerase chain reaction.

Table 3

Studies Involving SeptiFast Multiplex PCR

Author (Year)	Study Design	Population	Sample Size	Conclusions
Avolio (2010) ³	Single center, prospective, observational,	Adult, emergency	144	PCR and blood culture detected the same pathogen in 30 cases (56.6%) out of the 53 positive cases. However, PCR missed detected pathogens in 13 cases and blood culture missed detected 10 cases.
Dierkes (2009) ⁶	Single center, prospective, observational	Adult, intensive care	77	Out of 101 blood samples from 77 patients, 63 (62%) yielded concordant negative results, 14 (13%) concordant positive, and 9 (9%) were blood culture positive only.
Lehmann (2010) ⁷	Multicenter, international, retrospective	Adult, emergency general medicine, intensive care	189	A total of 13.1% of PCR tests may have enabled earlier adequate antimicrobial therapy. Costs-effectiveness analysis indicated a cost-effectiveness ratio of 3,107 per quality-adjusted life-year.
Louie (2008) ⁵	Single center, prospective, observational	Adult, emergency general medicine, intensive care	200	More than 68% of PCR results were confirmed by blood urine, and catheter culture.
Maubon (2010) ⁸	Single center, prospective, observational	Adult, oncology	110	PCR would have improved treatment in 11(10%) of patients and prompted immediate antimicrobial therapy not given initially in 3 patients.
Paolucci (2009) ⁹	Single center, prospective, observational	Neonatal, intensive care	34	Bloodstream infections were detected in 7/34 (20.6%) patients with blood culture or PCR. In 3 cases, blood culture and PCR were in agreement. In 4 cases, PCR identified the presence of pathogen in the blood samples when cultures were unproductive.
Yanagihara (2010) ¹⁰	Multicenter, prospective, observational	Adult, surgical, hematology, emergency	212	PCR identified a pathogen in 11.3% (45/400) samples compared to 8.0% (32/400) by blood culture analysis. Among antibiotic pre-treated patients, PCR detected more bacteria and fungi and was less influenced by antibiotic exposure compared to blood culture (P=0.02).

Abbreviations: PCR, polymerase chain reaction