

Changing Microbiological Pattern of Pediatric Febrile Neutropenia

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Introduction

Febrile Neutropenia (FN) is undoubtedly the commonest emergency in children with malignancy, especially those receiving chemotherapy. Even in this 'era of antibiotics' FN continues to be one of the major cause of morbidity and mortality in children with cancer; limiting the gains achieved with the chemotherapeutic agents [1]. Febrile neutropenia is defined as a single oral temperature of >38.3°C (101°F) or a temperature of >38°C (100.4°F) for more than 1 hour with an absolute neutrophil count (ANC) <500/mm³ or an ANC that is expected to decrease to <500/mm³ during the next 48hrs [2]. The risk of infection is related to the duration and severity of neutropenia. The prevalence varies widely and estimated to be 12.8% in children between 1- 9 yrs but increases to 17.4% in those aged 10-19 yrs [3].

Attributes that guides the management considerations in FN include: (1) fever in a neutropenia child is considered to be due to infection unless proved otherwise; (2) microbiological diagnosis is possible in only about 10-30% cases of pediatric FN [4]; Organisms with low virulence or those considered as potential contaminants in an immunocompetent patient can lead to serious infection in presence of neutropenia; (3,4) co-infection with multiple organisms are common and untreated infection can rapidly disseminate and lead to fatality. Among the infectious causes of FN in children, bacteria outnumber

other agents (viral, fungal and parasitic); discussion in this paper will be limited to microbiology of bacterial agents in FN only. During the 1960s and 1970s, mortality from FN was in the tunes of 60-70% [5]. Subsequently, empirical use of antibiotics in FN demonstrated [6,7] a striking reduction in the mortality. This paved the way for the present practice of empirical broad spectrum antibiotics in this group of patients. Clinicians further realized that all the children with neutropenia and fever were not at a same risk of having an invasive bacterial infection. The host vulnerability to infection and related complications depends on the patients' underlying disease and the chemotherapy they receive [5]. Indeed an audit of all hospital admission for pediatric FN during the year 2012 in US [8] revealed that 39% of the discharges had a short length of stay (SLOS) of ≤ 3 days; viral infection and upper respiratory infection comprising the majority with 66.4% of them had no identifiable infections. This has led to the risk based approach and use of intravenous or oral antibiotics in 'low risk' patients [9]. Another important paradigm in the management of pediatric FN is use of antibiotic prophylaxis. Primary prophylaxis for *P. jirovecii* pneumonia has decreased associated morbidity and mortality in children with FN [10]. Trimethoprim/sulfamethoxazole, amoxicillin/clavulanate and fluoroquinolones have been used as antibacterial prophylaxis in these children with success, but has been linked with the risk of emergence of antibiotic resistance [1]. Past several decades have witnessed substantial change in the bacterial etiology of pediatric febrile neutropenia (Table 1).

Author	Country	Study period	Predominant organisms	Antibiotic sensitivity pattern
al-Fawaz IM et al. [11]	Saudi Arabia	1983-89	GM +ve 54%; CONS (19.7%), <i>Streptococcus</i> spp. (18%); <i>P. aeruginosa</i> (19.7%)	NA
Bakshi et al. [12]	India	1992-2002	GM -ve (67%); <i>E. coli</i> (45.7%), <i>S. aureus</i> (39%)	NA
Celkan et al. [13]	Turkey	1995-2001	GM +ve (60%); CONS (40%)	High rates of resistance to penicillin, erythromycin and cephalosporins in <i>Staphylococcus</i>
Dubey et al. [14]	India	1998-99	GM -ve (83%); <i>Klebsiella</i> (46%), <i>E. coli</i> (27%)	Fifty percent of both <i>Klebsiella</i> and <i>E. coli</i> were resistant to both cefotaxime and amikacin
Lai et al. [15]	Taiwan	1999		
El-Mahallawy et al. [16]	Egypt	1999	GM +ve (51.2%); polymicrobial (13.7%); CONS (16.2%), <i>S. aureus</i> (13.4%)	Forty isolated organisms were resistant to all used antibiotics
Gupta et al. [17]	El Salvador	2001	GM +ve (61%); polymicrobial (43%); CONS (30.4%), <i>pseudomonas</i> (17.4%)	NA

Duncan et al. [18]	England	2001-02	GM +ve (82%); CONS (64.2%)	Resistance to gentamicin in 15.8% CONS isolates
Sanboonrat et al. [19]	Thailand	2006-07	GM -ve (52%); <i>A. baumannii</i> (16%), <i>E. coli</i> (12%), <i>Klebsiella</i> (12%)	NA
Aslan et al. [20]	Turkey	2007-10	Gram +ve (56.4%); CONS (31.7%), MRSA (7.9%); <i>E. coli</i> (5.7%)	Forty percent of the <i>enterococcus species</i> vancomycin resistant; 50% <i>pseudomonas</i> resistant to meropenam
Bothra et al. [21]	India	2009-10	GM -ve (78.2%); <i>E. coli</i> (29%), <i>S. aureus</i> (26%)	GM -ve mostly sensitive to carbapenems, amikacin, netilmicin, cefoperazone-sulbactam and piperacillin-tazobactam but resistant to cefotaxime, ceftazidime and ciprofloxacin; most GR +ve resistant to amoxicillin-clavulanate, but sensitive to erythromycin, amikacin, netilmicin and ciprofloxacin.
Al-Mulla et al. [22]	Qatar	2004-11	GM +ve (55%); CONS (40%)	All GM +ve susceptible to linezolid and streptogramins; all <i>K. pneumoniae</i> susceptible to imipenem, meropenem, and amikacin; <i>P. aeruginosa</i> 100% susceptible to all antipseudomonal antibiotics
Miedema et al. [23]	Netherlands	2004-11	GM +ve (73%); CONS (39%), <i>streptococcus</i> (26%)	All GM +ve susceptible to vancomycin; CONS often resistant to penicillin, flucloxacillin, gentamicin; GM -ve highly susceptible to ceftazidime, piperacillin/tazobactam, imipenem, and aminoglycosides
El-Mahallawy et al. [24]	Egypt	2011	GM +ve (72.4%); CONS (58%)	51% isolated strains multidrug resistant
Rose et al. [25]	India	2012-14	GM -ve (82.6%); <i>klebsiella</i> (12.8%); CONS (31.4%)	Among GM -ve 24% carbapenem-resistant and 49% ESBL; Among GM +ve 33% VRE and 15% MRSA
Siddaiahgari et al. [26]	India	2013	GM -ve (85.4%); <i>E. coli</i> (37%), <i>pseudomonas</i> (23.5%)	GM -ve ESBL, carbapenem resistance and pan resistance in 31.4%, 5.6% and 2.3% respectively
Hagag et al. [27]	Egypt	2012-15	GM -ve (55.5%); <i>pseudomonas</i> (31.5%), <i>S. aureus</i> (25.9%)	GM -ve 40% resistant to ceftazidime 36.6% to cefoperazone and 13.3% to imipenem; GM +ve 50% resistant to oxacillin, 37.5% to imipenem and 12.5% to cefepime

Table 1: Large epidemiological studies on pediatric febrile neutropenia, GM -ve=Gram negative; GM +ve =Gram positive; CONS=coagulase negative staphylococci; MRSA=Methicillin resistant *Staphylococcus aureus*; VRE=Vancomycin resistant *enterococcus*; ESBL=extended spectrum β -lactamase.

Apart from the time period of study, the microbiology of febrile neutropenia is largely dependent on the regional differences based on socio-economic and healthcare developments [11-27]. Data from European Organization for Research and Treatment of Cancer (EORTC) during 1973-1994, reveals a decreasing incidence of Gram negative agents from 71% to 31% while Gram positive infection rose from 29% to 69% [28]. A 15 yrs (1995-2010) data from Turkey on children with acute lymphoblastic leukemia (ALL) and FN showed an increasing incidence of febrile neutropenia during this period. Gram positive and Gram negative organisms were equally frequent with CONS and *E. coli* being the being the commonest Gram positive and Gram negative organisms respectively [29]. Till the 1990s the predominant etiological organism of pediatric FN world over were Gram positive bacteria but during the first decade of the 21st century Gram positive organisms became more prevalent specially in the developing countries with CONS (coagulase negative *Staphylococcus aureus*) being the most frequently isolated agent. Again during the present decade there seems to be a re-emergence of Gram negative organisms, particularly multidrug resistant (MDR) [11-27]. The same

has been echoed in the study by Mikulska et al. [30], who found that a questionnaire based data obtained in 2011 reported predominance of Gram negative organisms compared to the published data between 2005-2011. It is also worth mentioning that the studies from developing countries such as India [12-14,21-26] have consistently demonstrated a predominance of Gram negative organisms, probably because of less use of central venous catheters. It is not only the predominant organism but their antibiotic sensitivity pattern that decide the choice of empirical antimicrobial therapy in children with FN.

Infection with antibiotic-resistant bacteria has emerged as a serious threat to children with fever and neutropenia. Mikulska et al. [30] in their review of studies between 2005 and 2011 revealed very high rates of antimicrobial resistance. In a retrospective review of all cases of Gram negative bacteraemia in children with febrile neutropenia from 2003-2010 at the Royal Children's Hospital Melbourne [31], revealed that 15% episodes were due to antibiotic resistant (AR) organisms. Factors independently associated with AR GN bacteremia were high-intensity chemotherapy, hospital-acquired bacteremia and isolation of

AR GN bacteria from any site within the preceding 12 months. Though, episodes of AR GN bacteremia were associated with longer hospital stay including longer intensive care unit length of stay and a higher rate of invasive ventilation, no increase in mortality was identified. Another study reported 38% isolates to be multidrug resistant and it was also associated with unfavorable outcome [32]. Risk factors for infection with such organisms were found to be hospitalization, Gram-negative organisms, presence of clinical focus of infection, reduced ANC, prolonged duration of neutropenia, and previous intake of antibiotics. Antibiotic susceptibility data of Gram negative isolates from children with FN between 2001 and 2013 at a single centre in Italy [33] revealed out of total 263 strains evaluated 27% were resistant to piperacillin-tazobactam, 23% to ceftazidime, 12% to meropenem and 13% to amikacin. Concomitant resistance to β -lactam and amikacin was detected in 6% of strains for piperacillin-tazobactam, 5% for ceftazidime and 5% for meropenem. During the study period there was a nonsignificant increase in the proportions of strains resistant to β -lactams indicated for monotherapy, and also increase in the resistance to combined therapies. El-Mahallawy et al. [34] have documented a substantial rise in the multidrug resistant organisms between 2006 and 2011 (38% vs. 51%) at a single centre in Egypt. In a more recent study from Korea [35], 34.4% episodes of febrile neutropenia were found to be due to ESBL producing strains of *E. coli* and *K. pneumoniae*. Again, there were no increased complications including mortality rates compared to non-ESBL producing organisms. It was also observed that 90.5% of the ESBL-producing isolates were susceptible to piperacillin/tazobactam or cefepime in combination with aminoglycoside. Therefore, authors concluded that empirical therapy with these combinations might be more useful for febrile neutropenic children, instead of β -lactam monotherapy in places with high prevalence of ESBL-producing organisms. Another alarming report from India [36] revealed 59% of Gram negative isolates to be ESBL producing; multidrug resistance was seen in 48%, extreme drug resistance in 32% and pan drug resistance in 16% of Gram negative isolates. Colistin was the most sensitive antibiotic (75% sensitivity) and in significant number of cases the only salvage option. A recent systematic review of randomized control trials in pediatric FN [37] concluded that antipseudomonal penicillin and fourth-generation cephalosporin monotherapy were associated with similar failure and mortality rates as aminoglycoside containing combination therapy. The current recommendations also advise monotherapy as initial empirical antibiotic therapy in pediatric FN [3-9]. Further, Outpatient management and oral antibiotics were found to be safe in low-risk FN with no infection-related mortality observed in any patient and no significant differences in outcomes compared with inpatient management and intravenous therapy. But the authors have rightly appreciated that combination empirical antibiotic therapy will be appropriate in settings with high rates of gram-negative antibiotic resistance. They further added that, a consensus regarding the minimum level of bacterial resistance for adopting combination therapy will be difficult as it will require individual institutions to balance the risk and theoretical benefits as well as their individual preferences. Nevertheless, it is incumbent on the institutions to offer strategies to monitor, prevent, and appropriately manage these infections. Simultaneously, there is need to address the current infection control issues pertaining to the children with haematological malignancy based on currently available recommendations [38].

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