Febrile neutropenia – issues and management

Dr K M Chang
MRCP, FRCP, FRCPA(Haem)
Dept of Haematology
Hospital Ampang
Definition of febrile neutropenia

• FN is defined as an oral temperature >38.5 C or two consecutive readings > 38 C for 1-2 h and an absolute neutrophil < 500/uL or expected to fall below 500/uL
  • Axillary temperature is discouraged

• Definitions are not hard-and-fast rules
  • Some patients may be hypothermic < 36 C
  • Vomiting and diarrhoea, tachypnoea or lethargy and mental disorientation may be early signs
Severity of FN is associated with severity and duration of neutropenia
Factors affecting outcome of FN

- Severity of neutropaenia
  - <100/uL mortality 80% vs 27% <1000/uL

- Duration of neutropaenia
  - <7d, >14d
  - Response rates 95% vs 79% vs 32%

- Other factors
  - Outcome of disease/remission status
  - Regimen related
  - Stem cell transplant
  - Organ function/involvement
  - Age
Which are the common sites for infection

<table>
<thead>
<tr>
<th>Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloodstream</td>
<td>46.5</td>
</tr>
<tr>
<td>Mouth and pharynx</td>
<td>18.5</td>
</tr>
<tr>
<td>Skin and soft tissues</td>
<td>14</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>11</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>6</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>2</td>
</tr>
<tr>
<td>Other sites</td>
<td>1</td>
</tr>
</tbody>
</table>
Skin infection
Mucosal Barrier Injury

• Oral mucositis
  • 60-100%

• Risk factors
  • Pt factors
    – Age, gender, nutritional status, oral flora, salivary fxn, oral hygiene
  • Treatment factors
    – Antimetabolites - methotrexate, alkylating agts, TBI, idarubicin

• Gut injury
Risk factors

• Genetics
  – Def in mannan-binding lectin
    • Imp component in innate immune system
    • Longer median duration of fever 20.5d vs 10 d, p=0.014
    • <1000ug/L
  – Low mannose-binding Lectin conc assd with severe infection in pt with haem cancers undergoing chemo
    • 255 pt, 569 cycles
    • MBL<500ug/L
    • Severe infection incidence higher, no diff in outcomes
      » CID 2007:44(15 June)
  – Cytokine gene polymorphism
    • TLR-4 mutations increase susceptibility to Gm neg
    • ^pro-inflammatory TNF-a, IL-6, IL-8
    • Low anti-inflammatory IL-10, IL-1RA
Systemic inflammatory markers

- Prediction of outcome in cancer pt with febrile neutropenia: comparison of MASCC risk-index score vs procalcitonin, CRP, SAA and IL-1b, 6, 8, 10
  - MASCC score predictive of outcome, measurement of PCT, CRP, SAA, IL-1b, 6, 8 and 10 limited value
  - Eur J of Cancer Care, 2007, 16, 475-83

- Assessment if systemic infl markers to differentiate a stable from deteriorating clinical course in febrile neutropenia
  - Higher daily PCT and IL-6 in pt with complications
  - No markers to predict deterioration
  - Eur J of Haematology, 2005, 74, 297-303

- Change of procalcitonin predicts clinical outcome of febrile episodes in haem malignancies
  - Decreasing PCT to <70% of maximum value predicts freedom from recurrent fever
  - Support Care Cancer 2006, 14, 1241-45
Hosp Ampang survey

- Feb 2007
- Cultures pos 54/341 (15.8%)
- Gm pos 31 (57%)
- Gm neg 21 (39%)
  - E coli 9 Klebsiella 4 Ps spp 4
- Yeast 2
Risk assessment for incidence of FN

• **Low risk** – incidence 5-20%
  • Standard chemo for solid tumors, lymphoma, myeloma and autologous PBSCT
  • Mild mucositis
  • Expected duration of neutropenia < 7 days

• **High risk** – incidence 80-100%
  • Induction/Consolidation chemotherapy for acute leukaema, allogeneic SCT
  • Severe mucositis
  • Expected duration of neutropenia >= 7 days
When to suspect FN in casualty

- Cancer patients who have been exposed to chemotherapy for the past 60 days
  - Most chemo nadirs D 11 – 14
  - Some chemos may have delayed nadirs 4 – 6 weeks
What to do in a suspected FN

• Time is **CRUCIAL** – triage in emergency lane even if clinically looks stable
  • May rapidly deteriorate within 4-6h

• Conduct a quick P/E and physical exam
  • Diagnosis and last chemo
  • Find out primary team who is responsible
  • Assess the presenting symptoms – fever, vomiting, diarrhoea, cough, dysuria, respiratory difficulties, abdominal pain and any bleeding symptoms including headache and blurring of vision
Look for possible primary infection site...

- Mouth – teeth, gums, pharynx, thrush
- ENT- nasal/sinus tenderness
- Eye
- Upper GI symptom, oral thrush
- Lung
- Perineum- anal pain
- Diarrhea
- CNS
- Muscle tenderness
- Skin rash, eechymoses
- Vascular cathether tenderness
Decide if patient has **severe sepsis**

- Sepsis is a systemic inflammatory response (SIRS) triggered by an infection.
- SIRS define as 2/> of the following
  - Temp > 38 or <36
  - HR > 90
  - RR > 20
- Severe sepsis
- Septic shock
- **Immediate** blood C&S
  - Start potent broad spectrum antibiotics
  - Iv fluid resuscitation
  - O2 therapy
  - Inotropes
  - Refer to HDW
Investigations

First line
- Blood C&S (at least 5 mls)
- Throat, sputum and urine cultures
- CXR
- DIVC screen, if indicated – platelet, PT, aPTT, fibrinogen, D-dimer
- C-RP

Second line
- Blood fungal C&S
- Serum galactomannnan, Mannan/antimannnan
- CT scan lungs, abdomen
- BAL, LP, ECHO etc
What empiric antibiotic is appropriate

• Immediate empirical antibiotic (within 6 h), with antipseudomonal cover at onset of fever is CORNERSTONE of management

• MONOTHERAPY with broad spectrum beta-lactam antibiotics is as effective as beta-lactam + aminoglycoside in uncomplicated FN
? Rationale for Empirical Therapy

• EORTC - fever is the only sign 50%  
  - No localizing signs of infection

• Severity of infection is dependent on:-
  – absolute neutrophil count
  – duration of neutropaenia
  – wbc <0.1 ×10⁹/L
  (Bodey, 1966)

• Mortality with Gm neg sepsis 40%
  (Schirupff 1977, Klastersky, 1986)
Febrile neutropenia in high-risk patients (IDSA)

- Anti-pseudomonal Penicillin + Beta-lactamase Inhibitor (A-I)
  - or
- Carbapenem (A-I)
  - or
- (3rd- or 4th-Generation Cephalosporin (A-I)

- + Aminoglycoside or FQ (B-III)
  - Severe sepsis or septic shock
  - High incidence or suspicion of infection with *P. aeruginosa* or resistant Gram-negative bacteria
  - Pneumonia

- + Glycopeptide (B-III)
  - Severe sepsis or septic shock
  - Intravascular catheter-related infection
  - High incidence or suspicion of infection with resistant Gram-positive bacteria
  - Skin or soft-tissue infection/pneumonia
How to recognise patients at HIGH RISK of complications

IDSA-ECIL 2011 guidelines

- MASCC score < 21
- Profound neutropenia (ANC<100/uL) for > 7 d
- Comorbid medical problems
  - Haemodynamic instability
  - Severe oral mucositis, vomiting, diarrhoea
  - Mental status disturbances
  - Intravascular catheter infection
  - New pulmonary infiltrate, hypoxaemia, underlying chronic lung dis
  - Hepatic insufficiency
  - Renal insufficiency

THESE PATIENTS NEED URGENT ATTENTION, IMMEDIATE ANTIBIOTICS AND CONSULT WITH SENIORS
What to do with patients at low risk of severe complications

• Consult the primary team
• Admit for stabilisation over 1-2 days before considering discharge
Which Therapy to choose

• No formula
• Hospital factors
  – Depends on local institution
  – Bacteriological statistics
  – ESBL incidence
  – Incidence of Gm pos org
  – Antibiotic cost
• Host factor
  – Organ failure
  – status of underlying disease
  – severity of neutropaenia
  – expected duration of neutropaenia
  – clinical severity
Be wary of changing landscape

- **Bacteria**
  - ESBL- or carbapenemase producing Enterobacteriaceae
  - MRO – Acinetobacter, MR Pseudomonas spp, Stenotrophomonas
  - Staphylococci with raised vancomycin MICs >2mg/L
  - VRE
- **Mycobacterium**
- **Fungi**
  - Azole- resistant Candida
  - Aspergillus infections
  - Zygomycetes
- **Viral infections**
  - CMV
  - EBV
  - Adenovirus, BK virus
- **Protozoa**
  - Disseminated Toxoplasmosis
  - Cryptosporidium
Viral infection
What to do next

• Daily evaluation

• Consider new symptoms and signs and clinical status

• If clinically deteriorating or no improvement at 72 to 96h, consider
  – Escalation therapy
  – ESBL or MRO or MRSA/CoNS
  – Antifungal treatment
When to consider Vancomycin

• Haemodynamic instability or other evidence of severe sepsis or pneumonia

• Colonisation or previous infection with MRSA

• Catheter-related sepsis
  • Chills/rigors with infusion
  • Tunnel infection

• Skin or soft tissue infection at any site
When to suspect fungal infection

• Mucositis, thrush.
• Difficulty or pain when swallowing
• Skin lesions
• Suspicious pulmonary infiltrates
• Fundal exudates
• Prolonged steroid/antibiotic use (>1 week)
What do I do?

• When do I downgrade?
  – Clinically stable with no localising sign
  – No multiresistant isolate
  – ANC increasing

• When do I stop therapy?
  – 72h after defervescence
  – ANC > 0.5 or recovering
  – No localising sign or isolate
Fungal infection
Persistent fever

• If ANC recovering
  • Fungal infection
  • Line sepsis
  • Drug fever
  • Resistant disease

• If ANC not recovering
  • Fungal infection
  • Multiresistant organisms
  • Resistant disease
Options for Multiresistant organisms

- **Glycopeptide non-susceptible Gm-pos**
  - Oxazolidinone (Linezolid) AII
  - Cyclic lipopeptide (daptomycin) BII
  - Stretogramin (quinupristin/dalfopristin) BIII
  - Tigecycline BIII – low blood levels, few data, limited experience in FN

- **Carbapenem resistant Enterobacteriaceae**
  - + Colistin BII
  - + Tigecycline BIII
  - + aminoglycosides BIII
  - + fosfomycin CIII

- **Beta-lactam resistant P. aeruginosa**
  - + Colistin AII
  - + Fosfomycin CIII

- **Beta-lactam resistant Acinetobacter**
  - + Colistin BIII
  - + Tigecycline BIII
When do I consider growth factors (G-CSF)?

- Prophylactic use of G-CSF may be considered in patients where the anticipated risk of fever and neutropenia is > 20% (AII)
- G-CSF not recommended in established FN
  - IDSA guidelines 2010
  - Reduces duration of fever, neutropenia and hospital stay
- May be considered in certain subsets
  - Severe sepsis
  - Pneumonia, fungal infections
  - Neutropenic colitis
Supportive measures

- Hand hygiene
- Isolation
- Food – neutropenic diet
- Skin and oral care incl bowel habits
- Plants and animals
- Visitors
- Infection control team
Take home messages

• Febrile neutropenia is an emergency
• High index of suspicion
• Assess for severe sepsis syndrome and high risk
• Institute antibiotics immediately after blood cultures
• Consider supportive measures
• Have an institutional protocol on FN management in the emergency dept