Management of Febrile Neutropenia

Introduction
The significant successes in hematological cancer chemotherapy in the last 40 years have been tempered through the ‘innocent casualty’ phenomenon of creating a highly immunocompromised milieu fruitful for opportunistic infections, whose morbidity and mortality threaten outcome.\(^1\)

Bodey is credited with the first clear documentation of the link between infection and neutropenia.\(^2\) He observed that the mortality of most patients who had infection and neutropenia was 90%.\(^2\) (Fig. 1).

Bacterial Pathogens
Bacteria are the predominant organisms. In the late 1950’s/early 1960’s Gram+ve organisms were the commonest, particularly Staphylococcus aureus. The late 1960’s/early 1970’s were typified by Gram-ve of gastrointestinal tract origin, particularly Escherichia coli, Klebsiella spp and Pseudomonas spp. By the 1990’s Staphylococcus spp including coagulase negative organisms, Streptococcus spp and Enterococcus spp were increasingly seen as Gram-ve diminished.\(^3\)\(^4\) This cyclical profiling (Fig. 2) is of both great interest and alarm since organisms such as coagulase-negative staphylococci and S. viridans associated with toxic shock had previously not been encountered as potent pathogens.\(^5\) Gram-ve organisms have reappeared recently.\(^6\) Many ‘new’ bacteria have been documented including vascular device associated Stomatococcus mucilaginosus, Leuconostic spp, the myonecrotic/severe mucositis agent Clostridium septicum, vancomycin enterococcal resistance and mycobacterial blood stream infections.\(^7\)\(^9\) Of great concern is escalating antibiotic resistance.

Correspondence
MICHAEL ELLIS, Department of Internal Medicine, FMHS, UAE University, Al Ain, UAE
Tel.: +971 3 7157608, Fax: +971 3 7672995
Email: Michael.Ellis@uaeu.ac.ae
Reasons for the changing profile of bacterial organisms include increased chemotherapy intensification (more severe mucositis), use of prophylactic antibiotics (suppress Gram-ve at the expense of Gram+ve), and increased technological sophistication (breach of the mechanical skin and mucosal barriers secondary to the plethora of invasive devices). Despite increasing efforts to contain opportunistic bacterial sepsis with infection-control policies including antibiotic restrictions, the rate of bacteremias among all febrile-neutropenic episodes has increased by around 25% to an incidence figure of 28% in recent years.

Fungal Pathogens
Invasive fungal infections (IFI) are increasingly seen. Candidemia currently is the 4th commonest bloodstream infection in North America. Aspergillus has emerged as the lead fungal pathogen. Moulds other than Aspergillus spp, particularly the agents that cause mucormycosis make up 25% of all invasive mould infections. 40% of patients who die with cancer have an IFI. The mortality of invasive aspergillosis among bone marrow transplant recipients is 50%; the presence of a non-Candida IFI after human peripheral stem allo-transplantation increases mortality three times. Overall susceptibility of C. albicans to fluconazole has decreased. Non-albicans spp., such as C. krusei with resistance to fluconazole have emerged. The widespread use of voriconazole, with excellent activity against Aspergillus infections, has been so effective against this mould that mucormycosis with inherent resistance to voriconazole has emerged. Amphotericin-B resistant A. terreus has become as frequent as A. fumigatus (normally the most frequent of the Aspergillus spp) in selected cancer units which have a higher proportion of more critically ill and more immunocompromised patients. Unusual moulds have now established themselves including Scedosporium, Fusarium.

Management of the patient with febrile neutropenia of acute onset
Current IDSA guidelines stipulate that at onset of fever in a NP patient, a careful clinical evaluation including perineal and vascular access site inspection should be performed to exclude a focus for fever/infection followed by immediate sampling of blood for culture and prompt institution of empirical (if no focal source) broad spectrum antibiotics intravenously. This approach has seen a dramatic reduction in bacteremia associated mortality, to <5%, in such patients. For coverage of the most likely pathogens an aminoglycoside (gentamicin) plus an antipseudomonal penicillin (piperacillin-tazobactam) or cephalosporin (ceftazidime) or carbapenem (imipenem) with vancomycin should be used for MRSA.

This ‘blundermycin’ approach is highly cost-ineffective since not all patients with FN require intravenous broad-spectrum administrations, and many have fever of a non-infectious origin (eg thromboembolic disease). Considerable attention has been given in recent years to ‘risk stratification’ – that is, to identify the subgroup of patients who might be safely managed with a more simplified and streamlined antibiotic regimen, for example on an out-patient monitored basis. Several meta-analyses of randomized controlled clinical studies comparing oral (quinolone based) with intravenously administered empirical treatment for FN have confirmed the safety and efficacy of the oral option in patients deemed to be at ‘low risk’ for not responding to oral treatment or developing a serious medical complication such as sepsis associated hypotension. The challenge is to delineate those criteria used to define the low risk patient. Two major models have been derived – the Talcott and the MASCC classifications. They utilize demographic and clinical data such as age, clinical status and medical history to identify low risk patients with less than 10% chance of developing a severe complication.

There have been two further innovative developments in this area. The first is an evaluation of inflammatory markers and early phase reactant proteins as adjunctive information in risk assessment. For example, PCT levels rise within 2 days of onset of FN which are sustained
in those patients more likely to develop severe or unstable infection.\textsuperscript{30,31} High IL-6 and IL-8variably predict subsequent complications of FN.\textsuperscript{30,32} The patients in such well defined low risk groups have few complications, when early discharged on oral medications. Clearly, however, the findings represent an important step forward in rationalization of antibiotic treatment, offering the potential for cost savings, reduction in adverse drug events, decreasing resistance drive, reducing hospitalization and improving quality of life.

Prophylactic antibiotics
The current IDSA guidelines\textsuperscript{22} speak strongly against the use of antibiotics to prevent fever in neutropenic patients. Although the frequency of febrile episodes and infections have been shown to be reduced by this approach, there has been no solid evidence of an impact on all-cause or infection related mortality. Concern has been mooted over toxicity, antibiotic resistance and fungal overgrowth. However many of these issues had previously eluded answers because the statistical power of clinical trials had been insufficient. The 9283 patients meta-analysis by Gafter-Gvili is therefore a significant advance.\textsuperscript{33} The authors showed a highly significant reduction in all-cause as well as infection related mortality with prophylactic antibiotics (RR 0.67 and 0.58 respectively (p<0.001)).

The ‘Significant’ study used a cohort of severely neutropenic patients with solid tumors and demonstrated a reduction using levofloxacin prophylaxis in the proportion of febrile episodes, probable infection and hospitalization during the first as well as subsequent chemotherapy cycles, but there was no impact on infection deaths.\textsuperscript{34} The Gimema study also explored the use of levofloxacin prophylaxis in a severely neutropenic leukemic population and showed a trend towards reduction in all-cause mortality but no effect on infection deaths.\textsuperscript{35} A recent further meta-analysis by Gafter-Gvili addressed specifically the resistance issue.\textsuperscript{36} There were 7878 patients from 56 trials. Those patients who received quinolone prophylaxis did not have an increased rate of colonisation with resistant organisms or an overall rate of infection with resistant organisms. On the basis of these recent findings antibiotic prophylaxis should probably now no longer be withheld from neutropenic patients.\textsuperscript{37}

Preventing infection: targeting the enterocyte
The gastrointestinal tract is the primary reservoir of organisms, particularly Gram-ve and yeasts that are the source of microbemia in the neutropenic patient. These organisms translocate across the intestinal barrier which has been rendered permeable due to cytotoxic chemotherapy induced crypt cell apoptosis, cellular dysmorphism and intercellular tight junction opening.\textsuperscript{38} Other factors are contributory in the genesis of bacteremia of gut origin: intraluminal bacterial load, intestinal motility, macrophage dysfunction, hypogammaglobulinemia A, malnutrition and trace element depletion and nitric oxide mediated endotoxin damage.\textsuperscript{38} Knowledge of such mechanisms has provided some interesting prospects for intervention. These have included the use of selective inducible NO synthase inhibitors, immunonutrition via enteral feeding supplemented by glutamine, probiotic therapy with \textit{Lactobacillus} spp and hyperoxia.\textsuperscript{38}

Several growth factors such as Growth Hormone, Transforming Growth Factor-β and granulocyte colony stimulating factor are known to have proliferative effects on the enterocyte. Recombinant human interleukin-11 (rhIL-11) has potent anti-apoptotic and anti-mucositis activity. In a recent double blinded placebo controlled clinical trial, when administered prophylactically to patients undergoing chemotherapy, rhIL-11 prevented the increase in intestinal permeability that was documented in a matched control group which received placebo.\textsuperscript{39} This observed effect of rhIL-11 on permeability was associated with a significant reduction in bacteremia, delayed onset of first bacteremic event and reduced the bacterial load. (Fig. 3). This novel finding of a cytokine reducing the frequency of bacteremia through a shielding gastrointestinal cytoprotective mechanism offers
Patients not responding after 3-7 days of empirical broad spectrum antibiotic therapy and have no microbiological or clinical evidence of focal infection (antibiotic unresponsive neutropenic fever, AUNF) are at increased risk for the development of an invasive fungal infection (IFI). The use of empirical antifungal therapy with conventional amphotericin B (CAB) was shown to be significantly effective in improving the ‘overall’ response, non-significantly improved the emergence of an IFI and reduced IFI related deaths.\textsuperscript{41} 90% of patients with AUNF who do not receive CAB do not develop an IFI, indicating a highly cost-ineffective policy; CAB use has a high rate of adverse reactions, including chills and rigors but particularly nephrotoxicity which occurs in 1/3\textsuperscript{rd} of patients, and which directly causes increases in death rate, hospitalization and health care costs.

**Available antifungal drugs for treating AUNF**
The development of lipid associated amphotericin B products has led to greatly improved efficacy and reduced toxicity. Their relative aggregate efficacies have been reviewed by Ostrosky-Zeichner.\textsuperscript{42} The liposomal (LAB) product appears to have the least toxicity and most efficacy. On the basis of animal and human studies LAB is the preferred polyene for this indication.\textsuperscript{43-45} LAB has been compared to voriconazole (VRC) and the overall composite performance score indicated that VRC did not meet pre-determined non-inferiority criteria.\textsuperscript{46} LAB has been compared with Caspofungin (CSP) for FN.\textsuperscript{47} Although the overall success rate was identical, considerable concern has been raised over the intrinsic design issues of this trial. The further concerns over the bacteriostatic activity of CSP\textsuperscript{48} and its missing coverage for a number of the emerging new IFI such as Mucor has caused concern among clinicians, some of whom have not found such a favorable response.\textsuperscript{49} A thorough review of all the published studies which compared two different drugs in febrile neutropenia suggests that the overall success rate is around 45\% irrespective of which drug is used.\textsuperscript{50}

**Selection of patients for empirical or pre-emptive antifungal therapy**
When CAB was first introduced into clinical practice, fungal diagnostics were insensitive, unspecific and delayed, so late implementation of CAB was
associated with extremely high mortalities from established IFI. The current era of improved, more sensitive and specific fungal diagnostics coupled with less toxic antifungal therapy has had a major impact on empirical therapy management.

Current diagnostic emphasis has shifted away from invasive techniques which provide samples to demonstrate fungal hyphal invasion (patients too ill or thrombocytopenic) or to culture the fungus (takes too long and requires expertise), towards a variety of non-invasive non-culture based methods which are safe and rapidly performed.

**The CT halo sign**

Plain chest radiography is highly insensitive for specific and early invasive pulmonary aspergillosis (IPA) diagnosis. Patients with AUNF and IPA undergoing high resolution CT (HRCT) scanning early will have detectable lesions of IPA at a median of 10 days of AUNF, some as early as 1-3 days of AUNF. A central nodule surrounded by a glow-blush of the administered IV contrast medium is called the ‘halo’ sign and is virtually pathognomonic of IPA in the particular patient setting of AUNF (Fig. 4). Improvement in survival from IPA from 50% to 80% is achievable using routine systematic CT scanning to guide the institution of early antifungal drug treatment. The current survival rate from IPA in Tawam Hospital’s hematology unit is 90% using this approach (Fig. 5).

**Blood and serology testing**

**β-D glucan (BDG)**

Based on the observation that the BDG component of fungal cell walls can activate the horseshoe crab’s coagulation system, this phenomenon has been captured to generate a spectrophotometric assay for BDG. Two commercial kits are available – the Glucatell or Fungitell assay which uses enzymes from Limulus polyphemus amebocytes and the Fungitec-G assay which uses Tachypleus tridentates enzymes. The Glucatell assay has 100% negative predictive value and ≥96% specificity when defining a positive test as 2 sequential values of BDG of ≥60 pg/ml, AML subjects, matched with healthy controls. A recent large multicenter evaluation using just one single sample per patient gave sensitivities, specificities, PPV and NPV values of 69.9%, 87.1%, 83.8%, 75.1% respectively. The Glucatell assay was evaluated in Tawam Hospital recently in a population of 100 patients from the UAE with hematological malignancy undergoing chemotherapy and anticipated neutropenia. Using 2 consecutive values of BDG of ≥80 pg/ml to define a positive result, our sensitivities, specificities, PPV and NPV values were 86.8%, 76.2%, 76.7%, 86.5%. The overall test accuracy was 81.3% (Fig. 6).

Our own experience is that the BDG test may be a useful adjunctive tool for tailoring empirical antifungal treatment in the FNP patient. A possible paradigm might be to screen all patients for...
BDG from onset of neutropenia (or from 1st day of AUNF) and to give antifungal treatment only to those patients whose test was positive. The choice of antifungals might further be decided through results of HRCT scanning in that patients with early halo signs would receive liposomal amphotericin B whilst those with normal scans could be given caspofungin or even fluconazole. Patients with spurious low level glucan readings should not receive antifungals but continue with observation and other appropriate investigations.

Limitations of the BDG test include its ability to detect ‘generic’ fungi only, its inability to detect agents of mucormycosis and Cryptococcus spp, the possibility of false positive results with certain biologics such as immunoglobulins and cellulose.55,56

Galactomannan

In contrast to the pan-fungal BDG test, galactomannan (GM) detects only Aspergillus. The Platelia test is a double-sandwich ELISA that incorporates the B 1-5 galactofuranose-specific EBA2 monoclonal antibody, and is FDA approved for IA diagnosis. The first major publication was by Maertens in 1999 with sensitivity, specificity, PPV and NPV all > 92%.57 However, subsequent clinical validation studies whilst confirming the very high specificity and NPV, have reported highly variable sensitivities, which have ranged from 0-90% with several in the range of 50%.58 Several factors appear to influence the performance of the GM test: the cut off values (which have been reduced from 1.5 to 0.5 ng/ml), the prevalence of IA in the studied population (the higher the prevalence the more reliable the test), the clinical stage at which IA presents (abscesses or cavities may not release GM into the circulation), the phase of the fungal growth (galf antigens are released during the log growth phase) and the use of antifungal drugs.59 As with BDG testing, there are several false positive tests that require explanation and identification. In appropriate settings GM testing is reliable and could find a role in rationalising empirical antifungal therapy.60

Alternative dosing schedules of polyenes

Triggered by the inconsistency of thoroughly validated clinical studies of serological and blood testing techniques, empirical therapy will remain a treatment option for the foreseeable future. However since the drug-acquisition cost of the newer antifungal agents is high, there is a need to explore alternative dosing approaches. The favorable performance of liposomal amphotericin B (LAB) with high Cmax, elevated AUC, non-linear kinetics and rapid blood clearance to saturate the reticulo-endothelial system and other tissues offers the possibility of intermittent dosing.61 In a randomized open clinical trial at Tawam Hospital patients with AUNF received either conventional dosing with LAB at 3mg/kg/day for 14 days or 10mg/kg on day 0, 5mg/kg on days 2 and 5. In this pilot feasibility study there was no difference in adverse drug events. The overall success as measured by a 5-point composite outcome

Fig. 6: Comparison of bg levels in patients with aunf and IFI

Fig. 7: Amphotericin B concentrations in bone marrow 1-7 days after drug discontinuation
score was similar at 67% vs 66%, or time to defervescence at 8.4±6.1 vs 8.8±5.1 days or by the proportion of patients developing a +ve serological test by fungus by GM BG or PCR at 27% vs 28%. The levels of amphotericin B in the bone marrow aspirate taken 1 day after the completion of the 14 days standard dosing and 7 days after the 3rd dose of the intermittent high dose regimen showed persistence of the drug in that tissue (Fig. 7). The results therefore suggest that an intermittent high dose regimen may be administered safely to patients with AUNF, without loss of efficacy, provides a bone marrow (and probably other tissues) deposition of the drug and offers cost savings of 50%.

**Novel candidate opportunities in the neutropenic patient**

Multiple opportunities harvested from recent new understandings at the molecular level are presenting for evaluation as diagnostic and/or interventional therapeutic adjuncts. These include mannose binding lectin and pentraxin 3. RANTES is a CC chemokine released in response to pyrogenic signals such as bacterial infections, whose role is to regulate the trafficking and activity of white cells to sites of infection. Patients dying from severe sepsis had very low and irrecoverable RANTES levels compared to patients matched for similar diseases whose levels recovered prior to recovery from infection. This is also true for patients with IFI – the patients who recover from IPA recover RANTES but not in the case of patients who die from IPA. One explanation may be that adequate RANTES are essential in order to regulate optimally the recovering neutrophils and other cells in serious infection. If that is so, then the effect of a recombinant RANTES preparation could be explored in an animal model.

**Modifying the immunological milieu in neutropenia**

An unfavorable outcome from infection in the host may be partly due to target organ damaging excessive pro-inflammatory response, for example by an unopposed TNFα driven action. This mechanism is manifest in the recurrent generalized autoinflammatory syndrome TRAPS. Various therapeutic approaches have been based on this understanding. The use of anti-TNFα antibody treatment has not been found effective except in a sub-population with elevated IL-6 levels. The use of corticosteroids in patients with severe sepsis and a sub-optimal synacthen test has however been proven beneficial. Thrombo-therapeutics has also returned some exciting observations and secured clinical benefits for patients – recombinant activated protein C has been proven to significantly reduce mortality in patients with septic shock.

Another approach may be to create a pre-infection immunological milieu beneficial to the host when subsequent infection occurs. For example by raising soluble TNFR1 levels through administration of rhIL-11 (Fig. 8).

**The neutrophil itself**

It is generally accepted that restoration of the neutrophil quantity or quality is mandatory for successful outcome of FN. Hence supporting the patients to permit successful completion of planned chemotherapy of a planned dose is crucial. Granulocyte/monocyte colony stimulating factors have been available for several years to increase both quantity and quality of neutrophils and other cells. Their use decreases hospital-stay and possibly infection-mortality. Guidelines have
been produced by the two North American bodies the American Society of Clinical Oncology and the National Comprehensive Cancer Network. The European Organisation for Research and Treatment of Cancer has produced the most up to date guidelines.

**Conclusion**

Neutropenia presents a great hurdle to achieving overall success of chemotherapy or transplantation in the patient with hematological malignancy. The previous philosophy of treating every FN patient with antimicrobials or preventing all possible infections with prophylaxis has evolved to one commensurate with basic science findings of pathogenic molecular mechanisms and clinical observations. The current management of neutropenia attempts a logical, evidence-based approach to the complication of fever utilizing diagnostic information from surrogate markers and specific fungal diagnostics as well as administering less toxic drugs in a more directed fashion to patients. Greater awareness of the need to restore the host immune system, particularly by correcting neutrophil deficiency has also had an impact on management. Finally the emergence of widespread antimicrobial resistance has triggered investigations for novel approaches to prevention and management of infection in this patient population.

**References**


60. Maertens J, Theunissen K, Verhoef G, Verschakelen


