Febrile Neutropenia
Symptoms, Diagnosis,
Treatment and Best Practice

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The risk of infection increases with the severity and duration of neutropenia.
Definition of Febrile Neutropenia

Fever: Single oral temperature $\geq 38.3^\circ$C or persistent temperature $\geq 38.0$ °C for $>1$ hour

Neutropenia: ANC $< 0.5$, or ANC $< 1.0$ and a predicted decline to $< 0.5$ over next 48 hrs. (ANC= absolute neutrophil count)
FEBRILE NEUTROPENIA

• Incidence of infection directly correlates with the depth and duration of neutropenia.
• FN is associated with significant morbidity and mortality
• Often dose-limiting
• Historically: Hospitalization for evaluation and initiation of IV broad-spectrum antibiotics
• Leading to reduced QOL
# What is the Risk?

## Incidence of Febrile Neutropenia

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Induction-remission for AML</td>
<td>70-90%</td>
</tr>
<tr>
<td>Elderly patients receiving CHOP</td>
<td>35-45%</td>
</tr>
<tr>
<td>Patients with NHL</td>
<td>10-20%</td>
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## Mortality Estimates from Febrile Neutropenia

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<table>
<thead>
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<tbody>
<tr>
<td>Solid tumours</td>
<td>5%</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>Up to 11%</td>
</tr>
<tr>
<td>Gram-positive bacteremia</td>
<td>5%</td>
</tr>
<tr>
<td>Gram-negative bacteremia</td>
<td>18%</td>
</tr>
</tbody>
</table>
Predisposing Factors

- Malignancy
  - Type
  - Advanced/refractory
  - Obstructive
- Surgical risk
- Grade of neutropenia
- Disruption of mucosal barriers
- Corticosteroid use
More than half of FN events occur in the first cycle of chemotherapy.

- Breast cancer: 58%
- NSCLC: 50%
- SCLC: 71%
- Colon cancer: 80%
- Non-Hodgkin's lymphoma: 53%
- Hodgkin disease: 57%
- Ovarian cancer: 54%

NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer

FN PATIENT EVALUATION

• Careful history & physical examination
• Prior fungal infection/candidiasis may recur during subsequent neutropenia
• Prolonged neutropenia is associated with invasive fungal infections
• Neutropenia duration correlates with the risk of serious infectious complications
FN PATIENT EVALUATION

- History & physical examination
- Differential CBC
- RFT, LFT, Electrolytes & uric acid
- At least 2 sets of blood cultures & culture specimens from sites of suspected infection.
- Urine analysis
- CXR
MUCOSITIS

• May occur following chemotherapy treatment

• Severe mucositis may be very difficult to distinguish from herpes infection

• The presence of oral candidiasis is associated with impaired immunity
IMPORTANT CLINICAL SETTINGS IN PATIENTS WITH FN

• Typical signs of infection may be blunted or even absent as a result of immunosuppression

• Recent clostridium difficile colitis should raise a suspicion of recurrent infection in a patient presenting with FN and diarrhea

• Patients undergoing corticosteroid treatment: This raises the possibility of opportunistic infection (such as P carinii)
SPECIFIC ASPECTS OF THE CLINICAL EXAMINATION IN FN

- Ophthalmologic and anterior sinuses examinations
- Detailed inspection of the skin and nails
- Inspection of the skin and nails may reveal lesions suggestive of systemic infection
  - ecthyma gangrenosum caused by P aeruginosa
  - erythematous papules caused by disseminated candidiasis
ECTHYMA GANGRENOSUM CAUSED BY P AERUGINOSA
ERYTHEMATOUS PAPULES CAUSED BY DISSEMINATED CANDIDIASIS
SPECIFIC ASPECTS OF THE CLINICAL EXAMINATION IN FN

• Inspection of catheter sites and surgical wounds and biopsies
• Inspection and palpation of the perineum and perianal regions
• An ENT specialist consultation may be warranted in some cases
RISK ASSESSMENT

Temperature >38.5°C and ANC <0.5x10⁹/l
Prompt assessment and vigorous resuscitation if needed

Calculate MASCC score

High risk
Inpatient broad spectrum intravenous antibacterial therapy

Low risk
Inpatient oral antibacterial therapy for some cases
<table>
<thead>
<tr>
<th>Group</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Inpatients (at the time of fever onset)</td>
</tr>
<tr>
<td>II</td>
<td>Outpatients with acute comorbidity requiring, by itself, hospitalization</td>
</tr>
<tr>
<td>III</td>
<td>Outpatients without comorbidity but with uncontrolled cancer</td>
</tr>
<tr>
<td>IV*</td>
<td>Outpatients with cancer controlled and without comorbidity</td>
</tr>
</tbody>
</table>

*Group IV is considered to be low risk.*
RISK ASSESSMENT MASCC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Burden of illness: no or mild symptoms</td>
<td>5</td>
</tr>
<tr>
<td>Burden of illness: moderate symptoms</td>
<td>3</td>
</tr>
<tr>
<td>Burden of illness: severe symptoms</td>
<td>0</td>
</tr>
<tr>
<td>No hypotension (systolic BP &gt;90 mmHg)</td>
<td>5</td>
</tr>
<tr>
<td>No chronic obstructive pulmonary disease</td>
<td>4</td>
</tr>
<tr>
<td>Solid tumor/lymphoma with no previous fungal infection</td>
<td>4</td>
</tr>
<tr>
<td>No dehydration</td>
<td>3</td>
</tr>
<tr>
<td>Outpatient status (at onset of fever)</td>
<td>3</td>
</tr>
<tr>
<td>Age &lt;60 years</td>
<td>2</td>
</tr>
</tbody>
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OUTPATIENT ANTIBIOTIC THERAPY
FOR FN

- The Index consists of seven independent prognostic factors with an assigned integer value
- The index consists of the sum of these integers
- Patients with a MASCC risk index equal or greater than 21 identifies low-risk patients with a positive predictive value of 91% (specificity 68% and sensitivity 71%)
- The Index has been validated by other institutions in their respective patient populations and clinical settings
# RISK ASSESSMENT CISNE

<table>
<thead>
<tr>
<th>Explanatory Variable*</th>
<th>No. of Points</th>
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<tbody>
<tr>
<td>Eastern Cooperative Oncology Group performance status ≥ 2</td>
<td>2</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1</td>
</tr>
<tr>
<td>Chronic cardiovascular disease</td>
<td>1</td>
</tr>
<tr>
<td>National Cancer Institute Common Toxicity Criteria mucositis of grade ≥ 2</td>
<td>1</td>
</tr>
<tr>
<td>Monocytes &lt; 200/μL</td>
<td>1</td>
</tr>
<tr>
<td>Stress-induced hyperglycemia</td>
<td>2</td>
</tr>
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</table>

*The six variables are integrated into a score ranging from 0 to 8, which classifies patients into three prognostic classes: low risk (0 points), intermediate risk (1 to 2 points), and high risk (≥ 3 points).
High-risk patients

- Prolonged neutropenia: >7 days Duration
- Profound Neutropenia (absolute Neutrophil count [ANC] <100 cells/mm3)
- Medical co-morbid conditions, including hypotension, pneumonia, new-onset abdominal pain, or neurologic changes.
- Such patients should be initially admitted to the hospital for empirical therapy.
Low-risk patients

- Short duration neutropenia (<7 days duration)
- No or few comorbidities are candidates for oral empirical therapy
- Stable renal and hepatic function
EMPIRIC ANTIBIOTIC THERAPY

• In the early 1970s, Schimpff and colleagues conducted a study of patients with cancer and FN who were treated empirically with carbenicillin and gentamicin.

• Treatment of patients with P aeruginosa infection had dramatic survival improvement compared to historic controls.

• This study was the basis for empiric combination antibiotic therapy.
• Local epidemiological bacterial isolate and resistance patterns are crucially important in determining first-choice empirical therapy, since coverage for MRSA or resistant Gram-negative bacteria may be required.
ORAL ANTIBIOTIC THERAPY

• A recent review has concluded that inpatient oral antibacterial therapy can be safely substituted for conventional intravenous (i.v.) treatment in some low-risk FN patients, namely those who are haemodynamically stable.
MONOTHERAPY

• Recent data has shown that prompt empirical usage of a broad spectrum beta-lactam antibiotic with anti-pseudomonal activity is sufficient as an initial treat for FN

• Meta-analyses of a combination treatment with a broad spectrum beta-lactam antibitiitotic with anti-pseudomonal activity and aminoglycoside antibiotic resulted in increased toxicity and similar survival
AMINOGLYCOSIDE ANTIBIOTICS

• The addition of aminoglycoside antibiotics (which used to be the standard of care) should be limited to patients who are hemodinamically **unstable**

• Ciprofloxin is an important alternative to aminoglycoside antibiotics in this setting (as part of a combination regime), particularly in those patients with impaired renal function
EMPIRIC DUO-THERAPY REGIMENS

• There are highly effective monotherapy regimens for neutropenic fever

• Initial empiric duo-therapy regimens may be most appropriate in unstable patients

• In institutions in which multidrug-resistant pathogens are frequently encountered
ADDITION OF VANCOMYCIN TO AN EMPIRIC REGIMEN

• Catheter-associated infection by coagulase-negative staphylococci has become the most common cause of bacteremia in patients with cancer

• Among the common gram-positive infections in neutropenic patients, the following are typically resistant to cephalosporins
  – MRSA
  – coagulase-negative Staphylococcus species
  – Enterococcus species
ADDITION OF VANCOMYCIN TO AN EMPIRIC REGIMEN

- Increased proportion of infections by gram-positive bacteria led to the rationale to add vancomycin to an empiric regimen for FN

- Change in the proportion of infections in neutropenic patients from predominantly gram-negative to gram-positive bacteria
ADDITION OF VANCOMYCIN TO AN EMPIRIC REGIMEN

- Vancomycin addition to the initial empiric regimen was not associated with any benefit with regard to
  - duration of fever
  - morbidity
  - mortality related to gram-positive infections

- Initial empiric antibiotic coverage with vancomycin or other anti gram-positive bacterial pathogens should be avoided

- This approach is associated with higher toxicity and increased cost and no improvement in overall outcome
What Is the Role of Growth Factors (Filgrastin) in Management of FN

- CSFs are not generally recommended for treatment of established fever and neutropenia

- Maybe be used very complicated pts

- CSFs should be considered as prophylactic only
PERSISTENT FEVER IN THE NEUTROPENIC PATIENT

- Close observation after selection of initial empiric regimen for FN
- Daily physical examination throughout the duration of FN
- Initial antibiotic regimen modifications made based on new findings
- Antibiotic therapy should be continued for the duration of FN
OUTPATIENT ANTIBIOTIC THERAPY FOR FN

• Patients with a risk index greater than 21 may be candidates for outpatients antibiotic therapy for FN

• Prospective randomized studies have suggested that patients in the lowest risk group are reasonable candidates for carefully monitored empiric outpatient antibiotic therapy
OUTPATIENT ANTIBIOTIC THERAPY FOR FN

• Important limitations exist in making broad conclusions
  – The prospective studies each enrolled fewer than 200 patients
  – lacked sufficient power to detect small differences between treatment groups
  – Pooling data from different studies in the form of a meta-analysis is difficult
    • due to the differences in eligibility criteria
    • choice of antibiotics
    • criteria for hospital admission and discharge
    • criteria for a successful outcome
OUTPATIENT ANTIBIOTIC THERAPY FOR FN

• Although outpatient antibiotic therapy for FN neutropenic patients is widely used

• This approach can not be considered routine standard care

• Randomized clinical trials with sufficient statistical power are required to further define more precisely patients for whom outpatient management of neutropenic fever is safe
KEY ISSUES FOR OUTPATIENT MANAGEMENT

• Observation of low risk patients by experienced adequate staff
• Facility must be in proximity to an emergency care facility
• Adequate infrastructure for emergency management
• These facilities should also include fluid resuscitation, intravenous antibiotics and high care facility in the institution treating the patient
CONCLUSIONS

• Major progress has being made in the treatment of FN over 4 decades

• Additional research is required to resolve controversies
Thank You
Personalised Cancer Care