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ORIGINAL ARTICLE

Paired blood cultures increase the sensitivity for detecting pathogens in both inpatients and outpatients

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Abstract

The objective of this study was to show the differences between paired blood cultures (PBC) versus single blood cultures (SBC) in the microbiologic yield, the sensitivity to detect pathogens and the time to positivity (TTP). We performed a retrospective study examining 112,570 blood culture samples over a 5-year period from July 2011 to May 2016 in the BacT/ALERT® 3D automated blood culture system (bioMérieux, Marcy l'Etoile, France). Bacteria and yeasts were identified using the VITEK® 2 Compact system (bioMérieux, Marcy l'Etoile, France). True-positives and contaminated bottles were defined and analysed separately. We analysed TTP and adherence to blood volume guidelines for a convenience sample of 510 and 999 sequential positive cultures, respectively. Out of 49,438 PBC samples, 5810 (11.7%) were positive. In 63,132 SBC samples, 4552 (7.2%) were positive ($p < 0.0001$). In PBC, 5371 (10.9%) were true-positives and 439 (0.9%) contaminants. In SBC, 4095 (6.5%) were true-positives and 457 (0.7%) contaminants. In the inpatient departments (IPD), the most common isolate was *Escherichia coli* ($n = 1373$), followed by *Klebsiella pneumoniae* ($n = 1206$), whereas in the outpatient departments (OPD), the most common isolates were *Salmonella typhi* ($n = 612$) and *S. paratyphi* A ($n = 278$). In the analysis of TTP, 98% grew within 72 h, 91% within 48 h and 89% within 36 h. In the blood volume analysis, 90% of the cultures had optimal blood volume. A significantly higher positivity rate was seen in PBC compared with SBC. Our study adds to the increasing evidence of improved microbial yield of clinically significant bacteria and fungi by performing PBC instead of SBC and adhering to blood volume collection guidelines.

Introduction

The detection of bacteraemia and fungaemia is traditionally one of the most important functions of clinical microbiology laboratories. Blood cultures are an essential diagnostic tool for all patients with suspected or proven serious infections and recommended by international guidelines [1]. Starting effective antibiotic treatment as early as possible, following early identification of pathogens, significantly impacts the disease outcome [2, 3]. It is recommended that at least two sets of blood cultures should be obtained, each from different peripheral sites [4]. Single blood cultures (SBC) are associated with a lower sensitivity to detect bacteraemia, as well as difficulty in differentiating contaminants from clinically significant pathogens when growing in a single set [5]. At least two blood culture bottles per set are recommended in the majority of conditions; however, the clinical condition determines the number of cultures needed [6, 7]. Moreover, manufacturers of blood culture systems and media have improved their products, and there has been a marked trend toward the use of automated systems. As blood culture yield is affected by blood volume, the number of blood culture bottles and sets obtained [8], the culture system used and the clinical condition, we conducted a retrospective study on a large blood culture database to describe the microbial yield and the factors related to blood culture positivity.

Materials and methods

Study design

We conducted a retrospective, descriptive, multi-centre study over 5 years of blood culture data from the Max Healthcare group of 14 hospitals, managed by a single healthcare entity in

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India. Max hospitals account for approximately 13,000 inpatient admissions every year, operating 2500 inpatient beds, as well as outpatient clinics with both Indian and international patients. The cohort was composed of patients from outpatient and inpatient departments (OPD and IPD, respectively), including inpatient intensive care units, evaluated between July 1, 2011 and May 31, 2016. The hospitals' blood culture policy adheres to Clinical and Laboratory Standards Institute (CLSI) recommendations [4]. We evaluated whether predictable gains existed in terms of detection of the most common microorganisms by the use of paired blood cultures and also in terms of time to detection of positivity in any of the two bottles detected first. We performed a descriptive analysis of microbial growth from positive bottles, true-positivity and contamination rates, time to positivity (TTP) and blood volume effect on paired blood culture sets and single blood culture sets (PBC and SBC, respectively). For these analyses, blood culture data and selected clinical patient data were retrieved from the electronic laboratory database. The study was initiated post-approval from our hospital's Scientific & Ethics committee.

Definitions

Paired blood culture set (PBC) A paired blood culture set was defined as two separate sets of blood cultures drawn from different peripheral venous sites or two separate sets of blood cultures where one was taken from a peripheral site and the other from a central catheter [4].

Single blood culture set (SBC) A single blood culture set is defined as a single blood culture set drawn from either a peripheral venipuncture or a central vein catheter [4].

True infection (bacteraemia or fungaemia) Microorganisms which represented true infection when isolated from blood cultures include *Staphylococcus aureus*, *Streptococcus pyogenes*, *S. agalactiae*, *S. pneumoniae*, *Escherichia coli* and other members of the family Enterobacteriaceae, *Pseudomonas aeruginosa* and other Gram-negative non-fermenting rods, *Bacteroides fragilis* group and *Candida* species. The common commensals (i.e. diphtheroids [*Corynebacterium* spp. not *C. diphtheriae*], *Bacillus* spp. [not *B. anthracis*], *Propionibacterium* spp., coagulase-negative staphylococci [including *S. epidermidis*], viridans group streptococci, *Aerococcus* spp., *Micrococcus* spp. and *Moraxella* spp.) were taken as true-positives only if they were cultured from two or more blood cultures which were drawn on the same or consecutive days and on separate occasions [9].

Polymicrobial infection with the same organisms in more than one culture sample was also considered to represent true bacteraemia if associated with fever (body temperature > 38.3 °C), rigors and/or hypotension (systolic blood pressure < 90 mmHg) [10].

Time to positivity (TTP)

TTP was defined as the time between the start of incubation in the BacT/ALERT® 3D system and the time that the automated alert signal indicated growth. For this analysis, a convenience sample of 510 sequential blood cultures from a single tertiary care Max group hospital in Delhi was analysed over a period of 5 months from January to May 2016.

Blood culture procedure

Blood samples were obtained by nursing staff from general wards and critical care units, or by trained phlebotomists from the OPD. Before collecting the blood sample, the skin was disinfected with 0.5% chlorhexidine in 70% isopropyl alcohol. The antecubital fossa was the preferred sampling site using a sterile needle and syringe. The blood samples from central vein catheters were obtained from needleless caps that were disinfected with 0.5% chlorhexidine in 70% isopropyl alcohol. A 'set' in our hospital system is defined as two BacT/ALERT® aerobic bottles. Each blood culture set consisted of two charcoal-based aerobic bottles (BacT/ALERT FA; bioMérieux, Marcy L'Etoile, France) until May 2013, after which resin-based aerobic bottles (BacT/ALERT FA Plus; bioMérieux, Marcy L'Etoile, France) were used. Hospital guidelines recommend that a blood volume of 8–10 mL be injected into each of the two bottles. All the samples of blood cultures were transported directly to a central laboratory by healthcare staff. All the bottles were loaded into the instrument at all times of the day (24 h a day, 7 days a week) by lab personnel. All bottles were incubated until microbial growth was detected or for a maximum of 5 days. The number of hours in the blood culture system prior to the detection of growth for each bottle was recorded by the instrument.

Two aerobic BacT/ALERT® 3D bottles were used for PBC in all IPD and OPD patients above the age of 12 years and one bottle for SBC for all children under the age of 12 years. All positive bottles underwent Gram staining and were systematically sub-cultured at 35 °C (± 2 °C) onto Columbia sheep blood and chocolate agar plates incubated in 5–10% CO_2 and a MacConkey agar plate under aerobic conditions. For PBC, TTP of the first bottle in a set was defined as the TTP for that set if the same organism appeared in both bottles.

Identification of isolates

Isolates from positive blood cultures were processed for identification and susceptibility testing on the VITEK® 2 Compact system (bioMérieux, Marcy l'Etoile, France).

Data analysis

All the relevant blood culture and patient data were exported to and analysed within Microsoft Excel 2007 (v12.0.4518.1014). Differences between proportions and ratios (i.e. sensitivity, culture yields) were assessed using a two-proportion *z*-test and *p*-values less than 0.05 were considered statistically significant.

Results

During the 5-year period of analysis, a total of 112,570 blood culture sets were processed, of which 49,438 (43.9%) were PBC and 63,132 (56.1%) were SBC. Among the 63,132 SBC sets, 7.2% were positive (6.5% true-positives and 0.7% contaminants) (Figs. 1 and 2). Among the 49,438 PBC sets, 11.8% were positive (10.9% true-positives and 0.9% contaminants) (Figs. 1 and 2). The *p*-values are both < 0.001 for the difference in overall and true-positivity between SBC and PBC. PBC produced a relative difference of 68% more true-positives than SBC, detecting true bacteraemia or fungaemia in 2164 more patients than would have been found if the SBC positivity rate is used as a reference in the PBC cohort. The description of the true-positive isolates can be seen in Table 1, while the list of contaminants is shown Table 2.

In the 5371 true-positive PBC sets, 5476 isolates were identified (some sets contained multiple isolates). Of these 5476 pathogens, 3597 (65.7%) were Gram-negative bacteria, 1181 (21.6%) were Gram-positive bacteria and 698 (12.7%) were yeast. In the 4095 true-positive SBC sets, 4105 isolates were identified. Of these 4105 pathogens, 3183 (77.5%) were Gram-negative bacteria, 599 (14.6%) were Gram-positive bacteria and 323 (7.9%) were yeast.

Of all true-positive isolates (SBC and PBC), Gram-negatives constituted 70.8%, Gram-positives 18.6% and yeast 10.7%.

The top five organisms isolated across all true-positives were *E. coli* (*n* = 1482) and *S. typhi* (*n* = 1255), followed by *K. pneumoniae* (*n* = 1242), *A. baumannii* (*n* = 728) and *S. aureus* (*n* = 563). These top five constitute 55% of the total true-positives both in PBC and SBC. The most common yeast isolated was *C. tropicalis* (*n* = 297). On analysis of samples obtained from IPD patients, the most common true-positive isolate was *E. coli* (*n* = 1373), followed by *K. pneumoniae* (*n* = 1206). In OPD patients, the most common true-positive isolates were *S. typhi* (*n* = 612) and *S. paratyphi* A (*n* = 278).

Time to positivity (TTP)

Five hundred and ten consecutive blood culture sets with available TTP data were included in the study. The mean TTP was 21.8 h, while the median TTP was 18 h (range: 4–96 h). A TTP histogram is shown in Fig. 3. Ninety-eight percent of positive blood cultures grew within 72 h, 91% within 48 h and 89% within 36 h of bottle placement in the blood culture system.

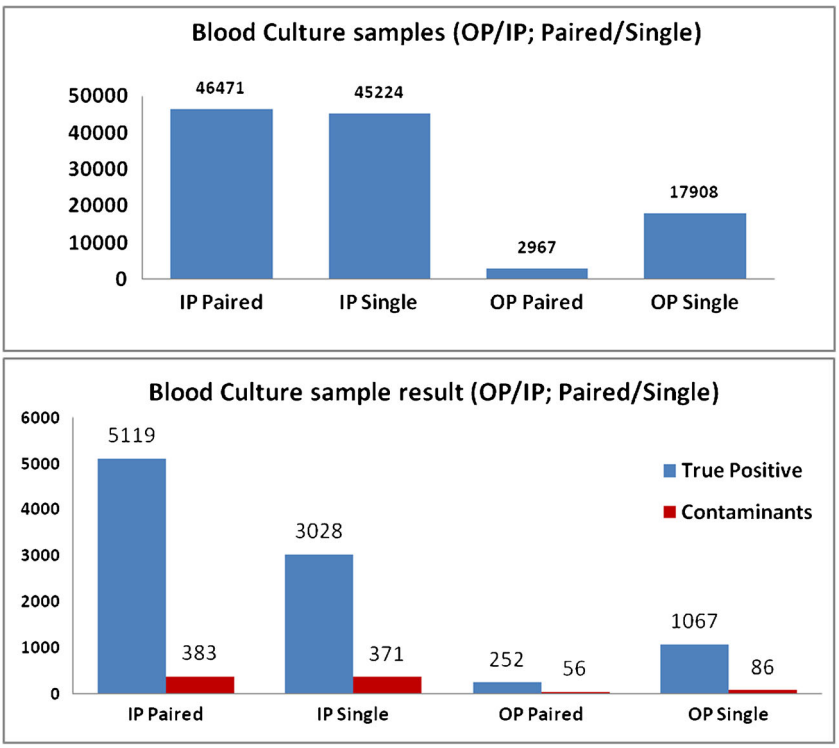

Fig. 1 Blood culture data analysed over a 5-year period (OP/IP; paired/single). OP: outpatient; IP: inpatient; paired: paired blood culture sets; single: single blood culture set

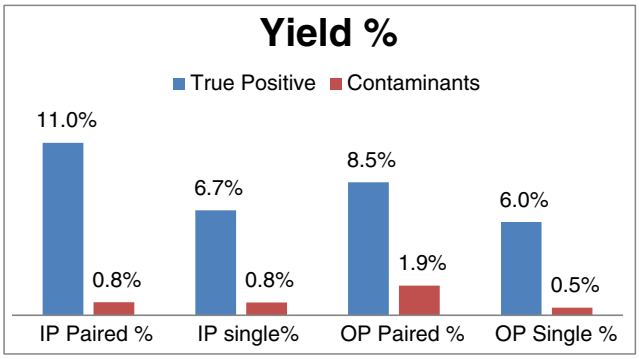

Fig. 2 True-positives and contaminants (OP/IP; paired/single). OP: outpatient; IP: inpatient; paired: paired blood culture sets; single: single blood culture set

In this subgroup analysis, 24 sets grew a *Candida* species. The median TTP for *Candida* (30.5 h) was longer than for bacteria but ranged from 8 to 83 h. Most yeast grew within 48 h.

Blood volume

Our hospital guidelines indicate that the optimal volume of blood per culture bottle should be 8–10 mL in individuals above 12 years of age, 4 mL in children aged 3–12 years, 0.5 mL for newborns up to 1 month of age and 1.0 mL in infants aged 1 month to 3 years. By following the markings on the Bact/ALERT® bottles for blood volume calculation, we determined that, of the 999 consecutive samples in this subgroup analysis, 895 (90%) complied with hospital guidelines.

Discussion

We believe that this current analysis of 112,750 blood culture sets is the single largest study of its kind conducted in India. We previously published a blood culture study in 2012 from one of our hospitals, which was approximately one-tenth of the present sample size [11]. We decided to re-evaluate the practice and yield of blood cultures in our large hospital network, after conducting education aimed at improving the frequency of PBC and the volume of blood obtained.

In the current study, we found a significantly higher yield from PBC compared to SBC, in both inpatients and outpatients. This higher yield in PBC is consistent with the 2004 Cockerill study, which reported the results of a similar study from 163 patients [7].

The study has the limitation that organisms were classified as pathogens or contaminants without performing a patient chart review, and this could have resulted in misclassification of some isolates. Gram-negative non-fermenting rods are increasingly considered as true pathogens in blood cultures and were classified as 'true-positives', as previously documented, for example, with *Acinetobacter* species and *Pseudomonas putida*.

In our study, the overall incidence of fungal bloodstream infections among the true-positive blood culture samples was 10.7%, with diverse species of yeast isolated. Non-*albicans Candida* species accounted for 79.1% of yeast isolates, with *C. albicans* making up 20.9% of this group. This is consistent with other data from India, where non-*albicans Candida* is predominant [12]. One hundred and seventy-nine blood culture sets yielded growth of *C. haemulonii*, as identified in the VITEK® 2 system. All *C. haemulonii* were further characterised by whole-genome sequencing and were identified as *C. auris* at the National Culture Collection of Pathogenic Fungi (NCCPF) at the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. *Candida auris*, a multidrug-resistant species, has recently emerged as an important challenge in the management of patients in intensive care units of India [13].

The total number of organisms isolated in our analysis is larger than the total number of blood culture samples due to cases with polymicrobial bacteraemia. Polymicrobial bacteraemia was found in 115 of the total of 9466 (1.2%) blood cultures analysed. Significantly more polymicrobial growth was seen in PBC (105/5371 or 2.0%) than in SBC (10/4095 or 0.24%).

Out of all true-positive blood culture sets, Gram-negative bacteria were isolated in 70.8%, Gram-positive cocci in 18.6% and yeast in 10.7%. The organism incidence matches similar epidemiological studies from India and south-east Asia [14]. The five most common organisms account for 56.3% of all isolates.

Coagulase-negative staphylococci (CONS) are often blood culture contaminants but, in our series, they made up 2.7% of the true-positive blood cultures. CONS are an increasingly important pathogen, making it important to try and differentiate true CONS bacteraemia from contamination by using PBC and not SBC. Some authorities have suggested that the number of positive bottles in a set is an important factor in determining the clinical significance of CONS in blood cultures. However, Mirrett et al. [15] and Peacock et al. [16] have found that this criterion is unreliable. In our study, among the true-positive CONS isolates, the top three species were identified as *S. haemolyticus*, *S. hominis* and *S. epidermidis*, in decreasing frequency.

Our contamination rate in PBC and SBC (< 1%) is substantially lower than that determined in our earlier study. In our previous study, the contamination rates were 3.25% in PBC and 1.08% in SBC [11]. The target rate of blood culture contamination should be less than 3% [17].

Table 1 True-positives (OP/IP; paired/single). OP: outpatient; IP: inpatient; paired: paired blood culture sets; single: single blood culture set

True-positives	IP paired	IP single	OP paired	OP single	Total
Achromobacter xylosoxidans	15	13	–	1	29
Acinetobacter baumannii	488	213	11	16	728
Acinetobacter lwoffii	52	26	1	10	89
Aeromonas hydrophila	9	5	–	–	14
Burkholderia cepacia	92	45	3	9	149
Chryseobacterium indologenes	33	12	–	3	48
Citrobacter freundii	8	5	1	2	16
Elizabethkingia meningosepticum	79	32	1	–	112
Enterobacter aerogenes	16	10	2	1	29
Enterobacter cloacae	103	69	4	12	188
Escherichia coli	862	511	26	83	1482
Klebsiella oxytoca	10	9	–	2	21
Klebsiella pneumoniae	809	397	7	29	1242
Ochrobactrum anthropi	8	3	–	2	13
Pantoea agglomerans	6	8	–	1	15
Proteus mirabilis	29	15	–	3	47
Pseudomonas aeruginosa	297	161	16	19	493
Pseudomonas putida	16	12	2	2	32
Pseudomonas stutzeri	19	15	1	17	52
Ralstonia paucula	6	9	–	1	16
Salmonella paratyphi A	81	101	49	229	460
Salmonella typhi	202	441	77	535	1255
Serratia marcescens	55	29	3	5	92
Sphingomonas paucimobilis	26	20	2	6	54
Enterococcus faecalis	131	62	7	10	210
Enterococcus faecium	213	142	1	1	357
Enterococcus gallinarum.	20	14	–	–	34
Staphylococcus aureus	320	193	15	35	563
Staphylococcus epidermidis	63	–	–	–	63
Staphylococcus haemolyticus	123	–	–	–	123
Staphylococcus hominis	71	–	–	–	71
Stenotrophomonas maltophilia	101	57	9	15	182
Streptococcus pneumoniae	47	26	–	8	81
Streptococcus pyogenes	12	6	–	1	19
Streptococcus sanguinis	6	3	–	3	12
Candida albicans	146	65	1	1	213
Candida famata	14	4	–	1	19
Candida glabrata	52	19	–	–	71
Candida haemulonii[a]	129	48	2	–	179
Candida krusei	7	18	–	–	25
Candida parapsilosis	91	54	6	2	153
Candida pelliculosa	7	7	–	–	14
Candida rugosa	11	1	–	–	12
Candida tropicalis	206	86	3	2	297
Other true-positives[b]	129	62	6	10	207
Totals	5220	3028	256	1077	9581

[a] Confirmed by the sequencing method as *Candida auris* at the National Culture Collection of Pathogenic Fungi (NCCPF) at the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

[b] *Aeromonas sobria*, *Alcaligenes faecalis*, *Brevundimonas diminuta*, *Burkholderia pseudomallei*, *Chryseobacterium meningosepticum*, *Citrobacter braakii*, *Citrobacter koseri*, *Empedobacter brevis*, *Enterobacter agglomerans*, *Enterobacter gergoviae*, *Enterobacter sakazakii*, *Francisella tularensis*, *Haemophilus influenzae*, *Morganella morganii*, *Myroides* species, *Proteus vulgaris*, *Providencia rettgeri*, *Providencia stuartii*, *Pseudomonas acidovorans*, *Pseudomonas fluorescens*, *Pseudomonas oryzihabitans*, *Ralstonia mannitolilytica*, *Raoultella ornithinolytica*, *Salmonella paratyphi* B, *Serratia fonticola*, *Enterococcus casseliflavus*, *Enterococcus raffinosus*, *Kluyvera ascorbata*, *Leuconostoc* species, *Listeria monocytogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus*, *Streptococcus bovis*, *Streptococcus dysgalactiae*, *Streptococcus equines*, *Streptococcus equisimilis*, *Streptococcus gallolyticus*, *Streptococcus mitis*, *Streptococcus mutans*, *Streptococcus oralis*, *Streptococcus salivarius*, *Streptococcus viridans*, *Candida guilliermondii*, *Candida kefyr*, *Candida lipolytica*, *Candida lusitaniae*, *Candida utilis*, *Cryptococcus neoformans*, *Geotrichum capitatum*, *Kodamaea ohmeri*, *Rhodotorula* species and *Trichosporon asahii*

Blot and colleagues performed one of the earliest studies that documented the clinical utility of TTP [18]. They showed that, because of its inverse association with the risk of mortality, TTP is a useful prognostic indicator among patients with bacteraemia.

Table 2 Contaminants (OP/IP; paired/single). OP: outpatient; IP: inpatient; paired: paired blood culture sets; single: single blood culture set

Contaminants	IP paired	IP single	OP paired	OP single	Total
Moraxella species	6	7	–	2	15
All coagulase-negative *Staphylococcus* (CONS)	363	333	56	65	817
Unidentified coagulase-negative *Staphylococcus* (CONS)	73	112	4	27	216
Staphylococcus haemolyticus	83	75	10	6	174
Staphylococcus hominis	59	51	20	15	145
Staphylococcus epidermidis	64	54	15	12	145
Staphylococcus saprophyticus	33	16	5	1	55
Staphylococcus capitis	17	6	1	3	27
Staphylococcus warneri	9	7	1	–	17
Staphylococcus cohnii	7	6	–	1	14
Diphtheroids	11	10	1	3	25
Micrococcus species	5	19	–	1	25
Streptococcus mitis	9	12	–	2	23
Streptococcus viridans	14	10	–	6	30
Other contaminants[a]	27	13	0	7	47
Totals	417	398	57	86	958

[a] *Acinetobacter haemolyticus*, aerobic spore-bearing bacilli, Neisseriae (non-pathogenic), *Staphylococcus intermedius*, *Staphylococcus auricularis*, *Staphylococcus caprae*, *Staphylococcus chromogenes*, *Staphylococcus sciuri*, *Staphylococcus xylosus*, *Staphylococcus simulans*, *Comamonas testosterone*, *Lactococcus garvieae*, *Streptococcus bovis*, *Streptococcus gallolyticus*

There was a substantial decrease in TTP after the application of resin-based blood culture bottles in the BacT/ALERT® 3D system, as compared to our previous data [11].

We have documented that 90% of the blood samples contained the recommended blood volume as per current guidelines. However, we have not analysed the effect of the volume of blood on the positivity rate in our database. We also did not analyse patients in whom more than two sets were obtained.

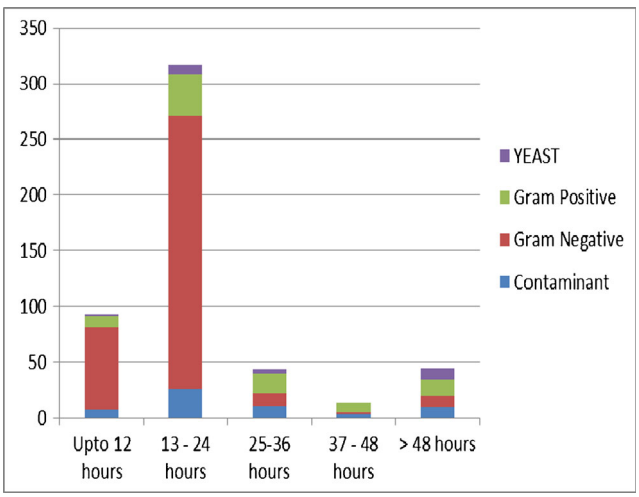

Fig. 3 Time to positivity (TTP) ($n = 510$)

Conclusion

In our large study, paired blood cultures (PBC) has a significantly increased true-positive pathogen yield compared to single blood cultures (SBC). Our study adds to the increasing evidence of higher microbial yield of clinically significant bacteria and yeast by following recommended blood culture practices with respect to performing PBC instead of SBC, adhering to blood volume guidelines and use of continuous-read automated blood culture systems. Earlier and more reliable detection of bacteraemia and fungaemia should have positive and beneficial effects on patient management.

In our study, the contamination rates in PBC and SBC were below the usual contamination rates seen in similar hospital settings in India, suggesting that our continuing education of phlebotomists can decrease contamination rates and improve the recovery rate of clinically significant bloodstream infections.

Automated blood culture and identification methods can reduce the time required for the processing of samples and reporting of results to clinicians, facilitating prompt diagnosis and treatment and avoidance of unnecessary additional testing and associated costs. Automation in clinical microbiology also has a positive impact on patient care by improving specimen traceability, reproducibility and quality.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

Ethical approval from institute Approved.

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