Original research article

COMPARATIVE EVALUATION OF BLOOD CULTURE BY CONVENTIONAL METHOD AND BACTEC USING BLOOD SAMPLES OF ICU PATIENTS & ANTIBIOGRAM OF ISOLATED PATHOGENS

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Abstract

Introduction: Sepsis is the leading cause of death in Intensive ICU patients worldwide.Blood cultures are the 'gold standard' for identifying pathogens causing septicemia and in directing appropriate antibiotic therapy.The present study was aimed to compare sensitivity of automated BACTEC 9120 blood culture system & conventional blood culture method in identifying true pathogenic organism, to compare the time needed for the detection of microorganisms by conventional method of blood culture and by automated BACTEC 9120 blood culture system and to evaluate the susceptibility pattern of antibiotics for pathogens isolated.

Material and Methods: Study was done over a period of one year from April 2015 to March 2016. A total of 636 blood samples were collected &subjected to blood culture by BACTEC 9120 and conventional method. The statistical tests applied were Sensitivity, Specificity, Positive predictive value, Negative predictive value, T-test & kappa statistics.

Results: Out of 636 blood samples clinically significant isolates were recovered from 85 samples by BACTEC, of which 74 were bacterial pathogens and 11 were candida. In conventional method out of 80 significant isolates 69 were bacterial and 11 were candida. Gram positive (majority Staphylococci) were more commonly isolated than Gram negative (majority Acinetobacter and E.coli). Mean time to detect was 19.47 hours and 3.02 days, by BACTEC 9120 and conventional method respectively. Vancomycin, Teicoplanin and Linezolid were found to be the most effective (100%) for gram positive bacteria and for gram negative bacteria Colistin (70-100%), Polymyxin-B (70-100%) were the most effective.

Conclusion: Sepsis is associated with prolonged hospital stay, increased costs & with a high mortality. The use of BACTEC BD blood culture system is better for rapid identification of blood borne pathogens followed by determining actual antimicrobial treatment in the scenario of multi drug resistance so as to improve patient's outcome.

Keywords: BACTEC 9120, Conventional blood culture, Sepsis, Antibiotic sensitivity and resistance.

INTRODUCTION

Blood stream infections (BSI) cause significant morbidity and mortality worldwide and are among the most common healthcare associated infections. Currently, such infections are the 13th leading cause of death and over the past two decades the age-adjusted rate from septicemia has risen by 78%.[1,2] Currently, slightly more than 50% of BSIs are hospital acquired i.e. nosocomial infections.[3,4]

Microorganisms present in the circulating blood, whether continuously, intermittently, or transiently, are a threat to every organ in the body. Microbial invasion of the bloodstream can have serious immediate consequences, including shock, multiple organ failure, disseminated intravascular coagulation (DIC), and death. Approximately 200,000 cases of bacteremia occur annually, with mortality rates ranging from 20% to 50%.[5]

Nowadays, bacterial drug resistance is an important problem and due to wide variations in bacterial drug resistance, results of studies and reports in one region or in one period of time are not necessarily true for other regions or period of time. They are related with a series of social, environmental and technological changes.[6] Rational and correct use of antimicrobial agents requires understanding of common pathogens and drug resistance patterns in the region.[7] Due to constantly evolving antimicrobial resistant

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patterns there is need for constant antimicrobial sensitivity surveillance. Determination of antibiotic sensitivity patterns at periodic intervals is mandatory in each region for the clinicians to be aware of the emerging pathogens that pose a threat to the community, to provide safe and effective empirical therapies, develop rational prescribing practices and make policy decisions in a hospital and finally assess the effectiveness of all.[8]

Sepsis is the leading cause of death in Intensive ICU patients worldwide.In a survey conducted in eastern India, severe sepsis (sepsis with organ dysfunction) constituted 17% of all admissions to the ICU. This cohort carried a very high mortality of 45%.[9] Early administration of an appropriate antimicrobial regimen in infected patients is associated with a better outcome andhence early diagnosis of bacterial infection is of primary importance. However some patients with an infection have minimal or even no symptoms or signs. Not all patients who appear septic demonstrate an infection, and the widespread administration of antibiotics to all these patients carries problems of antibiotic resistance, drug toxicity and increased medical costs.

Blood cultures are vital and are still considered to be the 'gold standard' and are most frequently used method to diagnose blood stream infections caused by bacteria and in directing appropriate antibiotic therapy.

Rapid diagnosis, timely and appropriate emperic treatment are crucial to the outcome of sepsis. Various commercial and automated systems for blood culture have been designed to enable rapid recovery of microorganisms. These systems vary in techniques used for detecting microbial growth, the types of broth media and media supplements available for use with each system, bottle atmospheres, the blood-to-broth ratio, the volume of blood to be inoculated and the use of shakers or agitation for aerobic bottles The introduction of automated laboratory systems such as the blood culture systems BACTEC (BectonDickinson, Franklin Lakes, NJ, USA) and BacT/Alert (bioMérieux, Marcy l'Etoile, France) have increased the sensitivity and efficiency of the detection of microorganisms.

Many studies have been done to evaluate a variety of commercially available blood culture systemsbut which of these systems is optimal for the isolation of a wide variety of microorganisms for a particular medical institution depends on various factors like financial resources, number of samples to be processed per day or the patient load & space provided for microbiology laboratory set-up.

MATERIALAND METHODS

This prospective study was conducted in Department of Microbiology on the patients of Intensive Care Unit of Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, U.P. a tertiary care hospital. Study was done over a period from April 2015 to March 2016. A Total of 636 samples were collected.

Inclusion Criteria

- Blood samples of critically ill patients admitted in ICU with suspicion of sepsis, with consent of patient or the attendant.
- Patients age >14 years.

Exclusion Criteria

- Blood samples of patients ≤ 14 years of age.
- Patients or their attendants who did not give consent.
- Patients not suspected of sepsis.
- Patients entering the ICU for short term post-operative observation.
- Moribund patients.

Sample: Blood samples (5-10 ml) were collected with aseptic precaution, and equally distributed to 2 study receptacles (the BACTEC Plus Aerobic/F resin bottle [Becton Dickinson] and the conventional broth based blood culture bottle containing 50 ml of Brain Heart Infusion broth. Bacteria isolated by both/single method of blood culture for each patient were subjected to identification with help of colony morphology, Gram staining and biochemical tests.

Antibiotic Susceptibility Testing: Antibiotic sensitivity testing were put up for bacterial isolates recovered by BACTEC 9120 by Kirby Bauer disc diffusion method using CLSI guidelines.

RESULTS

The blood samples from 636 patients after meeting the inclusion and exclusion criteria constituted the material for study and were evaluated by blood culture by both BACTEC and conventional method.

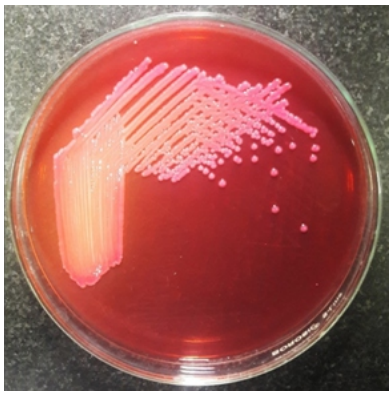

Fig.-1 : Colony shown on MacConkey agar after sub culturing from blood culture bottle

Among the 636 patients included in the study, there were 390 (61%) males and 246 (39%) females.

Total 18 (2.8%) blood cultures were judged to be contaminated, 11 were found in BACTEC and 18 in the conventional method. These isolates included Micrococci, Aerobic Spore-bearing Bacilli and Diphtheroids. (Fig.-1)

The blood cultures that were judged to be contaminated, in BACTEC ten were Micrococci and one was Diphtheroid. In conventional blood culture, 11 were micrococci, 7 were Aerobic Spore-bearing Bacilli and 1 Diphtheroid. There was no such contaminant which was isolated only in the BACTEC system and not in conventional blood culture.

Out of 636 blood samples, significant pathogenic isolates were recovered from 85 (13.3%) samples by BACTEC 9120 and from 80 (12.6%) samples by conventional blood culture. Out of these significant pathogenic isolates, Candida species were isolated in 11 samples by both BACTEC system and conventional blood culture (Fig.-2). Which constitutes 1.7% of the total number of samples processed and 12.9% of the significant pathogenic isolates. Out of these 11 Candida isolates, 3 were Candida albicans and 8 were Non-albicans Candida which included C.guilliermondii, C.tropicalis and C.intermedia.

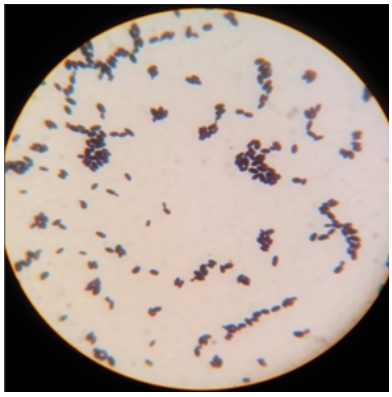

Fig.-2: Budding yeast cells (Candida) as seen on Gram staining done from subculture.

Out of 636 blood samples clinically significant bacterial isolates were recovered from 74 (11.6%) samples by one or both methods, of which 69 (10.8%) isolates were by both methods; however, for 5 samples (0.8%), growth was detected only with BACTEC system and not by the conventional blood culture. There were no bacterial isolates for which growth was detected with only conventional culture method and not by the BACTEC system.

Among the 74 positive cases found by BACTEC, 15% were between 15-30 years, 15% were between 31-45 years, 28% were between 46-60 years & 42% were of >60 years of age.

Among the 69 positive cases found by conventional blood culture method, 14.5% were between 15-30 years, 14.5% were between 31-45 years, 26% were between 46-60 years and 45% were of >60 years of age.

Out of 74 clinically significant bacterial isolates recovered by BACTEC system, 28 (38%) were gram positive and 46 (62%) gram negative bacteria. Out of 69 clinically significant isolates recovered by conventional blood culture method, 24 (35%) were gram positive and 45 (65%) gram negative isolates. (Fig.-3)

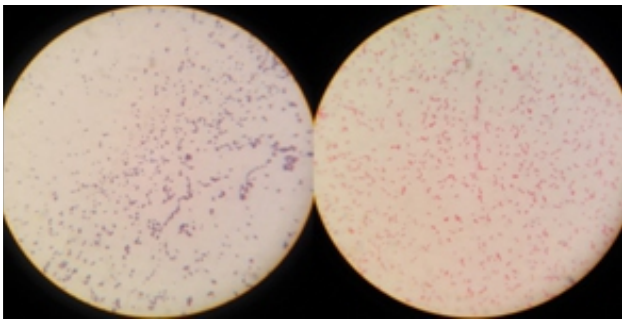

Fig.-3: Gram positive cocci and Gram negative bacilli as seen on Gram staining done from subculture.

Out of 74 culture positive cases, 3 were polymicrobial. In each of these 3 cases Candida species was isolated along with a bacterial isolate which included S.aureus, E.faecalis and P.aeruginosa.

Among 28 Gram positive isolates recovered by BACTEC, 22 (78%) were Staphylococcus aureus, 5 (18%) were Enterococcus faecalis and 1 (4%) was Coagulase Negative Staphylococcus aureus. Among 24 Gram positive isolates recovered by conventional blood culture, 19 (79%) were Staphylococcus aureus, 4 (17%) were Enterococcus faecalis & 1 (4%) was Coagulase Negative Staphylococcus aureus. (Table-1)

Among 46 Gram negative isolates recovered by BACTEC, 15 (33%) were Escherichia coli, followed by 10 (22%) Pseudomonas aeruginosa, 9 (19%) Acinetobacter baumannii, 7 (15%) Acinetobacter lwoffii, 4 (9%) Klebsiella pneumoniae and 1 (2%) Citrobacterfreundii.

Table-1: Gram positive isolates

ORGANISMS	BACTEC n (%)	Conventional n (%)
Staphylococcus aureus	22 (78%)	19 (79%)
Enterococcus faecalis	5 (18%)	4 (17%)
CONS	1 (4%)	1 (4%)
TOTAL	**28 (100%)**	**24 (100%)**

Among 45 Gram negative isolates recovered by conventional blood culture, 14 (31%) were Escherichia coli, followed by 10 (22%) Pseudomonas aeruginosa, 9 (20%) Acinetobacter baumannii, 7 (16%) Acinetobacter lwoffii, 4 (9%) Klebsiella pneumoniae and 1 (2%) Citrobacter freundii. (Table-2)

Table-2: Gram positive negative

ORGANISM	BACTEC n (%)	Conventional n (%)
Escherichia coli	15 (33%)	14 (31%)
Pseudomonas aeruginosa	10 (22%)	10 (22%)
Acinetobacter baumannii	9 (19%)	9 (20%)
Acinetobacter lwoffii	7 (15%)	7 (16%)
Klebsiella pneumoniae	4 (9%)	4 (9%)
Citrobacterfreundii	1 (2%)	1 (2%)
TOTAL	**46 (100%)**	**45 (100%)**

After 48 hours (day 2) the BACTEC 9120 system had recovered 93% of the total significant isolates while the conventional system recovered 57% only.

The average time to positivity (TTP) taken by BACTEC 9120 for gram-positive bacteria and gram-negative bacteria in this study were 20.82 hours and 18.13 hours respectively and the average time to positivity for all the organisms was 19.47 hours.

The average time to positivity taken by conventional blood culture for gram-positive bacteria and gram-negative bacteria in this study were 3.25 days and 2.80 days respectively and the average time to positivity for all the organisms was 3.02 days.

Therefore the mean time to positivity of significant bacterial pathogens was significantly less with the BACTEC 9120 than with conventional blood culture.

Antibiotic sensitivity testing were put up for bacterial isolates recovered by BACTEC 9120 by Kirby Bauer disc diffusion method using CLSI guidelines. The culture from peptone water were streaked on Mueller-Hinton agar (MHA) by lawn culture method and antibiotic discs were placed on inoculated MHA plates. The sensitive and resistant pattern for each antibiotic was noted after overnight incubation.

The Sensitivity, Specificity, Positive Predictive value and Negative predictive value of BACTEC 9120 was found to be 100%, 99%, 93.24% and 100% respectively against conventional blood culture.

BACTEC 9120 was hence observed to be sensitive (100%) as compared to conventional blood culture (93.24%).

On applying T-test for comparison of time to detection by BACTEC and conventional blood culture, following values were obtained:

T value was 13.67522162. Mean value for BACTEC was 18.95652174 and for conventional blood culture was 69.56521739 and the P value was <0.01 which is significant.

On applying Kappa as a measure of concordance between BACTEC 9120 and conventional blood culture (Kappa with linear weighting):

- Observed kappa value was 0.9606.
- Standard error was 0.0175.
- Confidence interval was 0.95.
- Lower and upper confidence limit was 0.9262 and 0.995.

Hence the agreement for detection of pathogenic bacterial isolates, between BACTEC 9120 and conventional blood culture is 0.96 which is significant.

DISCUSSION

The term 'sepsis' is used to define systemic inflammatory response to an infectious agent (bacterial, fungal, viral or parasitic). When managing septic patients, early diagnosis of the infection is the element which has the greatest impact on clinical course, treatment and patient survival. The unfavorable prognosis of patients with sepsis is partly due to delayed diagnosis.

Out of 636 cases included in the study 42% and 45% of the positive cases were detected in age group of >60 yearsby BACTEC and conventional method respectively.The percentage of positive blood cultures obtained, increased as

the age of patients from whom samples have been obtained, increased. This indicates the decrease in the strength of immune system and hence greater susceptibility to infections with increasing age.

The more number of male patients over females in this study might be due to the fact that males are the active and main earning member of most of the families till now, so they are more privileged to visit physician's chamber for treatment.The observations noted above are in concordance with Guidet and associates in their study on sepsis and organ dysfunctions who observed that the incidence of sepsis steeply increased above the age of 50 years and more frequently involving men.[10] Silva et al. also found that the mean age for patients with sepsis was 65.2 years with 58.7% of them being males.[11]

Out of 636 samples included in the study, 540 samples showed no growth of any microorganism by BACTEC and 538 samples showed no growth of any microorganism by conventional blood culture after 5 days and 7 days of incubation respectively. These were reported as negative for culture.

On identification of the microorganisms it was found that, in BACTEC blood culture 11 (1.7%) were contaminants

while 85 (13.3%) showed true pathogens. For conventional blood culture, 18 (2.8%) were contaminants while 80 (12.6%) showed true pathogens. Of the 18 (2.8%) blood cultures that were judged as contaminated, 11 were found in both systems (in 10 samples micrococci and in 1 sample diphtheroids), none in the BACTEC only and in 7 samples ASB, in the conventional method only. These probable contaminants were excluded from the analysis of positive cultures to define more precisely the performance of the BACTEC and conventional systems.

The blood cultures with significant pathogenic isolates were analyzed by gram staining and it was found that, out of 85 (13.3%) positive blood cultures by BACTEC, 11 were Candida, 28 were Gram positive and 46 were Gram negative bacteria. Out of 80 (12.6%) positive blood cultures by conventional method, 11 were candida, 24 were Gram positive and 45 were Gram negative bacteria. Out of these 11 Candida isolates, 3 were Candida albicans and 8 were Non-albicans Candida which included C.guilliermondii, C.tropicalis and C.intermedia. This shows the increased incidence of Non-albicans Candida than C.albicans in blood stream infections.

Out of the 74 pathogenic bacterial isolates recovered by BACTEC 38% (28) were Gram positive and 62% (46) were Gram negative. Out of the 69 pathogenic bacterial isolates recovered by conventional blood culture 35% (24) were Gram positive and 65% (45) were Gram negative. These results are consistent with the study done by Durmaz et al. who reported more Gram negative isolates than Gram positive isolates.[12]

Clinically significant bacterial isolates were recovered from 74 (11.6%) specimens by one or both methods of which 69 isolates were recovered by both methods, 5 in BACTEC only and none in the conventional system only ($P < 0.01$). In a similar study by Cetin ES et al[13] out of a total of 412 specimens, clinically significant microorganisms were isolated from 41 specimens (10%) by both the BACTEC blood culture system and conventional culture methods; however, for 62 specimens (14.9%), growth was detected only with the BACTEC system, although no growth was noted on conventional media. No isolates were detected with only conventional culture methods when no growth was seen in the blood culture system.

Out of 74 culture positive cases, 3 were polymicrobial. In each of these 3 cases a Candida species was isolated along with one bacterial isolate which included S. aureus, E. faecalis and P. aeruginosa.

Among the true bacterial pathogens isolated, Staphylococcus aureus was found in maximum number of cases, both, among the gram positive bacterial isolates and also among all the pathogenic bacterial isolates i.e. 22 by BACTEC and 19 by conventional method.

Second most common was Acinetobacter species among Gram negative and among all the bacterial isolates i.e. 16, by both, BACTEC and conventional method. These Acinetobacter isolates included both the species i.e. baumannii and lwoffii. But if individual species are taken into account then second most common bacterial isolate was E.coli among Gram negative and also overall.

Acinetobacter species has emerged as an important nosocomial pathogen that is often multidrug resistant and associated with life-threatening infections. A. baumannii, a clinically important species of Acinetobacter, has a tendency toward cross-transmission, particularly in ICUs where numerous outbreaks are encountered. A study done by Sofianou et al found gram-negative bacteria (83.2%), were predominant organism in ICU with a high proportion of Acinetobacter spp.[14] (35%) resistant to commonly used antimicrobial agents. In another study by Prashanth et al shows Acinetobacter baumannii accounted for 41.8% of all the infections.[15] These studies similar to our study which shows the higher prevalence of Acinetobacter species in ICU as compared to other gram negative bacteria.

In present study, maximum isolates of gram positive bacteria were Staphylococcus aureus [22 (78%) by BACTEC and 19 (79%) by conventional] followed by Enterococcus faecalis [5 (18%) by BACTEC and 4 (17%) by conventional] and coagulase negative Staphylococcus [1 (4%) by both BACTEC and conventional]. While gram negative bacteria comprised mainly of E.coli [15 (33%) by BACTEC and 14 (31%) by conventional] followed by P.aeruginosa [10 (22%) by both BACTEC and conventional method], Acinetobacter baumannii [9 (19%) by BACTEC and 9 (20%) by conventional method] , A.lwoffii [7 (15%) by BACTEC and 7 (16%) by conventional method], Klebsiella pneumoniae [4 (9%) by both BACTEC and conventional method] and Citrobacterfreundii [1 (2%) by both BACTEC and conventional method].

In the present study CoNS constituted 4% of the significant bacterial isolates which is similar to the study done by Poudel P et al. in which CoNS constituted 5% of the total isolates.[16]

The clinical significance of CONS when isolated from blood cultures should always be evaluated. Some studies have reported that up to 85% of CONS represent

contamination rather than true bacteremia.[17] However, in recent years, CONS have become an important nosocomial pathogen partly because of the increasing use of medical devices such as long term indwelling catheters, vascular grafts, and prosthetic heart valves and joints.[18] The results of this study were similar to a study done by Chimese MS etalaccording to which the most commonly isolated organism was found to be Staphylococcus aureus (25%) which is same as in our study.

Differences in secular trends in microorganisms isolated from blood have occurred over the past few decades. For example, notable differences in genera of bacterial pathogens and increased frequencies of yeasts are noted when this study is compared with that of Weinstein et al[19] and Cockerill et al[20]. In Weinstein's study E.coli was the most common isolate among all, followed by S.aureus, S.pneumoniae, K.pneumoniae, P.aeruginosa, Bacteroidesfragilis group, Enterococcus spp., group A Streptococci, Candida albicans and Non-albicans candida, in the decreasing order. In a study conducted by Cockerill et al., from 1984 to 1988, S.aureus was found to be the most common pathogenic isolate, followed by E.coli, Candida albicans, CoNS, P.aeruginosa, Enterococcus species, K.pneumoniae, Serratiamarcescens, S.pneumoniae and E.cloacae in the decreasing order and from 1989 to 1992, S.aureus was the most common pathogenic isolate, followed by E.coli, CoNS, Candida albicans, Enterococcus species, P.aeruginosa, K.pneumoniae, S.pneumoniae, Viridans group of streptococci and E.cloacae in decreasing order.19 In a study done by Gul Durmaz et al. from August 1996 to December 2001, CoNS was most common isolated followed by Candida, S.aureus, K.pneumoniae, P.aeruginosa, E.coli and Acinetobacter in the decreasing order.[12]

When time to positivity was compared, the mean time to positivity taken by BACTEC 9120 for the isolated pathogens was 19.47 hours and by conventional blood culture was 3.02 days. Therefore the mean time to positivity was significantly less with the BACTEC 9120 than with conventional blood culture.

Among the many antibiotics tested for gram positive bacteria vancomycin, teicoplanin and linezolid were found to be the most effective (100%) and for gram negative bacteria colistin (70-100%), polymyxin-B (70-100%), carbapenems (imipenem and meropenem) and cefoperazone+sulbactam were the most effective in this geographical region. Amikacin remains the principle antibiotic of choice based on its effectiveness on both gram positive and gram negative bacteria. Among the least effective antibiotics for gram positive bacteria were oxacillin, azithromycin and co-trimoxazole. 3rd and 4thgeneration cephalosporins and amoxycillin-clavulanic acid were found to be least effective for Gram negative.

Thus multidrug resistant bacterial species are a gigantic problem in the hospital setup. These infections are likely to affect the outcome in critically ill patients who require prolonged hospitalization. Further, more clinical studies are needed to identify causes for their multi drug resistant development, the economic impact of these infections, as well as to determine the most efficacious antimicrobial regimens and duration of therapy to maximize the outcome of these infections. This calls for stringent preventive measures which includes strict infection control practices and judicious use of antibiotics.

CONCLUSION

Sepsis is associated with prolonged hospital stay, increased costs & with a high mortality. The use of BACTEC BD blood culture system is better for rapid identification of blood borne pathogens followed by determining actual antimicrobial treatment in the scenario of multi drug resistance so as to improve patient's outcome.

Future Directions: Future generations may look back on blood cultures and antimicrobial therapy as halfway

technologies. Already, a variety of non-culture-dependent methods for demonstrating bacteremia exist. We can anticipate that someday a "microbial detection system" will screen blood specimens for all known microorganisms and thus eliminate the need for presumptive (as opposed to precise) therapy. Physical removal of microbes from the bloodstream, as opposed to killing the microbes with drugs, is already being discussed. Yet the ultimate strategy will always be prevention.

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