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ROLE OF SURVEILLANCE CULTURE IN MANAGEMENT OF NEUTROPENIC PATIENTS

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ABSTRACT

Context: Infections with Multi-drug resistant (MDR) organisms are often associated with increased morbidity and mortality in neutropenic children suffering from various cancers and undergoing chemotherapy. **Aims**: To assess the presence of MDR bacteria in stool specimen of children who were suffering from various cancers and were admitted for management to the hospital, in order to guide an earlier appropriate antimicrobial therapy. **Methods and Material**: The study involved pediatric patients of either sex diagnosed with different carcinomas treated at our hospital from June 2018 to January 2019. Stool cultures were sent within 72 hr of hospital admission and other cultures were sent when clinically indicated. MDR was defined as resistance of organism to >=3 classes of antibiotics. **Results:** A total of 55 stool surveillance samples from 50 pediatric patients showed presence of 67.14% MDR organisms. MDR E. coli was isolated at highest frequency. Equal prevalence of MDR organisms amongst both the sexes was observed (χ 2 = 0.96, P- value= 0.33). Blood cultures showed presence of both Gram positive and Gram-negative organisms. UTI was seen in 11 patients and 13.46% of MDR organisms were isolated from urine. Catheter tip culture isolated gram negative MDR organism. Very low concordance of 0% and 1.8% was found in blood culture and urine culture respectively with that of stool culture in isolation of same bacterial etiological agent. **Conclusion**: We do not recommend practical use of stool surveillance culture for management of febrile neutropenic patients. Studies are urgently needed to characterize in greater detail the exact colonisation rates in this population so that appropriate infection control, antimicrobial stewardship and treatment protocols can be implemented.

KEYWORDS: Neutropenic, Surveillance, Stool, Children, management.

INTRODUCTION

Improvement in supportive care strategies has played a major role in making the treatment of childhood cancers a success story. Delivery of highly myelosuppressive chemotherapy regimens has been made possible by prompt handling of the infective complications with empirical broad-spectrum antibiotics. The recent increase in the incidence of multidrug-resistant organisms (MDRO) has made the choice of empirical antibiotics difficult and limited. Infection with MDRO is associated with high mortality, jeopardizing our ability to deliver intensive chemotherapy, necessitating appropriate Infection Prevention and Control (IPC) measures and antibiotic stewardship.[1] Febrile Neutropenia (FN) in children treated for malignancy is a common and direct sequela of chemotherapy. Episodes of FN can be life-threatening, and demand prompt recognition, assessment and treatment with broad spectrum antibiotics. While in the majority of episodes no causal infection is identified, 10 to 20% are secondary to a bloodstream infection (BSI).[2]

In patients with haematological malignancies, bacterial infections represent a common complication because of immunosuppression related to disease or therapy, which often causes neutropenia and mucositis. MDRO infections represent an emerging problem in this patient cohort, with up to 45% mortality.[3]

After HD chemotherapy, patients undergo a period of severe neutropenia lasting up to 2 weeks. During this time, nearly 80% of the patients develop fever.[4] Bloodstream infections (BSI) occur in nearly 20% of the patients during neutropenia.[5] and are associated with higher mortality.[6]

Cancer patients are vulnerable to infections, including those with extended-spectrum β-lactamase producing Enterobacteriaceae (ESBL-PE), and most of these infections are associated with colonisation of the gastrointestinal tract. This is particularly concerning in the setting of cancer, as cytotoxic chemotherapy alters the gut microbiome and destroys the mucosal barrier[7]

Colonisation was defined as isolation of ESBL-PE from a rectal or faecal sample without evidence of gastrointestinal infection. This is important because colonisation was associated with an almost 13 times higher risk for developing BSI with ESBLPE. Screening measures should be evaluated to identify their clinical benefit in patients with malignancy.[8]

Active surveillance cultures allow early identification of MDRO carriers, for timely implementation of contact precautions to limit person-to-person spread.[9,10] Rectal surveillance cultures are most appropriate as Enterobacteriaceae are routine colonizers of the gastrointestinal tract, with the potential of gut-translocation causing blood-stream infections during the periods of immunosuppression.[11, 12]

MATERIALS AND METHODS

This single centre study evaluated data of 50 paediatric patients (<18 years of age) of either sex under care of Hematology-Oncology Department, diagnosed with neoplastic disorder having Absolute Neutrophil Count below 500 cells/µl. The study was carried out for a period of 8 months from June 2018 to January 2019.

The study was carried out in Department of Microbiology.

1. Surveillance culture

i. Rectal swabs and stool cultures were sent form admitted patients as part of active surveillance.
ii. The samples were cultured on UTI Chrome Agar and 5% Sheep blood agar plates followed by overnight incubation at 37°C.
iii. The bacteria from the sample were identified by the routine biochemical reactions
- Gram negative Bacteria- Indole, Citrate, Urease, Triple sugar iron test, Oxidase;
- Gram posistive Bacteria - Catalase, Coagulase, Bile esculin.

iv. Species identification was done by Automated Identification and Sensitivity System VITEK 2C, BioMérieux, Nürtingen, Germany.
v. Antibiotic susceptibility testing was performed according to Clinical and Laboratory Standards Institute guidelines 2018 using VITEK 2C and/or antibiotic Kirby Bauer disc diffusion method. Choice of antibiotic disks used was determined by Clinical and Laboratory Standards Institute (CLSI) guidelines 2018.

2. Blood culture

Blood specimen was taken with every fever episode and inoculated into culture bottles (BD BACTEC Peds Plus Aerobic/F and Mycosis IC/F, Becton Dickinson, Heidelberg, Germany).

3. Urine culture

Processing of specimen
• Culture: Done on 5 % Sheep Blood Agar and UTI agar
• Inoculation:

i. To evaluate the clinical significance of a growth in urine culture, estimation of the number of organisms present per ml of urine is essential.
ii. Well-mixed, un-centrifuged, undiluted urine was cultured on to BA and UTI Agar using a pipette that delivers 0.001 ml.
iii. All the inoculated plates were incubated aerobically at 37ºC.

• interpretation of counts: The significance of a positive urine culture is most reliably assessed in terms of the number of colony forming units (viable bacteria) present in the urine. The following was offered as a guide for midstream clean catch urine.
•<1000 CFU/ml INSIGNIFICANT bacteriuria; UTI-unlikely
• 1000- 100,000 CFU/ml PROBABLY SIGNIFICANT bacteriuria; UTI probable
• 100,000 CFU /ml SIGNIFICANT bacteriuria; UTI certain

For SPC, PCN and cystoscopic specimens, any CFU is significant irrespective of number.

4. CATHETER TIP CULTURE

• Processing of the sample
The tip was incubated in Brain Heart Infusion broth for 18-24 hours.
• Culture:
i. The broth was centrifuged and sediment was inoculated on UTI Chrome Agar and Sheep blood agar plates followed by overnight incubation.

• Identification of isolates
i. The bacteria from the sample were identified by the routine biochemical reactions.
ii. Species identification was done by Automated Identification and Sensitivity System VITEK 2C, bioMérieux, Nürtingen, Germany.

• Susceptibility testing of isolates:
ii. Antibiotic susceptibility testing was performed according to Clinical and Laboratory Standards Institute guidelines 2018 using VITEK 2C and/or antibiotic Kirby Bauer disc diffusion method.

RESULTS

Fifty (50) neutropenic paediatric patients under the age of 18 years undergoing chemotherapy were included in our study, of whom 31 (62%) were male and 19 (38%) were females.

Table 1: **Distribution Of Study Population Depending On The Diagnosis.**

Diagnosis	Male (%)	Female (%)	Grand Total
Lukaemia	24 (77.41%)	13 (68.42%)	37 (74.0%)
Lyphoma	2 (6.45%)	-	2 (4.0%)
Sarcoma	1 (3.22%)	4 (21.05%)	5 (10.0%)
Others	4 (12.90%)	2(10.52%)	6 (12.0%)
Grand Total	31 (62%)	19 (38%)	50 (100.0%)

The most common diagnosis was observed to be leukaemia with 37 patients (74.0%), followed by sarcoma with 5 patients (10.0%). Two patients (4.0%) had lymphoma and six patients (12%) were diagnosed with other type of cancer such as neuroblastoma, teratoma, multisystem LCH, SCID.

Table 2: Geographical Distribution Of Study Population.

Parts Of India	Number Of Patients	Percentage
East	1	2%
West	40	80%
North	8	16%
South	1	2%
Grand Total	50	100%

Since the study institute was located in western region of India i.e. Mumbai, 80% of the study population were from western region followed by 16% study population from north and 2% study population each from east and south region of India.

Table 3: Chemotherapy Drugs Used In Primary Treatment Of Study Population.

Drugs	Leukemia (%)	Lymphoma (%)	Sarcoma (%)	Neuroblastoma (%)	Lch (%)	Teratoma (%)
6-Mp	6.5					
Asparginase	11.7					
Bleomycin						33.3
Cytarabine	3.9	25				
Cyclophosphamide	3.9			75		
Cisplatin			18.2			
Carboplatin	1.3					33.3
Daunorubicin	9.1		18.2			
Doxorubicin	1.3		9.1			
Dexamethoxazone	3.9					
Etoposide	1.3		9.1			33.3
Fludarabine	2.6					
Fosfamide			9.1			
Idarubicin	2.6					
Leucovorin	11.7	25	9.1			
Mitoxanthrone	1.3					
Methotrexate	20.8	50	9.1			
Mesna	2.6		9.1			
Vincristine	14.3		9.1	25		
Vinblastine	1.3				50	

Study population diagnosed with Leukaemia(n=37) were treated with methotrexate (20.8 %), Vincristine (14.3%), Leucovorin (11.7%), Asparaginase (11.7%) and others. Population diagnosed with lymphoma (n=2) were treated with Methotrexate (50%), Cytarabine (25%) and Leucovorin (25%). Sarcoma was treated with Cisplatin (18.2%), Daunorubicin (18.2%) and others. Cyclophosphamide (75%) and Vincristine (25%) was used as chemotherapeutic regime for treating neuroblastoma (n=2). Multisystem LCH was treated with Vinblastine (50%) and teratoma had therapeutic regime of 33.3% each of Bleomycin, Carboplatin and Etoposide.

Table 4: Organisms Isolated From Surveillance Stool Culture.

Organism Isolated	MDR	NON-MDR	Grand Total
Acinetobacter baumanii	-	1	1(1.42%)
Citrobacter koseri	1	4	5(7.14%)
Escherichia coli	30	8	38(54.28%)
Enterobacter aerogenes	1	-	1(1.42%)
Enterococcus species	1	-	1(1.42%)
Klebsiella oxytoca	1	1	2(2.85%)
Klebsiella pneumoniae	12	6	18(25.71%)
Proteus mirabilis	-	1	1(1.42%)
Serratia liquefaciens	1	-	1(1.42%)
Shigella sonnei	-	1	1(1.42%)
Candida gullermondi	-	1	1(1.42%)
Grand Total	47(67.14%)	23(32.86%)	70

Total 55 stool samples were received from 50 patients for surveillance study yielding 70 isolates out of which 47 (67.14%) were found to be multiple drug resistant organism being resistant to more than equal to 3 classes of drugs and 23 isolates (32.86%) were not multi drug resistant organism . Escherichia coli was found to be common isolate from the specimen with a frequency of 38 54.28% out of which 30 were MDR and 8 were Not MDR followed by Klebsiella pneumoniae with a frequency of 18 (25.71%) out of which 12 were MDR and 6 were Not MDR. Citrobacter koseri isolated at a frequency of 5 (7.14%) had 4 Not MDR and 1 MDR. 1.4% each MDR isolated from the sample were EnterococcuS aerogens, Enterococcus spp and Serratia liquefaciens whereas 1.4% Not MDR isolated were Acinetobacter baumanii, Candida gullermondi, Proteus mirabilis and Shigella sonnei.

Antimicrobial susceptibility of E. coli isolated from stool for Tigecycline, Colistin, Amikacin, Meropenem, Gentamicin, Aztreonam and BL/BLI combinations was 100%, 100%, 76%, 63%, 58%, 15% and 23% respectively. Klebsiella pneumoniae isolated from stool showed 100% susceptibility to Colistin, 78% to Tigecycline, 44% to Amikacin, 33% to Ertapenem followed by 22% to Aztreonam and 16% to BL/BLI combination. Citrobacter koseri showed 100% susceptibility towards Aminoglycosides, Tigecycline, Colistin, followed by 80% for Meropenem and Piperacillin Tazobactam, 60% for Ciprofloxacin and Co-trimoxazole followed by 40% for Aztreonam.

One isolate of Candida guillermondii isolated from stool was sensitive to all antifungals tested including Fluconazole, Voriconazole, Caspofungin, Amphoterecin B, Flucytosine and Micafungin.

Table 6: Sex Wise Distribution Of Organisms.

Category	MDR	NON-MDR	Grand Total
Males	27	16	43
Females	20	07	27
Grand Total	47	23	70
χ^2		0.96	

Hypothesis Testing

Null Hypothesis (HO): There is no significant difference between occurrence of multidrug resistant organism between male and female.

Conclusion: since the calculated $\chi 2 = 0.96$ is less than the χ 2 table value i.e. 3.841 at 1 df, the null hypothesis is accepted at 5 % level of significance.

Table 6: Organism Isolated From Blood Culture Of Study Population.

Category Organisms	MDR(%)	NON-MDR(%)	No Growth(%)	Grand Total
Candida glabrata	1	-	-	1 (2%)
Coagulase Negative Staphylococci	-	1	-	1 (2%)
Klebsiella pneumoniae	3	-	-	3 (6%)
Pseudomonas aeruginosa	1	1	-	2 (4%)
Staphylococcus aureus	-	2	-	2 (4%)
Streptococcus pyogenes	-	1	-	1 (2%)
No Growth	-	-	40	40(80%)
Grand Total	5(10%)	5(10%)	40 (80%)	50

Blood cultures were performed to determine the blood stream infection in the paediatric patients. Blood stream infection was observed in 10 patients of which 5 (10%) were infected with multidrug resistant organism and 5 (10%) patients with non-multidrug resistant organism. Among the isolated organism 9 (18%) were bacteria and 1 (2%) was fungus. Among 9 bacteria, 5 (10%) were gram negative organism while 4 (8%) were gram positive cocci. No growth was observed for 40 patients (80%) in blood culture.

Among the isolated organisms MDR Klebsiella pneumoniae was isolated at highest frequency of 6%. 2% Candida glabrata was isolated which was MDR. In 4% isolated Pseudomonas aeruginosa, 2% each were MDR and Not MDR. Pan sensitive isolates of Coagulase negative Staphylococcus (2%), Staphylococcus aureus (4%), Streptococcus pyogenes (2%) were observed among the isolated organisms from blood culture.

Klebsiella pneumoniae showed 100% sensitivity to Colistin and Tigecycline, followed by 33% to Meropenem, Gentamicin and Cotrimoxazole. Pseudomonas aeruginosa showed 100% sensitivity to cefepime, Aminoglycosides, Fluroquinolones and Colistin and 50% sensitivity to Carbapenems. Two Methicillin Sensitive Staphylococcus aureus were isolated which were resistant only to fluoroquinolones, macrolides and Trimethoprim-sulphmethoxazole. Candida glabrata isolated from blood was resistant to all drugs Voriconazole, Fluconazole, Caspofungin, Micagungin and Amphoterecin-B.

Table 7: Organism Isolated From Urine Sample Of The Study Population

Category / Organisms	MDR(%)	NON-MDR(%)	No Growth(%)	Grand Total
Candida duobushaemullonii	-	1	-	1 (1.9%)
Candida krusei	-	1	-	1 (1.9%)
Escherichia coli	5	1	-	6 (11.53%)
Enterococcus faecium	1	-	-	1 (1.9%)
Enterococcus fecalis	-	1	-	1 (1.9%)
Klebsiella pneumoniae	1	-	-	1 (1.9%)
No Growth	-	-	41	41 (78.8%)
Grand Total	7(13.46%)	4(7.69%)	41 (78.8%)	52

Urine cultures were performed for suspected urinary tract infection (UTI) in the paediatric patients. UTI was observed in 11 patients of which 7 (13.46%) were infected with multidrug resistant organism and 4 (7.69%) patients with non-multidrug resistant organism. Among the isolated organisms, 9 (17.30%) were bacteria and 2 (3.84%) was fungus. Among 9 bacteria, 7 (13.46%) were gram negative organism while 2 (3.84%) were gram positive organisms. No growth was observed for 41 patients (78.8%). Among the 11.53% of the isolated E. coli, 9.6% were MDR whereas 1.9% were sensitive.1.9% isolated MDR each were Enterococcus faeceium and Klebsiella pneumoniae while 1.9% sensitive organism isolated each from the urine culture were Candida duobushaemullonii, Candida krusei and Enterococcus fecalis.

E. coli isolates showed 100% susceptibility to Colistin and Tigecycline, 83% to Meropenem and 50% to Aminoglycosides. E. fecalis showed resistance towards High Level Aminoglycosides, Fluoroquinoles and Tetracyclines whereas E. faecium isolate was resistant to all antimicrobials including Vancomycin except sensitivity towards Linezolid. Candida duobushaemullonii was sensitive only to Voriconazole and Flucytosine whereas Candida krusei showed susceptibility only to echinocandins.

Table 8: Organism Isolated From The Tip Culture Of Study Population

Category / Organisms	MDR(%)	No Growth(%)	Not Available(%)	Grand Total (%)
Acinetobacter baumanii	1	-	-	1 (2%)
No Growth	-	1	-	1 (2%)
Not Available	-	-	48	48 (96%)
Grand Total	1(2%)	1(2%)	48 (96%)	50

Catheter tip cultures were performed for suspected catheter related infection in the paediatric patients. catheter related infection was observed in 1 patient (2%) which was multidrug resistant gram-negative organism, Acientobacter baumannii. No growth was observed for 1 patient (2 %) and catheter tip sample was not available for 48 patients (96%).

A.baumannii was sensitive only to Tigecycline, Colistin, Gentamycin and Co-trimoxazole.

Table 9: Concordance Of Surviellance Stool Culture With Other Cultures Of Study Population

Outcome	Stool Culture V/S Blood Culture	Stool Culture V/S Urine Culture	Stool Culture V/S Tip Culture
Positive	0	1	0
Negative	55	54	2
Not Available	-	-	53
Total	55	55	55
% Positive	0%	1.8%	0%

Gut translocation was determined on the basis of the occurrence of same organism with similar antibiogram as to that isolated from the stool surveillance sample. 1.8% of same organism were found in urine culture with respect to that of stool culture which indicates colonization from gastrointestinal tract. However, no correlation in the isolated organism was found with respect to blood and catheter tip culture of the neutropenic patients. Urine culture had grown MDR E. coli as same organism as that of stool culture.

DISCUSSION

Patients with cancer represent a high-risk population for development of serious infections. [13, 14]. Infections continue to challenge clinicians involved in the care of neutropenic patients. Management of neutropenia has become an even bigger challenge with increasing infections by MDRO. The source of infection in immunocompromised children is often endogenous, with most MDRO organisms routinely colonizing their skin and mucosal surfaces, causing infections when physical and/or immunological defences of the host are breached by chemotherapy and/or disease.[15]

Here we present a study to determine the role of surveillance stool culture for detecting the infectious agents during the period of neutropenia in paediatric patients undergoing chemotherapy. Our study had population diagnosed with leukaemia at highest frequency of 74%, mainly from western region of India, since the institute was located at Mumbai. High prevalence of MDRO was observed among the isolated organisms of the stool culture for the surveillance study.
The increased prevalence of MDR bacteria in the community could be multifactorial in origin. Easy availability of antibiotics without prescription, overuse of antibiotics in agriculture, antibacterial soaps and gels and triclosan in plastics are important reasons for the increasing presence of MDR bacteria in food and water sources in resource-challenged settings.[16, 17]

There is paucity of data on surveillance stool cultures in paediatric cancer patients from India. Community-based studies from India have shown that prevalence of MDR bacteria in stool ranges from 24 to 38%.[18,19] The lower rates of MDR bacteria seen in these studies could be due to community sampling versus hospital-based sampling. Furthermore, these studies only looked at E. coli isolates in healthy children.

In our study, 67% of patients had grown MDR bacteria in the stool within 72 hr of admission to the hospital. E. coli was isolated at the highest frequency from the surveillance stool sample with 63% of them being MDR in nature. In a study by Shankar et al, the most common MDR bacteria isolated from stool was E. faecalis in 46% of patients followed by E. coli in 28% of patients.[20]

Surveillance cultures were reported as useful predictors of drug resistant bacterial infections, especially in ventilator associated pneumoniae and bacteraemia.[21, 22], however our findings are in contrast to that. E. coli being isolated at highest frequency of 54.2% in our study, other organism isolated includes Klebsiella spp (28%) followed by Citrobacter koseri (7.1%). Other organisms included Acinetobacter baumannii, Enterococcus spp, Proteus mirabilis, Serratia liquefaciens , Shigella sonnei and a fungus i.e. Candida gullermondii as predominant flora from the samples with equal occurance of MDR in both males and females. Many surveillance studies have shown that E. coli, Klebsiella species and P. aeruginosa remain the three primary Gram-negative pathogens in neutropenic patients and caused 45–60 % of documented Gram-negative infections.[23] Other Enterobacteriaceae (Citrobacter spp., Enterobacter spp., Proteus spp., and Serratia spp.) are less common, although institutional differences in frequency do exist.[24]

Low blood culture positivity (20%) was observed in our study with equal frequency of 10% each of MDR and sensitive organism from the blood culture. Blood stream infection was observed with Klebsiella pneumoniae followed by Staphylococcus spp, Pseudomonas, Streptococcus and Candida glabrata. In study by Babu KG et al, Gram-positive organisms were isolated predominantly in blood stream infection with S. aureus as most common isolate, followed in decreasing order of frequency by E. coli, A. baumannii, Klebsiella pneumoniae, and CoNS.[25]

Predominance of Gram-negative bacilli in FN has been well established by several studies done in India and other developing countries.[26] Our study shows equal prevalence of gram positive and gram-negative organism in Blood stream infection in neutropenic patient at our institute.

Our study recorded that E. coli dominated among the isolated organism from urine sample of the study population with majority of them being MDR followed

by Enterococcus spp, Klebsiella pneumoniae and Candida spp in urinary tract infection. Bacterial infection predominates during the initial 7-10 days of neutropenia. As neutropenia persists beyond this duration, fungal infections begin to develop. Infections caused by Candida spp and Aspergillus spp are documented most often being pathogenic in this setting[27,28] Paediatric studies show variability in predominance of Gram negative and Gram-positive organisms.[29]

In our study, catheter tip culture indicated the presence of Acinetobacter baumannii a gram-negative organism. A study by Zakhour et al, a predominance of Gram-positive organisms, with coagulase negative staphylococcus accounting for most of the cases with numbers being comparable to majority of older paediatric studies was observed.[30-32]

Our study showed a low concordance between the same etiological agent in blood, urine and tip culture with that of stool culture. Organism with same antibiogram i.e. MDR E.coli involved in urinary tract infection was observed to be same as that isolated in stool surveillance sample of the patient. In contrast, in a study by Shankar et al, patients with positive stool cultures had a significantly higher blood culture positivity and mortality in comparison to patients with negative stool cultures. There was also a no concordance in our study between the MDR organism in the stool and blood, but it is usually the patients endogenous gut flora that is responsible for the bacteraemia.[33] In 1972, Schimpff et al. showed a link between the presence of organisms in the stool and subsequent risk for infection.[34]

CONCLUSION

Patients with malignancy represent a high-risk population for colonisation with MDR organisms and this colonisation is associated with a significant increase in the risk of blood stream infections with these resistant microbes. We do not recommend practical use of stool surveillance culture for neutropenic patients. Screening measures and proactive monitoring of vulnerable patients should be evaluated as part of the management protocols in order to tailor appropriate empirical therapy in this population. Strict adherence to antimicrobial stewardship is urgently warranted to prevent further spread of these resistant pathogens.

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