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Bacterial Isolates from Neutropenic Febrile Pediatric Patients and their Sensitivity Patterns to Antibiotics

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Abstract

Patients on cytotoxic therapy often develop neutropenia and fever. Our interest was to identify the common pathogens isolated from such patients and to study the sensitivity patterns of these organisms to the antibiotics used in their treatment. Thus, guidelines can be established by hospitals to identify which antibiotics can be used in the treatment of these patients when the results of cultures and sensitivities are not available. We conducted a retrospective study of neutropenic pediatrics presenting to AKUH from July, 1990 to June, 1996. A total of 153 isolates in 35 different patients were studied. Samples for culture were taken from the sites at risk. The majority of samples consisted of blood, stool, pus and urine. Twenty stool samples were also sent for microscopy. Malignancies were both hematological and non-he.matological. Gram negatives were isolated in 52.9%, gram positives in 33.9% and parasites in 13.2%. Salmonella paratyphi B was the most commonly isolated organism, followed by Pseudomonas aeroginosa, Giardia lamblia was the most common parasite. Sensitivity patterns of these organisms to antibiotics studied showed that Escheria coli had the lowest sensitivity rate being only 40% sensitive to Aztreonani and 64% sensitive to Ofloxacillin. A comparison was made between our findings and those reported in literature, as well as the risk factors for developing neutropenia. A guide to management is also discussed (JPMA 48:287,1998).

Introduction

Cytotoxic drugs are the mainstay of treatment for patients with malignant disease. The development of neutropenia is one of the outcomes of chemotherapy, with the potential hazard of developing infection. This has somewhat been offset by the use of Colony Stimulating Factors and antibiotics[1]. However, despite these measures the treatment of neutropenic patients still presents a problem for the health professionals. Once febrile, about 80% of patients will develop infection, even if a clinical focus is not detectable at that time[2,3]. Because culture and sensitivity reports are available after a few days, it is imperative that individual institutions be aware of the predominant pathogens in their setup and their sensitivities to various antibiotics. Of even greater interest is the situation encountered when treating pediatric patients. Pediatrics, especially in our part of the world, present a unique subset because of their own risks and management problems.

At present, while data from the West[2,3] still forms the major portion of literature, data from developing parts of the world is still scarce. The purpose of this paper is thus to identify the major pathogens that am responsible for infection in neutropenic children in our hospital and to look at the sensitivity patterns to antibiotics that are commonly used in their treatment. This knowledge can be useful when initiating empiric therapy immediately upon admission of the neutropemc patient, which can then be modified upon culture and sensitivity reports, when they become available.

Materials and Methods

We earned out a retrospective analysis of all the pediatric patients presenting to the Oncology service

with culture proven bacterial isolates presenting with fever secondary to neutropenia during a seven-year period from July, 1990 to June, 1996. A total of 153 isolates were documented from 351 atients. Neutropenia was defined as a WBC count <500mm . Neutropenic fever developed either as a result of chemotherapy or secondaiy to bone marrow infiltration due to the underlying neoplastic process. All the patients had either hematological or non-hematological underlying neoplasms. The data were analyzed on Epinfo Version 6 and SPSS for Windows.

Results

We documented 153 positive isolates from 35 pediatric patients. This included 133 cultures and 20 microscopy samples.Underlying neoplasms included acute lymphocytic leukemia, acute myeloid leukemia, Ewing's sarcoma, Hodgkin's lymphoma and Osteogenic sarcoma.

Key Points

- Empiric antibiotic therapy must be initiated without delay in neutropenic patients who present with fever, in order to reduce morbidity and mortality.
- Gram negative organisms were isolated with the highest frequency, but parasites have also been found to be predominant pathogen in our setup.
- Pseudomonas was found to be 100% sensitive to most of the tested antibiotics, while E. coli, (although sensitive to Amikacin and Ceftazidime) is showing high levels of resistance to most other tested drugs which are more commonly used.
- Owing to the high frequency of isolated parasites, it can be suggested that anti-parasitic agents e.g., Metronidazole should be included in the empiric therapy for neutropenic children.

Twenty-five patients were male and 10 were female. Fifty-four (40.6%) cultures were from the blood and 23 (17.3%) were from pus/wound sites (Table 1).

Table I. Main culture sites.

Culture sites n=133	Frequency	Percentage
Blood	54	40.6
Wound/Pus swabs	23	17.29
Stool	21	15.8
Urine	16	12.0
Throat swabs	5	3.8

Amongst the isolates, 52.9% were gram negatives and 33.9% were gram positives. Parasites were 13.2%. Individually, the most common organisms isolated were Salmonella paratyphi B (15%) and Pseudomonas aeroginosa (12.8%). Giardia lamblia (75%) was the most common parasite (Table II).

Table II. frequency distribution of individual isolates.

Total organisms - an overview (n=153).		
Gram negatives	81	52.9%
Gram positives	52	33.9%
Parasites	20	13.2%
Individual organisms (cultures and isolates).		
Name of organism	Frequency (n=153)	Percentage
Acinetobacter species	6	3.92
Aeromonas hydrophilia	7	4.57
B-hemolytic streptococcus	7	4.57
Bacillis species	4	2.61
Blastocystis hominis	5	3.27
Enterococcus species	5	3.27
Enterobacter species	6	3.92
Escheria coli	13	8.50
Giardia lamblia	15	9.80
Hemophillus influenzae	2	1.30
Klebsiellae pneumoniae	2	1.30
Pseudomonas aeroginosa	17	11.11
Pseudomonas species	2	1.30
Staphylococcus aureus	15	9.80
Staphylococcus epidermidis	8	5.23
Staphylococcus saprophyticus	2	1.30
Salmonella typhi	3	1.96
Salmonella paratyphi B	20	13.07
Salmonella paratyphi A	1	0.65
Streptococcal species	12	7.84
Streptococcus viridans	1	0.65

Fifty-four organisms were cultured from blood of which 10 (18.5%) were Staphylococcal species. Of the 23 organisms from pus and wound swabs, there were 9 (39.1%) Pseudomonas aemginosa. Salmonella paratyphi B was isolated from 19 (90.5%) of 21 stool specimens and E. coil from 9(56.3%) of 16 urine specimens (Table III).

Table III. Common organisms cultured from most frequent culture sites.

Organism	Blood	Urine	Stool	Wound/pus
Gram positives				
Staphylococcus aureus	5	-	-	7
Staphylococcus epidermidis	8	-	-	-
Staphylococcus species	10	-	-	-
Streptococcal species	-	-	-	2
Streptococcus viridans	1	-	-	-
Enterococcal species	2	-	-	-
Gram negatives:				
Escheria coli	4	9	-	-
Pseudomonas aeroginosa	7	-	-	9
Klebsiella pneumoniae	1	-	-	-
Salmonella species	4	-	20	-
Acinetobacter species	-	3	-	1
Aeromonas hydrophilla	7	-	-	-

On microscopy 15 (75%) of stool specimens were positive for Giardia lamblia. Antibiotic sensitivity rates are presented in Table IV.

Table IV. Sensitivities of the most frequently isolated organisms to the commonly tested antibiotics.

Antibiotics	Salmonella (%) n=20	Pseudomonas (%) n=17	E.coli (%) n=11	Staph aureus (%) n=15
Amikacin	-	100	100	93
Aztreonam	65	100	40	-
Ceftazidime	-	100	100	-
Ofloxacillin	100	100	64	-
Piperacillin	-	100	-	-
Cloxacillin	-	-	-	100
Erythrocyn	-	-	-	66

The most common antibiotics to be tested were Amikacin, Aztreonarn, Ceftazidime, Ofloxacillin,

Piperacillin, Cloxacillin and Erythrocyn. Pseudomonas was 100% sensitive to all these antibiotics.

Discussion

Malnourishment due to impoverish, lack of personal and social hygiene, presence of unique internal flora due to diseases which are endemic in our region, as well as a trend towaitis outpatient management in an attempt to minimize cost of treatment are some of the factors which cause the management of pediatrics to be a challenge. Children with cancer are prescribed different chemotherapy programs than adults and have different underlying diseases but are overall in better general health. Thus there are specific considerations which must be made for children who present with neutropenia and fever. Identification of infective organisms must be prompt because various studies have shown that once a patient presents with neutropenia, there is a 10-80% chance of his being infected by a pathogen[2,3]. Infections are a consequence of several factors, which are outlined in Table V.

Table V. Factors associated with infection in immunocompromised individuals.

- Host defects induced by underlying malignancy
- Host defects induced by cytotoxic agents and chemotherapeutic manipulations including corticosteroids.
- Various invasive procedures including long term use of indwelling catheters.

A clinical focus of infection may not be present at the time of presentation, which may be the case in upto 75-80% of patients[4,5]. Furthermore documented infection is only seen in 25- 30% of patients[3]. Of the hospitalized patients, 67% are seen to develop infection[7,8]. Because the defence systems of such patients are unable to mount a substantial inflamniatoiy response, fever is most often the only sign of infection[9,10]9,10 The risk of infection is increased in the presence of oral mucositis or diarrhea, along with clinical instability, advanced disease and overt organ dysfunction". Infections account for nearly 50%of all cancermortalities in the hospital setting[12,13]. Unless broad-spectrum empirical antibiotic therapy is initiated within the first 24-48 hours, the risk of septicemic mortality increases by 50-60%[14], When neutrophils are less than 100 mm^3, there is a 20% chance of bacteremia[5], sepsis being lethal in 47% of infected neutropenics versus 14%[4] when granulocytes are greater than 1000 mm^3.
Western literature reports an increase in Gram positive infections as compared to Gram negative infections in the last decade or so[2,7,9,11,13,15,20] although Gram negative infections still prevail[17]. This is due to better control of Gram negative infections. Gram positive infections are associated with a lower morbidity and mortality and represent 55-60% of all episodes of bacteremia seen in these patients[15]. Some of the risk factors involved in the rise of Gram positive infections are shown in Table VI.

Table VI. Factors promoting the increasing incidence of gram positive bacteria.

- The use of infensive chemotherapy regimens.
- Reliance on indwelling subcutaneous tunneled intravascular devices such as intravascular catheters.
- Disruption of mucosal membranes of the alimentary canal associated with neutropenia.
- Widespread used of prophylactic antibacterial agents against gram negative organisms and therapeutic administration of antibiotics.
- Intensive and prolonged chemotherapeutic regimens.

We documented 52.9% of Gram negative infections versus 33.9% Gram positives. A study done by Bumey et al in the same institution documeted 54% Gram negative infections in adults, compared with 46% Gram positive infections (N=127)[1].

E. coli, Kiebsiella and Pseudomonas are the most common Gram negative infections[2,17]. Of these Pseudomonas and Enterobacter infections show the gravest prognosis[21]. Our study however, documented Salmonella paratyphi B followed by Pseudomonas aeroginosa, Staph. aureus and E. coil. Enterobacter is reproted to have been isolated more frequently at several centers[17] ,although we only documented 45%of this organism. The widespread use of third generation Cephalosporins are also causing the emergence of unusual bacteria such as Acinobacter[6], which was also isolated in our study. Of paramount interest is our finding that parasites accounted for 13.2% of our total organisms. Western literature attributes the finding of parasites due to the increasig usage of corticosteroids as part of the chemotherapy regime[22]. They report the isolation of organisms such as Pneumocystis carnii, Toxoplasma gondii, Strongyloides stercoralis, Ciyptosporidia and Chagas disease, especially in AIDS patients. Perhaps the endemic nature of this disease makes it a more common finding in our part of the world. This would require that drugs such as Metromdazole also be initiated empirically, at the time of presentation.

Appropriate empirical antibitoics should be selected on the basis of knowledge of antibiotic susceptibilities at each institution as much on the basis of studies from other institutions[13]. Parenteral antibiotics shouldbe prescribed fora minimum of 7 days in the hospital setting[18] but the resolution of fever, control of infection, clinical assesment and a neutrophil count greater than 500 to 1000 cells per mm^3 all need to be taken into consideration[11,23]. However many Western studies now prove that earlier discharge from hospital with continuation of treatment on an outpatient basis shows much promise as regards to diminishing the cost of treatment as well the general wellbeing of the patient[11,12,24,25]. However, this program needs to be approached with caution in our setting. Lack of patient education and inadequate compliance, along with unhygienic living conditions, precludes this form of treatment.

In our series the aminoglycoside Amikacin showed high susceptibility. A surprising finding was that E. coli was only 40% sensitive to Aztreonam. E. coli thus seems to be showing increasing resistance to a large number of antibiotics. Routine administration of aminoglycoside as well as the more powerful Vancomycinisa contmversial issue[13,26,27]. Use of Vancomycin is morn commonly being adivsed only in cases where there is no response to initial treatment, or when Gram positives have been isolated[27]. The use of anaerobic agent is advocated in cases where necrotizing gingivitis, perianal tenderness and acute abdominal pain (suggestive of typhlitis) occur9. In the end it is uncommon for the development of bacterial infection after the final course of chemotherapy, although Pneumocystis and viral infections do occur[11].

It is likely that with the advent of cytokines and even more with possibility to insert drug-resistant genes into hematopoeitic stem cells, the risk of infection will be decreased because the severity and duration of neutropenia will be minimized. Nevertheless attempts at decreasing hospital stay by outpatient management is yet not possible in our society and until then attempts at decreasing the risk of neutropenia and adequate antimicmbial therapy will remain the mainstay of treatment for the febrile neutropenic pediatric.

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