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新光吳火獅紀念醫院急診醫學部

# ER-Infection Combined Conference

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## Discussion

- Fever of Unknown origin (FUO)
- Febrile neutropenia (Netropenic fever)
- When FUO meets neutropenia

## Fever of unknown origin

- Fever of unknown origin
  - Definition
    - Fever>38.3'C
    - Duration>3 weeks or >1 weeks after inpatient investigation

TABLE 18-1 Categories of FUO

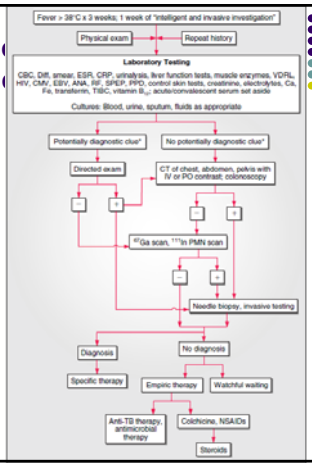
| Feature | Category of FUO | | | |
|---|---|---|---|---|
| | Nosocomial | Neutropenic | HIV-Associated | Classic |
| Patient's situation | Hospitalized, acute care, no infection when admitted | Neutrophil count either <500/μL or expected to reach that level in 1–2 days | Confirmed HIV-positive | All others with fevers for ≥3 weeks |
| Duration of illness while under investigation | 3 days[a] | 3 days[a] | 3 days[a] (or 4 weeks as outpatient) | 3 days[a] or three outpatient visits |
| Examples of cause | Septic thrombophlebitis, sinusitis, *Clostridium difficile* colitis, drug fever | Perianal infection, aspergillosis, candidemia | MAI[b] infection, tuberculosis, non-Hodgkin's lymphoma, drug fever | Infections, malignancy, inflammatory diseases, drug fever |

## Fever of unknown origin

TABLE 18-3 Ten Leading Causes of Classic FUO among Adults at Community Hospitals in the United States

| Cause | % of Total |
|---|---|
| Lymphoma | 16 |
| Collagen vascular disease | 16 |
| Abscess | 13 |
| Undiagnosed cause | 9 |
| Solid tumor | 8 |
| Thrombosis or hematoma | 7 |
| Granulomatous disease, nonmycobacterial | 5 |
| Endocarditis | 5 |
| Mycobacterial disease | 5 |
| Viral disease | 5 |
| Remaining causes | 11 |
| | 100 |

## Fever of unkn




## Febrile neutropenia

- Febrile neutropenia (Neutropenic fever)
- Definition (IDSA 2002 guideline):
  - Fever>38.3'C or fever>38'C for 1 hour
  - ANC<500 cells/ml or ANC<1000 with a predicted decrease to <500 cells/ml
- Fever can be the only infectious signs in patients with neutropenia
  - Febrile reaction involved neutrophils, endothelium, lymphocyte, macrophage…
  - Notably bacterial infection (especially Gram negative)
  - Common infection sites: lungs (25%); mouth and pharynx (25%); soft tissue; skin and CVC (15%); perineum (10%); GI/GU tract (5%) and the nose/sinuses (5%)

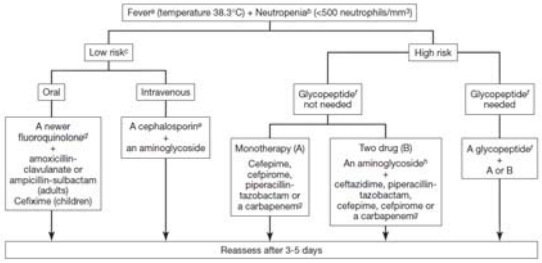
## Febrile neutropenia

- Pathogens:
  - Gram-negative in 80% of cases, gram-positive in 60% of cases
  - E. coli (29%), Pseudomonas aeruginosa (18%), Klebsiella sp (16%)

**Table 3. Medical complications in 72 febrile neutropenic patients with bacteremia due to a single pathogen, according to pathogen and Multinational Association for Supportive Care in Cancer (MASCC) score.**

| | No (%) of patients, by class of pathogen and risk group | | | |
|---|---|---|---|---|
| | Gram-negative | | Gram-positive | |
| Outcome | Low risk ($n = 13$) | High risk ($n = 20$) | Low risk ($n = 26$) | High risk ($n = 13$) |
| Resolution | | | | |
| Without complications | 11 (85) | 5 (25) | 20 (77) | 9 (69) |
| With complications | 2 (15) | 6 (30) | 5 (19) | 4 (31) |
| Death | 0 | 9 (45) | 1 (4) | 0 |

## Febrile neutropenia




Cheng Deh-lin et al. Guideline for the use of antimicrobial agents in patients with febrile neutropenia in Taiwan. J Microbiol Immunol Infect 2005;38:455-457

## Febrile neutropenia

**Table 3. Factors that favor a low risk for severe infection among patients with neutropenia.**

| |
|---|
| Absolute neutrophil count of >100 cells/mm³ |
| Absolute monocyte count of >100 cells/mm³ |
| Normal findings on a chest radiograph |
| Nearly normal results of hepatic and renal function tests |
| Duration of neutropenia of <7 days |
| Resolution of neutropenia expected in <10 days |
| No intravenous catheter-site infection |
| Early evidence of bone marrow recovery |
| Malignancy in remission |
| Peak temperature of <39.0°C |
| No neurological or mental changes |
| No appearance of illness |
| No abdominal pain |
| No comorbidity complications[a] |

**Table 1. Scoring system for risk of complications among febrile neutropenic patients, based on the Multinational Association for Supportive Care in Cancer predictive model [6].**

| Characteristic | Point score |
|---|---|
| Burden of illness | |
| No or mild symptoms | 5 |
| Moderate symptoms | 3 |
| No hypotension | 5 |
| No chronic obstructive pulmonary disease | 4 |
| Solid tumor or no previous fungal infection in hematologic tumor | 4 |
| Outpatient status | 3 |
| No dehydration | 3 |
| Aged <60 years | 2 |

Score>21: low risk

## Febrile neutropenia

- G-CSF administration
  - shorten the duration of neutropenia, but not morbidity
  - Not routinely recommended for uncomplicated patients
- Granulocyte transfusion +/- dexamethasone
  - No evidence of efficacy
  - use with caution of toxicities (CMV infection, fever, GVHD…)

## When FUO meets Neutropenia…

- Benign presentation?
  - 49% low risk group vs. 35% high risk group
  - Lack of evidence of localized infection
  - But higher mortality rate if FUO not respond to initial antibiotics treatment
- Repeated physical exam and history taking is needed
- Laboratory exam
  - CRP vs procalcitonin?
  - Procalcitonin level associated with systemic bacterial infection and response to antibiotics

## When FUO meets Neutropenia…

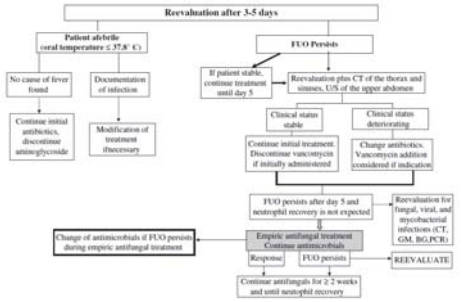



Fig. 2. Re-evaluation of the patient with febrile neutropenia during the episode. BG, β-D-glucan; CM, colistin methanesulfonate; PCR, polymerase chain reaction.

## When FUO meets Neutropenia…

- Neutropenia with no known chemotherapy or irradiation?
  - Causes other than infection are needed to be found

## Take home message

- Fever of unknown origin
  - Definition
  - Differential diagnosis
- Febrile neutropenia
  - Definition
  - Management: empiric antibiotics
- Detailed history taking and physical exams

## Thanks for your attention!


Reference:

1. Harrison's internal medicine, 17th edition
2. Hughes et al. 2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer. Clinical Infectious Diseases 2002; 34:730–51
3. Cheng Deh-lin et al. Guideline for the use of antimicrobial agents in patients with febrile neutropenia in Taiwan. J Microbiol Immunol Infect 2005;38:455-457
4. Anastasia Antoniadou MD et al. Fever of Unknown Origin in Febrile Leukopenia. Infect Dis Clin N Am 21 (2007) 1055–1090
5. Jean Klastersky. Management of Fever in Neutropenic Patients with Different Risks of Complications. Clinical Infectious Diseases 2004; 39:S32–7