Febrile Neutropenia

Symptoms, Diagnosis, Treatment and Best Practice

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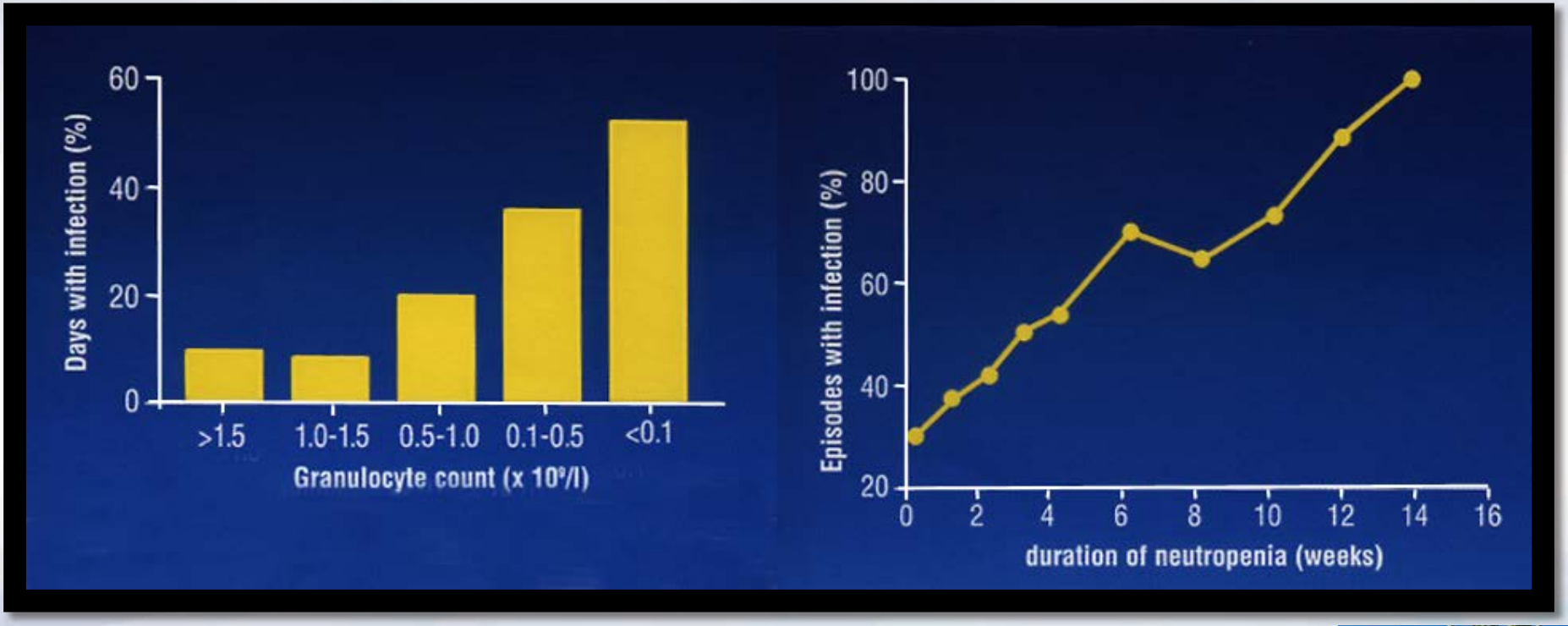
The risk of infection increases with the severity and duration of neutropenia



G.P. Bodey, Ann Int Med, 1966

Definition of Febrile Neutropenia

Fever: Single oral temperature ≥38.3°C or persistent temperature ≥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

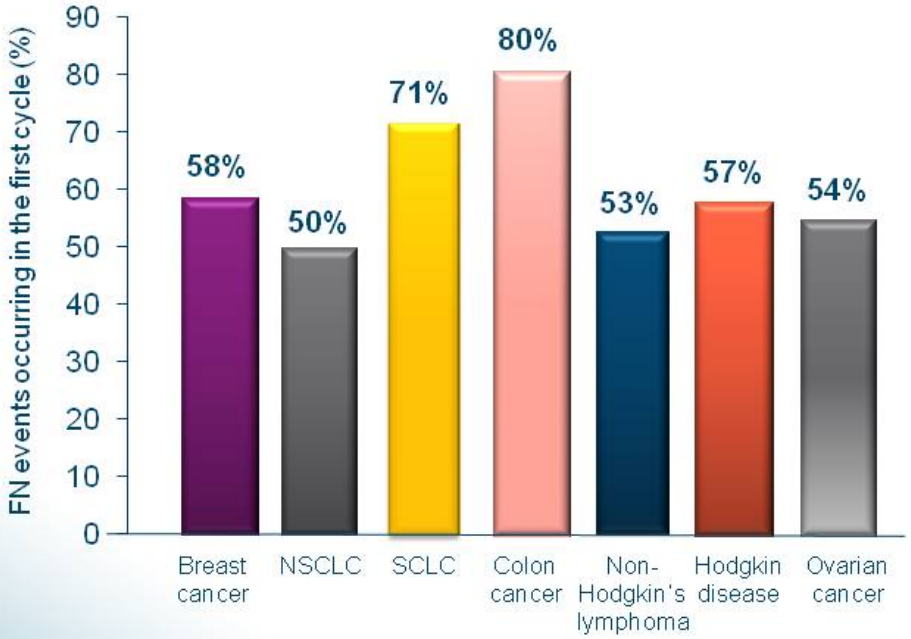
What is the Risk?

Incidence of Febrile Neutropenia	
Induction-remission for AML	70-90%
Elderly patients receiving CHOP	35-45%
Patients with NHL	10-20%
Mortality Estimates from Febrile Neutropenia	
Solid tumours	5%
Hematological malignancy	Up to 11%
Gram-positive bacteremia	5%
Gram-negative bacteremia	18%

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



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

Crawford et al. J Natl Compr Canc Netw 2008;6:109–18.

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

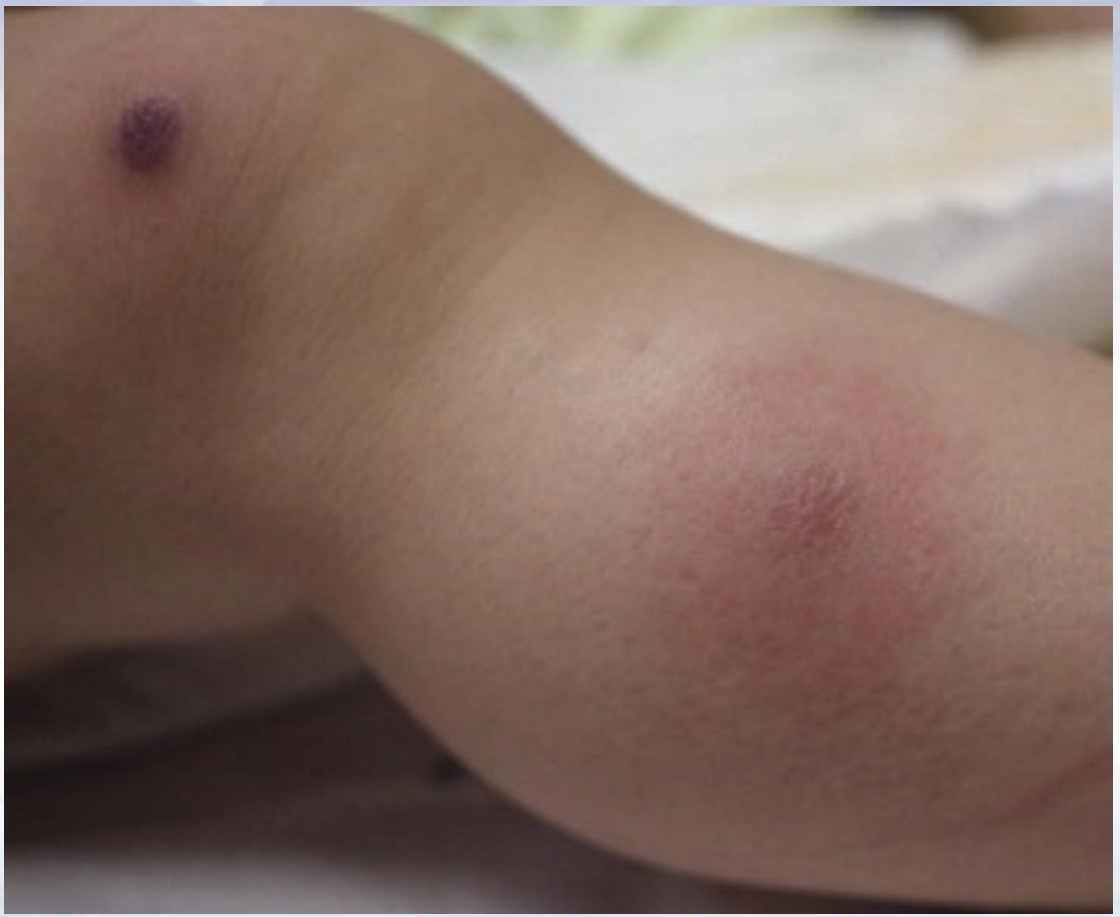
IMPORTANT CLINICAL SETTINGS IN PATIENTS WITH FN

- 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)

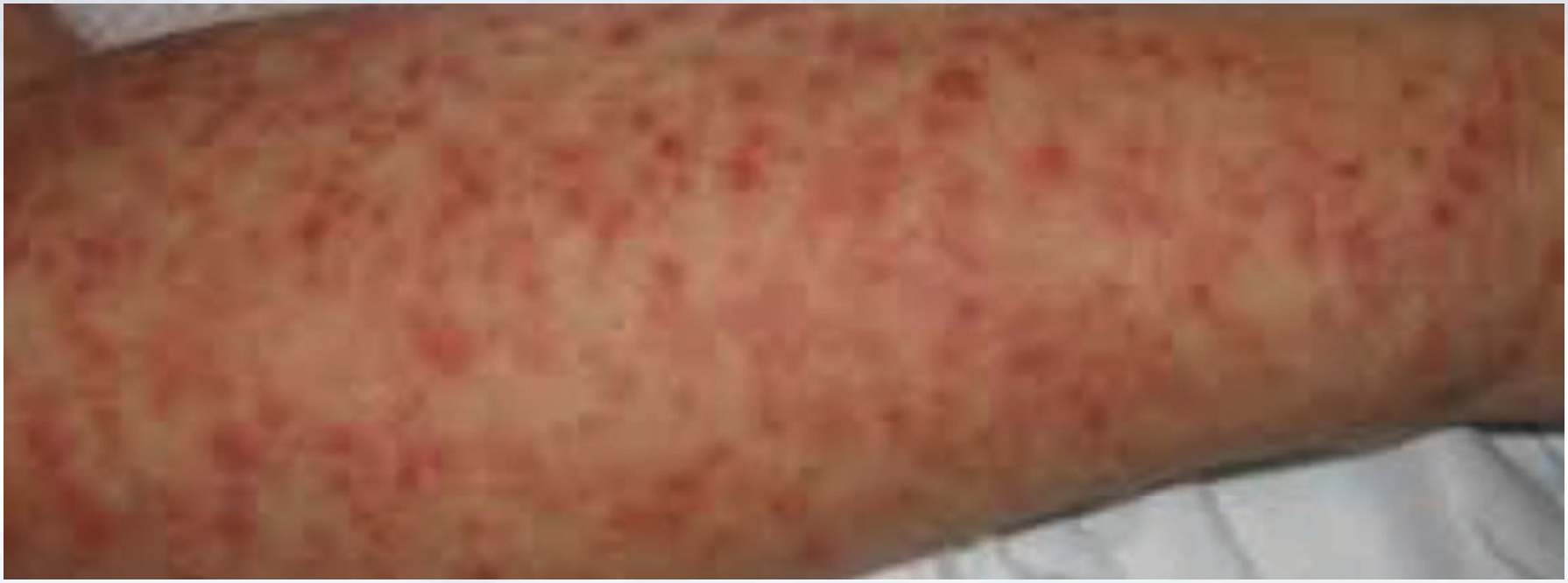
SPECIFIC ASPECTS OF THE CLINICAL EXAMINATION IN FN

- 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



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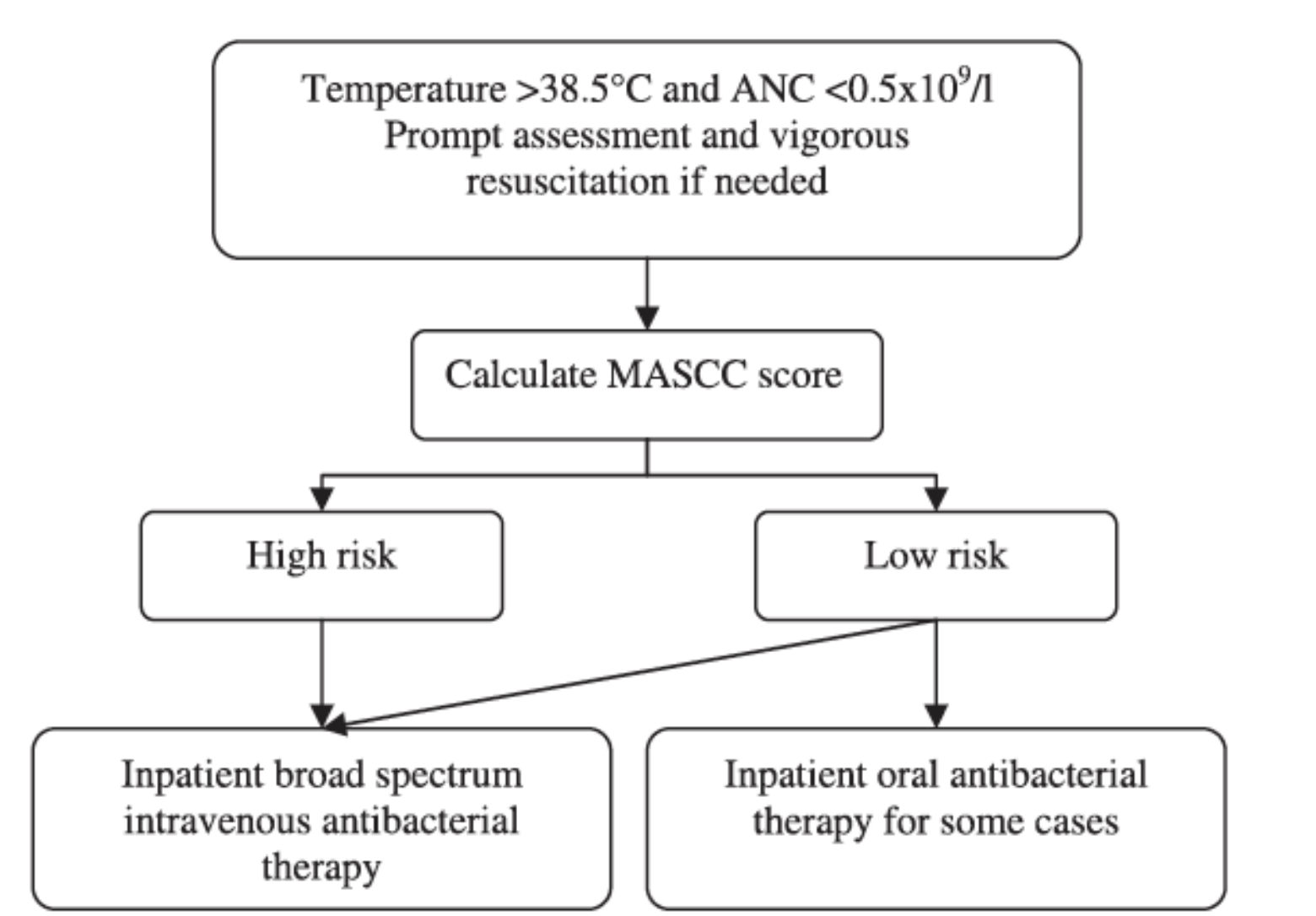
SPECIFIC ASPECTS OF THE CLINICAL EXAMINATION IN FN

- 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



RISK ASSESSMENT MASCC

Group	Characteristic
I	Inpatients (at the time of fever onset)
II	Outpatients with acute comorbidity requiring, by itself, hospitalization
III	Outpatients without comorbidity but with uncontrolled cancer
IV*	Outpatients with cancer controlled and without comorbidity

*Group IV is considered to be low risk.[6]

RISK ASSESSMENT MASCC

Characteristic	Score
Burden of illness: no or mild symptoms	5
Burden of illness: moderate symptoms	3
Burden of illness: severe symptoms	0
No hypotension (systolic BP >90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor/lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient status (at onset of fever)	3
Age <60 years	2

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 grater than 21 identifies low-risk patients with a positive predictive value of 91% (specificity 68% and sensitivity 71%)
- The Index has being validated by other institutions in their respective patient populations and clinical settings

RISK ASSESSMENT CISNE

Explanatory Variable*	No. of Points
Eastern Cooperative Oncology Group performance status ≥ 2	2
Chronic obstructive pulmonary disease	1
Chronic cardiovascular disease	1
National Cancer Institute Common Toxicity Criteria mucositis of grade ≥ 2	1
Monocytes < 200/μL	1
Stress-induced hyperglycemia	2

*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

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 antibitiotic 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 grater 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

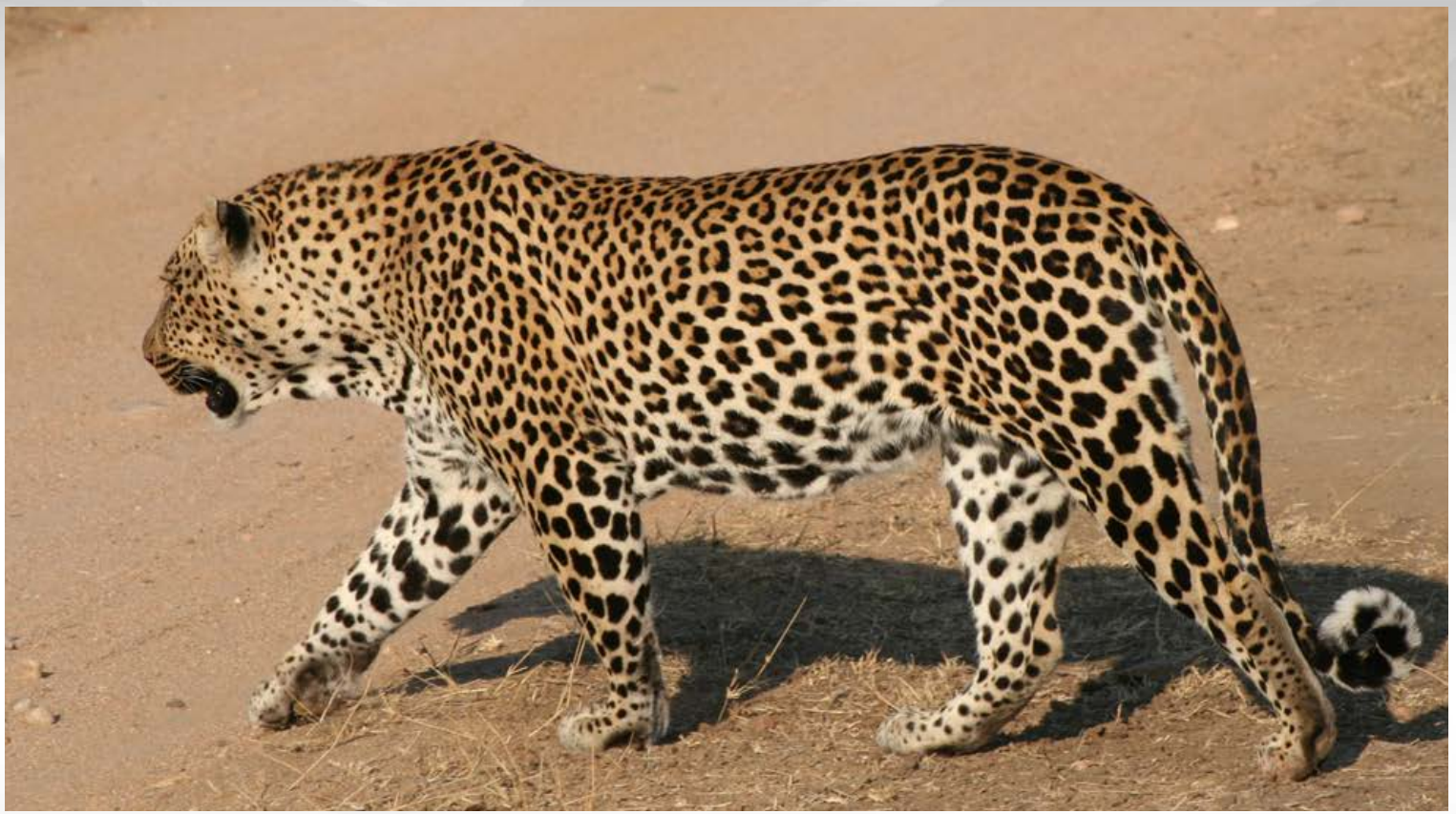
- Observation of low risk patients by experienced adequate staff
- Facility must be in proximity to an emergency care facility
- Adequate infrastructure for emergency management
- These facilities should also include fluid resuscitation, intravenous antibiotics and high care facility in the institution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



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Questions?