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Time to blood cultures positivity of microorganisms using a continuous-monitoring automated blood cultures system

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Abstract

Background: Previous studies showed that clinically significant pathogens were detected within 3 days of incubation using a continuous monitoring automated blood culture instrument.

Objectives: To determine time to blood culture positivity (TTP) of microorganisms using a BD BACTECT™ FX.

Methods: A cross-sectional study was conducted at Maharaj Nakorn Chiang Mai Hospital, Thailand from October to November 2014.

Results: One-hundred and eighty-one patients with 195 episodes of infection and 436 cultures were included in the analysis. Among 181 patients, 55.2% were male and the median age was 61 years (interquartile range (IQR) 50, 76). Of the 195 episodes of infections, the most common source was genitourinary tract (15.4%). Overall, the median TTP was 17 hours (IQR 11.5, 24.5), the shortest TTP was observed in *Streptococcus agalactiae*. Four-hundred and seventy-eight cultures (97.6%) and all (100%) were detected at 3 days and 5 days of incubation. Factors associated with TTP ≤24 hour were blood drawn from patients who had hematologic malignancy (odds ratio (OR) 9.6, 95% confidence interval (CI) 1.2, 74.3, $P = 0.030$), endocarditis and vascular infection (OR 8.7, 95% CI 1.1, 67.2, $P = 0.038$), thrombocytopenia (OR 2.4, 95% CI 1.3, 4.4, $P = 0.004$), clinical of systemic inflammatory response syndrome (SIRS) (OR 2.3, 95% CI 1.2, 4.5, $P = 0.014$), and not receiving antimicrobials within 72 hours before cultures taken (OR 2.2, 95% CI 1.4, 3.6, $P < 0.001$).

Conclusions: TTP varied depends upon the pathogens and clinical settings. However, bacteria were isolated from almost, but not all of the blood cultures within 3 days of incubation.

Keywords: bacteremia; blood culture; fungemia


Blood culture remains the gold standard for diagnosis of bloodstream infection. Time to blood culture positivity (TTP) depends upon the type of bacteria, whether they are true pathogens or contaminants, the severity of sepsis, and the underlying diseases [1–5]. Previous studies have shown that clinically significant pathogens were detected within 3 days of incubation

using continuous monitoring automated blood culture instruments, missing 3–5%, and raised the question whether 3 days are enough for blood culture incubation [2, 5–12].

Currently, a continuous automated blood culture instrument BD BACTECT™ FX (Becton, Dickinson and Company, Franklin Lakes, New Jersey) is used in our institution,

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Maharaj Nakorn Chiang Mai Hospital. The 5-day-incubation period is recommended as per the manufacturer instruction before reporting negative results [13].

The primary objective of this study was to determine the TTP of microorganisms growing in blood cultures drawn from adult patients. The secondary objectives were to (1) determine the cumulative probability of TTP of microorganisms, (2) the TTP among patients with and without clinical of systemic inflammatory response syndrome (SIRS), and (3) determine factors associated with the rapid growth of microorganisms.

Materials and methods

Study setting, design, and population

This retrospective study was approved by the Research Ethics Committee Faculty of Medicine, Chiang Mai University (certificate of approval no. 272/2014).

A cross-sectional study was conducted among patients receiving care at Maharaj Nakorn Chiang Mai Hospital from October 1 to November 30, 2014. All patients who met the following criteria were consecutively enrolled: (1) age ≥ 15 years old, (2) had blood cultures drawn at the emergency department, outpatient department, and/or inpatient units, (3) blood culture grew organisms, and (4) medical records were available for review.

Data collection

Demographic (e.g. age, sex, underlying diseases) and clinical characteristics including medical services, clinical of SIRS, source of infection, prior antimicrobial uses, organisms grew from blood cultures, and TTP for each blood culture bottle were collected. Patients with multiple episodes of infection were counted only once for analysis of demographic characteristics, but counted as the number of the episode for analysis of clinical characteristics.

Procedures for blood cultures

Blood culture was obtained by trained health care personnel using 2% alcoholic chlorhexidine or 75% alcohol followed by 10% povidone-iodine as skin antisepsis for peripheral venipuncture. The aseptic technique was also performed in blood obtained from central venous/arterial catheters. At least 10 mL of blood was obtained for each bottle and inoculated into aerobic blood culture bottle using BD BACTEC™ Plus

Aerobic/F culture bottles for bacteria processing on the BD BACTEC FX™ (Becton, Dickinson and Company, Franklin Lakes, New Jersey) at the central diagnostic laboratory, Maharaj Nakorn Chiang Mai Hospital. Anaerobic blood cultures were not routinely performed in our hospital. Each patient who had ≥ 2 blood culture bottles drawn should have been drawn at least 30 minutes apart, except for emergency conditions in which two blood cultures were drawn at the same time but from different venipuncture sites. Positive blood culture was reported immediately when the organism was detected, whereas negative blood culture was reported when no organism growth was observed after incubation for 5 days.

Definitions

Episode of infection was defined as the first positive blood culture in a series and judged by investigators according to clinical information.

TTP is defined as the beginning time of the blood culture incubation until the positive result was detected by the automated system. It is the standard practice in our hospital that blood culture bottle must then be sent to the central diagnostic laboratory as soon as possible, and usually within 30 minutes after blood drawn.

True pathogen is considered for *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Haemophilus influenzae*, *Escherichia coli* and other enterobacteriaceae, *Pseudomonas aeruginosa*, members of the *Bacteroides fragilis* group, all *Candida* species, and *Cryptococcus neoformans* [14–16].

Contaminant blood culture is considered if (1) 1 of 1 blood culture obtained or 1 of ≥ 2 blood cultures obtained grew coagulase-negative staphylococci, *Corynebacterium* spp., *Micrococcus* spp., *Bacillus* spp. not anthracis, or viridans group streptococci or (2) ≥ 2 blood cultures obtained within 48 hours grew coagulase-negative staphylococci, *Corynebacterium* spp., *Micrococcus* spp., *Bacillus* spp. not anthracis, or viridans group streptococci, in which the isolates were different, that is, different antibiograms [17]. However, in the presence of central venous or arterial catheters, the isolation of coagulase-negative staphylococci might be considered as a true pathogen by taking into account of the following factors: clinical manifestations, leukocyte count, imaging results, clinical course, response to therapy, and the absence or presence of other sites of infection.

Multiple isolates blood culture is defined if >1 microorganism was isolated from the same bottle or if two populations of the same microorganism with different antibiotic

susceptibility patterns were identified [5]. Only cultures from which a single organism was recovered were used to analyze time-to-positivity.

SIRS, sepsis, and septic shock were followed those of Levy et al. and has been described elsewhere [18].

Statistical analysis

Data were presented in mean \pm SD, median and IQR, number (%) as appropriate. Comparisons between groups were compared using Student's *t*-test or Mann Whitney *U* test for continuous data, and χ^2 test and Fisher's exact test for categorical data. TTP between groups was analyzed using Kaplan–Meier estimates and log rank tests. Factors associated with TTP within 24 hours were tested in univariate models. Factors with the $P < 0.10$ from univariate analysis were then tested in a multivariate logistic regression model using backward stepwise procedure. Statistical significance was set as two-tailed, with $P < 0.05$. All statistical analyses were performed using Stata statistical software version 11.0 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP.).

Results

During the study period, there were 6,961 blood cultures taken and 635 (9.1%) grew microorganisms. One-hundred and twenty-nine blood cultures were excluded as shown in **Figure 1**. There were 506 cultures contributed from 238 patients, 103 patients contributed 1 blood culture bottle;

88 patients contributed 2 blood culture bottles; 18 patients contributed 3 blood culture bottles; 11 patients contributed 4 blood culture bottles; 7 patients contributed 5 blood culture bottles; 6 patients contributed 6 blood culture bottles; 2 patients contributed 7 blood culture bottles; 2 patients contributed 10 blood culture bottles, and 1 patient contributed 24 blood culture bottles.

Seventy cultures (13.8%) were classified as contaminant blood cultures. Therefore, only true infection comprised of 436 cultures from 181 patients with 195 episodes of infection was included in the analysis of demographic and clinical characteristics.

Among 181 patients, 100 (55.2%) were male and the median age was 61 years (IQR 50, 76). The most common location where blood cultures were drawn was inpatient units (90.6%), which comprised of mostly from medical units (60.8%) and surgical units (23.8%). One-fourth of patients were admitted in critical care units.

The common underlying diseases were malignancy (34.8%), chronic kidney disease (12.7%), and diabetes mellitus (11.6%) as shown in **Table 1**.

Episodes of infections

There were 195 episodes of infection. The common clinical presentations were fever (73.3%), dyspnea (19%), and gastrointestinal symptoms (18%). Genitourinary tract infection was the most common source of bloodstream infection (15.4%), followed by gastrointestinal and hepatobiliary tract infection (14.9%) and catheter-related infection (12.8%). Blood cultures were taken while receiving antimicrobials in 55 episodes

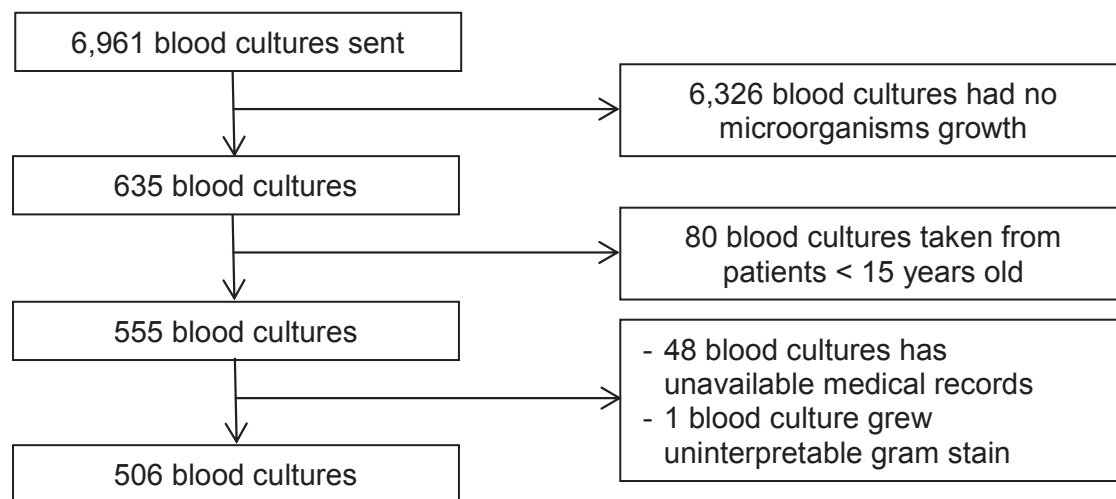


Figure 1. Blood cultures recruited for this study.

Table 1. Demographic characteristics of 181 patients whose blood cultures grew true pathogens

Characteristics	Number (%) N = 181
Male	100 (55.2)
Age (years) (median, IQR)	61 (50, 76)
Location where blood cultures were drawn	
Inpatient units	164 (90.6)
Critical care units	42 (23.2)
Noncritical care units	122 (67.4)
Medicine	110 (60.8)
Surgery	43 (23.8)
Orthopedics	5 (2.8)
Obstetrics and gynecology	3 (1.7)
Others	3 (1.7)
Outpatient department	10 (5.5)
Emergency department	7 (3.9)
Underlying diseases	145 (80.1)
Malignancy	63 (34.8)
Hematologic malignancy	18 (9.9)
Solid organ malignancy	45 (24.9)
Advanced chronic kidney disease (GFR <30 mL/min/1.73 m ²)	23 (12.7)
Diabetes	21 (11.6)
Disease result in neurocognitive impairment	14 (7.7)
Symptomatic heart failure or ejection fraction <40%	13 (7.2)
Cirrhosis	12 (6.6)
Hydronephrosis	8 (4.4)
HIV infection	7 (3.9)
Chronic obstructive lung disease	5 (2.8)
Gastrointestinal fistula	5 (2.8)
Rheumatologic disease	3 (1.7)
Post splenectomy	3 (1.7)
Post organ transplant	3 (1.7)
Aplastic anemia	2 (1.1)
Adult onset immunodeficiency syndrome	1 (0.6)
Received immunosuppressive agents	34 (18.8)

GFR, glomerular filtration rate; HIV, human immunodeficiency virus; IQR, interquartile range

(28.2%). Clinical characteristics of 195 episodes of infections are shown in **Table 2** and clinical parameters are shown in **Table 3**.

Time to blood cultures positivity

Among 506 blood cultures, 490 cultures grew single microorganism, 16 cultures contained 2 microorganisms. All 70 contaminant blood cultures contained Gram-positive bacteria which included coagulase-negative staphylococci (38 cultures), *Bacillus* spp. (22 cultures), *Corynebacterium* spp. (7 cultures),

Table 2. Clinical characteristics of 195 episodes of infections

Characteristics	Number (%) N = 195
Clinical presentations	
Fever	143 (73.3)
Dyspnea	37 (19.0)
Abdominal pain, diarrhea, nausea, vomiting	35 (18.0)
Altered mental status	30 (15.4)
Dysuria, flank pain, or cloudy urine	14 (7.2)
Source of infection	
Genitourinary tract	30 (15.4)
Gastrointestinal and hepatobiliary tract	29 (14.9)
Central venous catheter related	25 (12.8)
Respiratory tract	15 (7.7)
Skin, bone, joint, and soft tissue	12 (6.2)
Endocarditis and vascular system	8 (4.1)
Unidentified	72 (36.9)
Prior antimicrobial uses	63 (32.3)
Type of antimicrobials	
Antibiotics	62 (31.8)
Cephalosporins	16 (8.2)
Carbapenems	14 (7.2)
Quinolones	14 (7.2)
Vancomycin	13 (6.7)
Metronidazole	12 (6.2)
Penicillin	9 (4.6)
Trimethoprim/sulfamethoxazole	5 (2.6)
Colistin	3 (1.5)
Macrolides	1 (0.5)
Aminoglycosides	1 (0.5)
Others	3 (1.5)
Antifungals	9 (4.6)
Current use of antimicrobials at the time blood cultures were taken	55 (28.2)

and *Micrococcus* spp. (3 cultures). The list of microorganisms and TTP for each microorganism is shown in **Table 4**. Sixteen multiple isolates blood cultures were excluded from the analysis of TTP.

Overall, the median TTP was 17 hours (IQR 11.5, 24.5), the medians TTP for Gram-positive and Gram-negative bacteria were 17.5 (IQR 12.5, 23) and 14 hours (IQR 10.5, 20), respectively ($P = 0.004$). The median TTP for yeast was 27.5 hours (IQR 22, 38). *S. agalactiae* had the shortest TTP, followed by *Vibrio vulnificus*, *S. pneumoniae*, and *Streptococcus bovis* with the medians TTP of 5.5 (IQR 5.5, 6), 8.5 (IQR 8.5, 8.5), 10 (IQR 5, 12), and 10 (8.5, 12.5) hours, respectively.

Among contaminant blood cultures, medians TTP are shown in **Table 5**. The medians TTP for true pathogens and contaminants were 16 (IQR 11.5, 23), and 23 (IQR 18.5, 28) hours, respectively ($P < 0.001$). The median TTP for

Table 3. Clinical parameter of 195 episodes of infections

Sepsis parameters	Total number of available data	Number (%)
Body temperature <36 or >38.3°C	191	134 (70.2)
Heart rate >90 beat/min	191	168 (88.0)
Respiratory rate >20/min	190	105 (55.3)
Hypotension or shock	191	56 (29.3)
Altered mental status	191	30 (15.7)
Acute lung injury	153	27 (17.6)
Decrease urine output	141	22 (15.6)
Creatinine >2.0 mg/dL or increase >0.5 mg/dL	162	43 (26.5)
Lactate level (mmol/L) (median, IQR)	95	3.0 (1.7, 6.2)
Lactate level >1.0 mmol/L	95	91 (95.8)
White blood cells ($\times 10^3$ cells/mm ³) (median, IQR)	195	12.5 (7.7, 17)
White blood cells <4,000 or >12,000 cells/mm ³	195	136 (69.7)
Platelet count ($\times 10^3$ per/mm ³) (median, IQR)	194	161 (70, 261)
Platelet count <100,000/mm ³	194	71 (36.6)
Clinical systemic inflammatory response syndrome	191	172 (90.0)

IQR, interquartile range

Table 4. List of microorganisms and time to positivity

Microorganisms	Number of blood cultures (%)	Median time to positivity (hours) (IQR)
Overall	490 (100)	17 (11.5, 24.5)
Bacteria	433 (88.4)	15.5 (11.5, 22)
Gram-positive bacteria	214 (43.7)	17.5 (12.5, 23)
Staphylococci	123 (25.1)	19 (15, 23.5)
Coagulase-negative staphylococci	67 (13.7)	20.5 (18, 25)
<i>Staphylococcus aureus</i>	56 (11.4)	15.5 (12.5, 20.25)
Streptococci	50 (10.2)	12.25 (9.5, 15.5)
<i>Streptococcus bovis</i>	15 (3.1)	10 (8.5, 12.5)
<i>Streptococcus pneumoniae</i>	5 (1.0)	10 (5, 12)
<i>Streptococcus pyogenes</i>	5 (1.0)	11 (10, 12)
<i>Streptococcus agalactiae</i>	5 (1.0)	5.5 (5.5, 6)
Other Streptococci	20 (4.1)	15.5 (14, 17.25)
<i>Bacillus</i> spp.	22 (4.5)	17.25 (12.5, 25.5)
<i>Enterococcus faecium</i>	7 (1.4)	17.5 (16.5, 19)
<i>Corynebacterium</i> spp.	7 (1.4)	26.5 (23, 58.5)
<i>Micrococcus</i> spp.	3 (0.6)	87 (57, 90)
<i>Listeria monocytogenes</i>	2 (0.4)	19.5 (19.5, 19.5)

(Continued)

Table 4. Continued

Microorganisms	Number of blood cultures (%)	Median time to positivity (hours) (IQR)
Gram-negative bacteria	219 (44.7)	14 (10.5, 20)
<i>Escherichia coli</i>	55 (11.2)	12 (10.5, 15)
<i>Klebsiella pneumoniae</i>	35 (7.1)	10.5 (9.5, 13)
<i>Pseudomonas aeruginosa</i>	28 (5.7)	21 (17.5, 25.25)
<i>Acinetobacter baumannii</i>	17 (3.5)	11 (10, 12.5)
<i>Aeromonas sobria</i> and <i>A. hydrophilla</i>	17 (3.5)	10.5 (9, 13)
<i>Salmonella</i> spp.	14 (2.9)	12.5 (10.5, 16.5)
<i>Burkholderia cepacia</i>	10 (2.0)	22.25 (20, 39)
<i>Enterobacter cloacae</i> and <i>Enterobacter</i> spp.	8 (2.0)	22.5 (14.25, 54)
<i>Stenotrophomonas maltophilia</i>	8 (1.6)	18.5 (16.25, 26.5)
<i>Proteus mirabilis</i>	5 (1.0)	14 (13.5, 17)
<i>Elizabethkingia meningoseptica</i>	4 (0.8)	13.75 (12.25, 15)
<i>Citrobacter freundii</i> and <i>C. koseri</i>	3 (0.6)	10.5 (10.5, 13)
<i>Serratia marcescens</i>	3 (0.6)	18 (17, 29)
<i>Neisseria gonorrhoeae</i>	2 (0.4)	29.5 (29, 30)
<i>Vibrio vulnificus</i>	2 (0.4)	8.5 (8.5, 8.5)
<i>Campylobacter</i> spp.	1 (0.2)	45
Unidentified Gram-negative bacilli	7 (1.4)	32 (28.5, 43)
Yeast and other fungi	57 (11.6)	27.5 (22, 38)
<i>Candida</i> spp.	55 (11.2)	27 (22, 36.5)
<i>Candida tropicalis</i>	14 (2.9)	19.8 (19, 22)
<i>Candida albicans</i>	10 (2.0)	40.5 (34, 54)
<i>Candida parapsilosis</i>	3 (0.6)	41.5 (26.5, 87.5)
<i>Candida guilliermondii</i>	3 (0.6)	28 (26, 30)
<i>Candida glabrata</i>	3 (0.6)	61.5 (60.5, 71)
Unidentified <i>Candida</i> spp.	22 (4.5)	27.8 (25.5, 31)
<i>Talaromyces (Penicillium) marneffeii</i>	1 (0.2)	110.5
Unidentified dematiaceous fungi	1 (0.2)	82.5

IQR, interquartile range

coagulase-negative staphylococci which were true pathogens and contaminants were 18.5 (16.5, 20.5) and 22 (19.5, 25.5) hours, respectively.

Three-hundred and sixty-seven (74.9%) blood cultures grew within 1 day, 462 (94.3%) cultures grew within 2 days, 478 (97.6%) cultures grew within 3 days, 489 (99.8%) cultures grew within 4 days, and all 490 (100%) cultures grew within 5 days. Microorganisms with TTP >3 days were *Micrococcus* spp. (2 cultures), *Microaerophilic streptococci* (1 culture), *Corynebacterium diphtheria* (1 culture), *Burkholderia cepacia* (2 cultures), *E. coli* (1 culture), *E. cloacae* (1 culture), *Candida albicans* (1 culture), *C. parapsilosis* (1 culture), unidentified

Table 5. Median time to positivity comparing true pathogens and contaminant blood cultures

Organism	Total number	True pathogen		Contaminant blood cultures	
		Number (%)	TTP (IQR)	Number (%)	TTP (IQR)
Overall	490	420 (85.7)	16 (11.5, 23)	70 (14.3)	23 (18.5, 28)
Gram-positive bacteria	214	144 (67.3)	15.5 (12, 19)	70 (32.7)	23 (18.5, 28)
Coagulase-negative staphylococci	67	29 (43.3)	18.5 (16.5, 20.5)	38 (56.7)	22 (19.5, 25.5)
<i>Bacillus</i> spp.	22	0	–	22 (100)	17.25 (12.5, 25.5)
<i>Corynebacterium</i> spp.	7	0	–	7 (100)	26.5 (23, 58.5)
<i>Micrococcus</i> spp.	3	0	–	3 (100)	87 (57, 90)

IQR, interquartile range; TTP, time to blood culture positivity

Table 6. The cumulative median time to positivity for particular microorganisms

Microorganisms	N	Number (%) of organisms recovered on hours					
		≤12	≤24	≤48	≤72	≤96	≤120
Overall	490	142 (29)	367 (75)	462 (94.3)	478 (97.6)	489 (99.8)	490 (100)
Bacteria	433	141 (32.6)	347 (80.1)	415 (95.8)	425 (98.2)	433 (100)	433 (100)
Gram-positive bacteria	214	49 (22.9)	166 (77.6)	202 (94.4)	210 (98.1)	214 (100)	214 (100)
Staphylococci	123	18 (14.6)	94 (76.4)	119 (96.8)	123 (100)	123 (100)	123 (100)
Coagulase-negative staphylococci	67	5 (7.5)	48 (71.6)	65 (97)	67 (100)	67 (100)	67 (100)
<i>Staphylococcus aureus</i>	56	13 (23.2)	46 (82.1)	54 (96.4)	56 (100)	56 (100)	56 (100)
Streptococci	50	25 (0.5)	46 (92)	48 (96)	49 (98)	50 (100)	50 (100)
True pathogens	144	42 (28.2)	124 (86.1)	139 (96.5)	143 (99.3)	144 (100)	144 (100)
Contaminants	70	7 (10)	42 (60)	63 (90)	67 (95.7)	70 (100)	70 (100)
Gram-negative bacteria	219	92 (42)	181 (82.6)	213 (97.3)	215 (98.2)	219 (100)	219 (100)
<i>Escherichia coli</i>	55	30 (54.6)	48 (87.3)	54 (98.2)	54 (98.2)	55 (100)	55 (100)
<i>Klebsiella pneumoniae</i>	35	25 (71.4)	34 (97.1)	35 (100)	35 (100)	35 (100)	35 (100)
<i>Pseudomonas aeruginosa</i>	28	0	20 (71.4)	28 (100)	28 (100)	28 (100)	28 (100)
<i>Acinetobacter baumannii</i>	17	11 (64.7)	17 (100)	17 (100)	17 (100)	17 (100)	17 (100)
<i>Aeromonas</i> spp.	17	12 (70.6)	16 (94.1)	17 (100)	17 (100)	17 (100)	17 (100)
<i>Salmonella</i> spp.	14	6 (42.9)	13 (92.9)	14 (100)	14 (100)	14 (100)	14 (100)
<i>Burkholderia</i> spp.	10	0	7 (70)	8 (80)	8 (80)	10 (100)	10 (100)
Yeast and other fungi	57	1 (1.8)	20 (35.1)	47 (82.5)	53 (93)	56 (98.3)	57 (100)

dematiaceous fungi (1 culture), and *Talaromyces* (*Penicillium*) *marneffei* (1 culture). The details of cumulative TTP for particular microorganisms are shown in **Table 6**. The median TTP for patients with and without clinical SIRS was 16 hours (IQR 11.5, 23.5), and 21 hours (16, 39.5), respectively ($P = 0.002$).

Factors associated with time to blood culture positivity within 24 hours

Comparing characteristics between blood cultures grew within 24 hours and after 24 hours were shown in **Table 7**. Blood cultures grew ≤24 hours were more likely drawn from patients who had hematologic malignancy, received immunosuppressive agents, altered mental status, endocarditis or vascular

infection, clinical SIRS, high blood lactate, low white blood cell count, and low platelet count. On the other hand, blood culture grew >24 hours were more likely drawn from patients who had intravascular catheters, catheter-related infection, prior use of antimicrobials within 72 hours particularly carbapenems, vancomycin, and antifungals.

Multivariate analysis revealed that factors associated with TTP ≤24 hours were blood cultures drawn from patients with hematologic malignancy (OR 9.6, 95% CI 1.2, 74.3, $P = 0.030$), endocarditis and vascular infection (OR 8.7, 95% CI 1.1, 67.2, $P = 0.038$), thrombocytopenia (OR 2.4, 95% CI 1.3, 4.4, $P = 0.004$), had clinical signs of SIRS (OR 2.3, 95% CI 1.2, 4.5, $P = 0.014$), and not receiving antimicrobials within 72 hours before cultures were taken (OR 2.2, 95% CI 1.4, 3.6, $P < 0.001$).

Table 7. Comparisons of characteristics of patients with positive blood culture within 24 hours and >24 hours

Characteristics	Number of patients (%)		P
	TTP ≤ 24 hours (N = 367)	TTP >24 hours (N = 123)	
Male	206 (56.1)	75 (61.0)	0.400
Underlying diseases	300 (81.7)	101 (82.1)	1.000
Malignancy	134 (36.5)	32 (26.0)	0.037
Hematologic malignancy	50 (13.6)	1 (0.8)	<0.001
Solid organ malignancy	84 (22.9)	31 (25.2)	0.624
Receiving immunosuppressive agents	78 (21.2)	13 (10.6)	0.007
Diabetes mellitus	37 (10.1)	9 (7.3)	0.475
Cirrhosis	19 (5.2)	4 (3.2)	0.468
HIV infection	13 (3.5)	2 (1.6)	0.376
Post splenectomy	4 (1.1)	1 (0.8)	1.000
Post organ transplant	6 (1.6)	3 (2.4)	0.698
Clinical presentations			
Fever	277 (76.5)	90 (75.0)	0.805
Dyspnea	79 (21.8)	20 (16.7)	0.243
Altered mental status	58 (16.0)	9 (7.5)	0.022
Source of infections			
Genitourinary tract	41 (11.2)	12 (9.8)	0.739
Gastrointestinal and hepatobiliary system	44 (12.0)	21 (17.1)	0.167
Catheter related	52 (14.2)	28 (22.8)	0.034
Respiratory tract	23 (6.3)	4 (3.2)	0.258
Skin, bone, joint, and soft tissue	21 (5.7)	5 (4.1)	0.643
Endocarditis and vascular system	22 (6.0)	1 (0.81)	0.014
Central nervous system	2 (0.5)	0	1.000
Prior antimicrobials uses within 72 hours	129 (35.6)	64 (53.3)	0.001
Carbapenems	35 (9.5)	22 (17.9)	<0.001
Vancomycin	23 (6.3)	25 (20.3)	<0.001
Antifungals	17 (4.6)	20 (16.3)	<0.001
Current uses of antimicrobials at the time of blood culture taken	115 (32.5)	63 (51.2)	<0.001
Indwelling intravascular catheters	114 (31.1)	55 (44.7)	0.008
Clinical systemic inflammatory response syndrome	337 (93.1)	99 (83.2)	0.003
Body Temperature <36°C or >38.3°C	246 (68.3)	75 (63.6)	0.367
Heart rate >90 beats/min	336 (91.6)	110 (89.4)	0.470
Tachypnea	213 (59.7)	66 (55.5)	0.452
Hypotension or shock	116 (32.0)	46 (38.3)	0.221
Altered mentation	62 (21.0)	14 (14.9)	0.233
Acute lung injury	51 (17.7)	14 (14.3)	0.532
Lactate >3 mmol/L	100(59.5)	18 (32.7)	0.001
White blood cells <4,000 cells/mm ³	68 (18.5)	9 (7.4)	0.003
Platelet count <100,000/mm ³	127(34.6)	24 (19.7)	0.002
Gram-positive bacteria	166 (47.8)	48 (55.)	0.228
Gram-negative bacteria	181 (52.2)	38 (44.2)	0.228

Discussion

Our study reported that the positive rate of blood cultures was 9.1%. This number was not changed from the positive rate among 35,000 blood cultures tested in the year 2012 at our hospital (unpublished data). Previous studies reported that two-thirds of patients with sepsis had negative blood cultures

[6, 10, 12], which could be due to local infection, inappropriate blood culture collection either timing or blood volume, or receiving antibiotics prior to blood culture collection [10, 12, 16]. In conjunction with these reasons, the low positive rate in our study might be due to the low probability of bacterial infections in the patients as blood cultures were almost always taken in patients admitted and had fever. The contamination

rate in this study was 13.8%, which is higher than previous reports of <5% [19–21]. Previous studies reported that the contamination rate was high among blood cultures taken at the emergency department and not using alcoholic chlorhexidine as skin antisepsis [21, 22]. Although the contamination rate in this study was high among blood cultures taken at the emergency department (31.3%) and outpatient department (24.0%), these numbers contributed only 8% of all cultures (data not shown). In addition, 2% alcoholic chlorhexidine is recommended as skin antisepsis for adults in our hospital. This high contamination rate alerted the infection control team to emphasize healthcare personnel to comply with the guidelines for drawing blood cultures.

The median TTP among 490 cultures was 17 hours and 97.6% of microorganisms could be detected within 3 days. Microorganisms grew after 3 days included four fungi and eight bacteria. Among eight bacteria, three cultures were contaminants, three cultures were taken while receiving antibiotics (two for *B. cepacia* and one for *E. coli*), and two cultures were *Microaerophilic streptococci* and *Enterobacter cloacae*. The latter two cultures had another blood culture in the same set grew within 3 days. Four fungi were isolated after 3 days of incubation. If disseminated fungal infections were not suspected in these patients and blood cultures on medium mycologic culture bottles for TB/fungus were not performed, these clinical isolates would be missed. McGowan et al. reported time to positivity in children who had positive blood cultures using the BacT/Alert Microbial Detection System (Organon Teknika, Durham, NC), almost all significant positive cultures were detected by 72 hours [5]. Bourbeau and Pohlman had also reported that 97.5% of all clinically significant isolates were detected in the first 3 days of incubation with standard BacT/Alert blood culture bottles [2]. The authors suggested that it might not be necessary to routinely incubate blood culture bottles for more than 3 days if a continuous monitoring automated blood culture system is used [2]. From our point of view, as 2.4% of cultures would be missed if cultures were incubated for 3 days, we would suggest incubating blood cultures per manufacturer instruction which is currently 5-day incubation period.

We further demonstrated that TTP among Gram-negative bacteria (14 hours, IQR 10.5, 20) was shorter than Gram-positive bacteria (17.5 hours, IQR 12.5, 23). However, this significantly different in TTP might not have clinical relevance. Of note, *S. agalactiae* grew fastest among all clinical isolates (5.5 hours, IQR 5.5, 6). Comparisons with the TTP of the same organism, the TTP in our study was shorter than the study in pediatrics, e.g. 12.2 hours for *S. agalactiae* [5]. This could be explained by the volume of blood culture being obtained in pediatrics was smaller than in adults.

For contaminant blood cultures, the TTP was longer than true pathogens. However, there was also no difference in a positive rate between true pathogens and contaminants after 3 days of incubation. In addition, patients with clinical SIRS had shorter TTP than patients without clinical SIRS. However, the medians TTP in both groups were <1 day.

The TTP may depend on multiple factors, including the volume of blood inoculated, the time elapse from specimen collection to incubation, and the concentration of organism within the blood [1, 3, 7]. In our study, we demonstrated that factors associated with TTP <24 hours were an underlying disease of malignancy, endocarditis and vascular infection, thrombocytopenia, and clinical of SIRS. A study among patients with *E. coli* bacteremia also reported that rapid TTP (<7 hours) was noted in patients who had active malignancies and neutropenia [1]. In addition, a study among patients with nontyphoidal salmonella bacteremia, rapid TTP (<10 hours) was associated with endovascular lesion and higher bacteremia score [3]. However, a study among children with *S. pneumoniae* bacteremia, no clinical or laboratory parameters was associated with the early growth of organisms [23]. Underlying disease of malignancy may represent impaired host immune status. Clinical of SIRS, and endocarditis and vascular infection may represent a high concentration of organism within the blood. Thrombocytopenia may represent indirect evidence of severe infection and high concentration of organism in the blood. Current or prior uses of antimicrobials within 3 days of blood cultures taken were associated with TTP >24 hours as antimicrobials may delay the growth of the organism.

This study has several limitations. First, although we have the guideline for taking blood for cultures, we believed that the guideline may not be well complied. One of the indirect evidence was a high rate of blood culture contamination. Therefore, the volume of blood culture in each bottle and time from drawing blood cultures to incubated instruments may not be accurate. Those factors may responsible for low positivity rate and longer TTP in those cultures. Second, the study period was too short. Given the finding that four fungi were missed if the incubation period was 3 days during only a 2-month period, numbers of pathogens might be overlooked if the study period was extended.

Conclusions

TTP varied depends upon the pathogens and clinical settings. Although microorganisms were isolated from almost all of the blood cultures within 3 days of incubation, 2.4% of cultures would be missed. A 5-day incubation period per manufacturer instructions is still required.

Author contributions. RC contributed to the conception and design of this study. PK acquired the data. Both authors analyzed and interpreted it. PK drafted the manuscript and RC critically revised it. Both authors approved the final version submitted for publication and take responsibility for statements made in the published article.

Acknowledgments. We would like to thank Mr. Banyong Kantawa for his help in providing microbiological data.

Conflict of interest statement. The authors have completed and submitted the International Committee of Medical Journal Editors Uniform Disclosure Form for Potential Conflicts of Interest. None of the authors disclose any conflict of interest.

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