38.3 + 60

Febrile neutropenia

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Bannatyne Campus CPD Program ONCOLOGY DAY

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Presenter Disclosure

- **Faculty / Speaker's name: Mark Kristjanson**

- **Relationships with commercial interests: None**

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Mitigating Potential Bias

- Not applicable

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Learning Objectives

1. Describe (and more readily recognize) the spectrum of clinical syndromes with which neutropenic fever can present.
2. Understand and use the risk assessment tools that can guide the choice of an appropriate antimicrobial regimen for a given patient presentation with FNE.
3. Explain what clinical difference it makes to patients who present with FNE to receive appropriate initial empirical antibacterial therapy within 60 minutes of triage.

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INFECTION PREVENTION AND CONTROL
POLICIES, PROCEDURES, GUIDELINES AND PROTOCOLS

PROTOCOL TITLE: **Neutropenia Protocol – Identification and Management of Neutropenic Fever Syndromes**		
SECTION: Infection Control Services	PROTOCOL NO.: 12.500	APPROVED BY THE PRESIDENT AND CEO, CCMB *Original signed by Dr. S. Navaratnam*
DATE: February 6, 2012 Latest Review: May 8, 2017	PAGE: 1 of 22	

1.0 BACKGROUND:

1.1 Patients with cytotoxic therapy-induced severe neutropenia and mucositis are at risk for potentially life-threatening invasive bacterial infections. [1,2]

1.2 Risk factors for developing a neutropenic fever syndrome include older age, female sex, marrow invasion by cancer, reduced granulopoiesis, poor nutritional status, integumental damage, hematological malignancy, and active co-morbid conditions.[3,4]

1.3 Delayed and/or inappropriate treatment of neutropenic fever syndromes is associated with increased morbidity and mortality.[5]

1.4 Successful management of neutropenic fever syndromes in cancer patients is time-sensitive.[6] Timely intervention may be life-saving.[7]

1.5 Rapid triage to recognize and prioritize neutropenic sepsis syndromes for emergent initial empirical anti-bacterial therapy is critical to successful outcome of such events.[8]

Neutropenia

- Neutropenia, severe: ANC of <500 cells/mm^3 (<0.5 x 10^9/L)
- ANC < 1.0 x 10^9/L predicted decline in next 48H to <500 cells/mm^3
- Neutropenia, profound: ANC <100 cells/mm^3 (<0.1 x 10^9/L)
- Fever: a single oral temperature (T) ≥ 38.3ºC
- or > 38ºC (100.4ºF) for one hour
- or >38ºC (100.4ºF) at least twice over 12 hours

CCMB Neutropaenia Protocol February 6th, 2012

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SIRS: Systemic Inflammatory Response

The presence of ≥ 2 of the following:

- Body temperature of > 38°C or < 36°C;
- heart rate > 90 bpm;
- RR > 20/min or $PaCO_2$ of < 32 mmHg;
- WBC > 12 x 10^9/L or < 4.0 x 10^9/L or > 10% bands

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More Definitions

Sepsis Syndrome

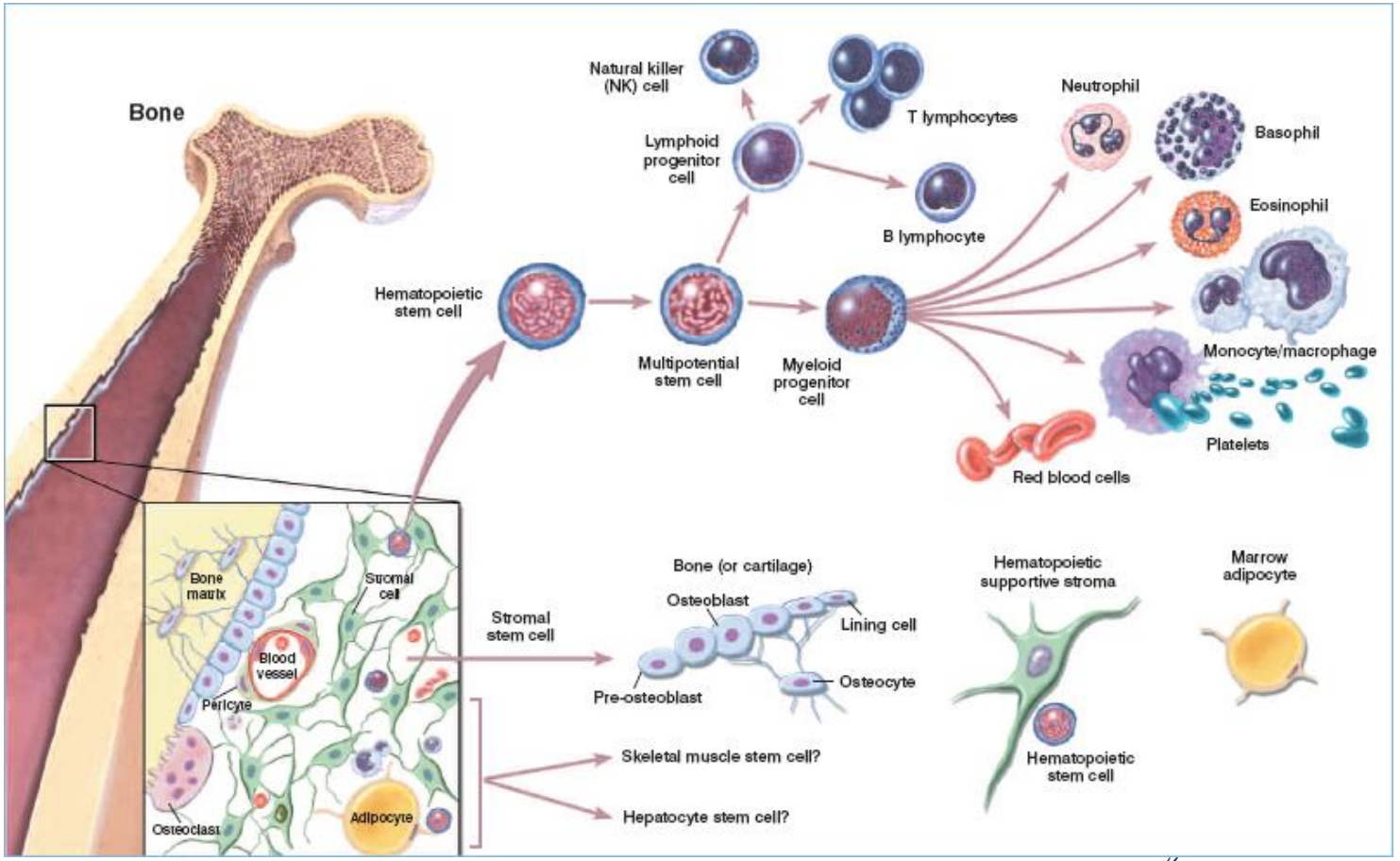
- The term “sepsis” is defined as SIRS that is as a result of a confirmed infectious process.

Severe Sepsis Syndrome

- sepsis syndrome + hypotension or hypoperfusion (e.g. lactic acidosis, oliguria, or confusion).

Septic Shock

- sepsis-induced hypotension despite adequate fluid resuscitation + evidence of hypoperfusion.



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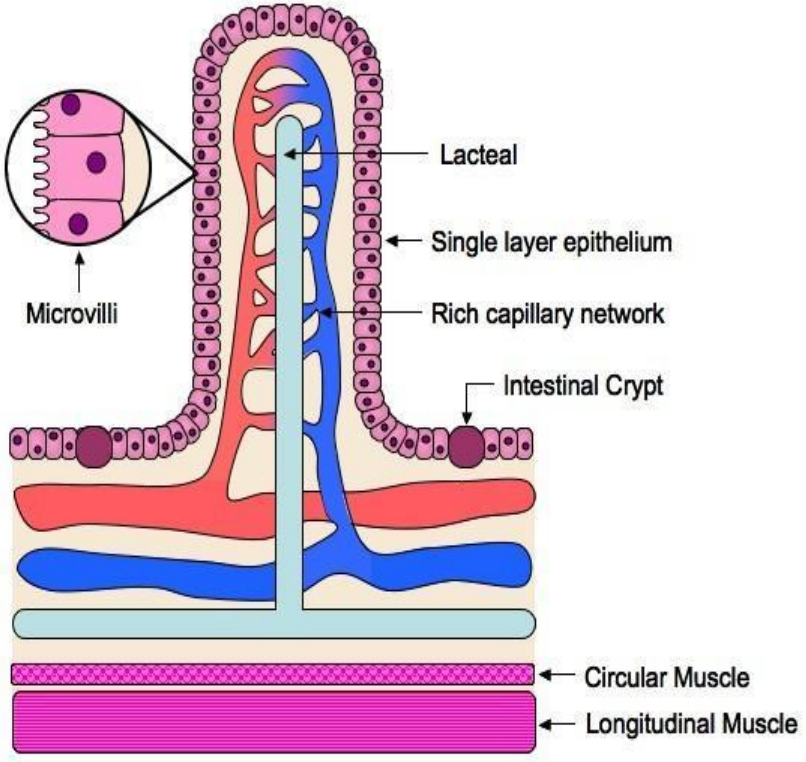
FNE: Pathophysiology



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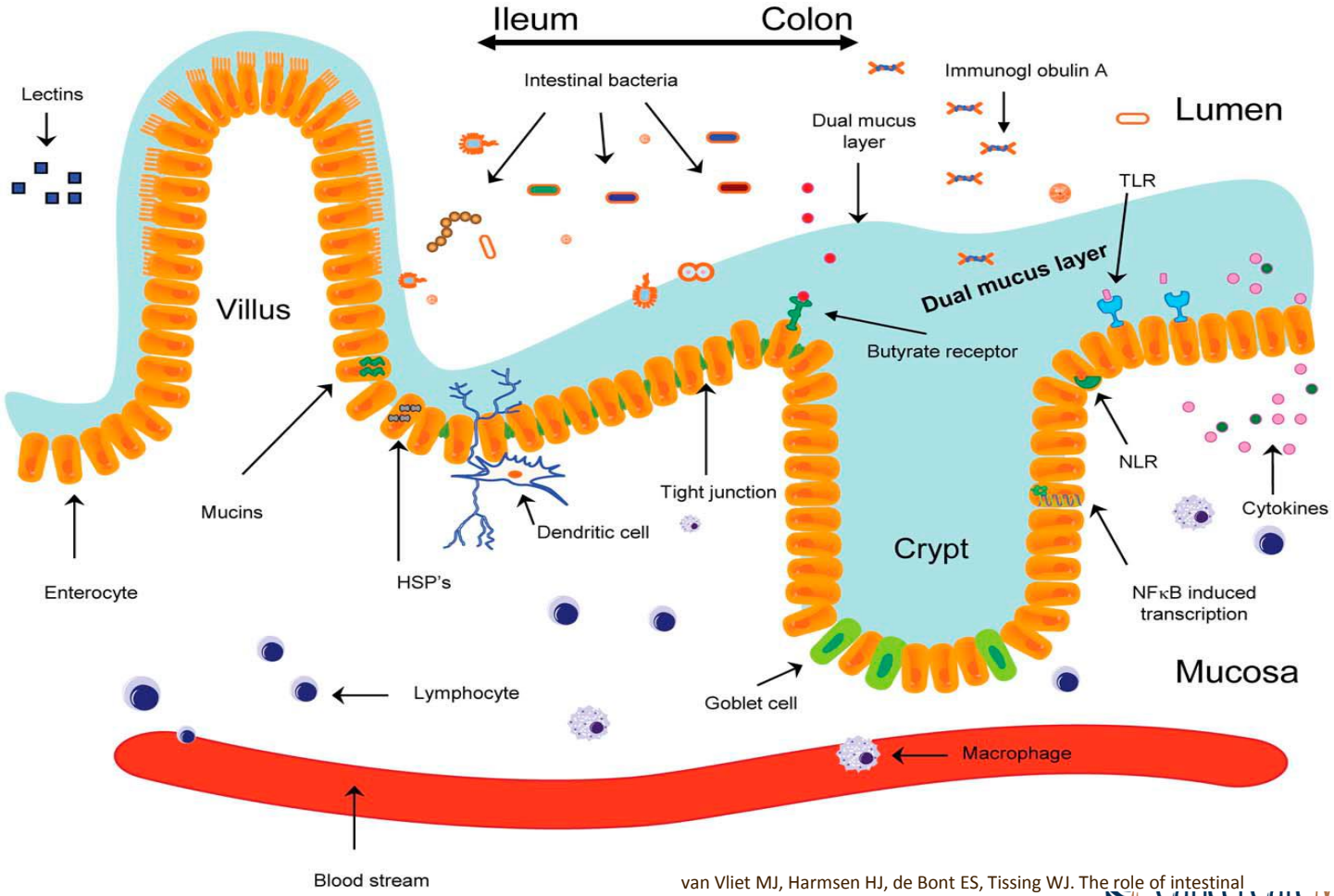
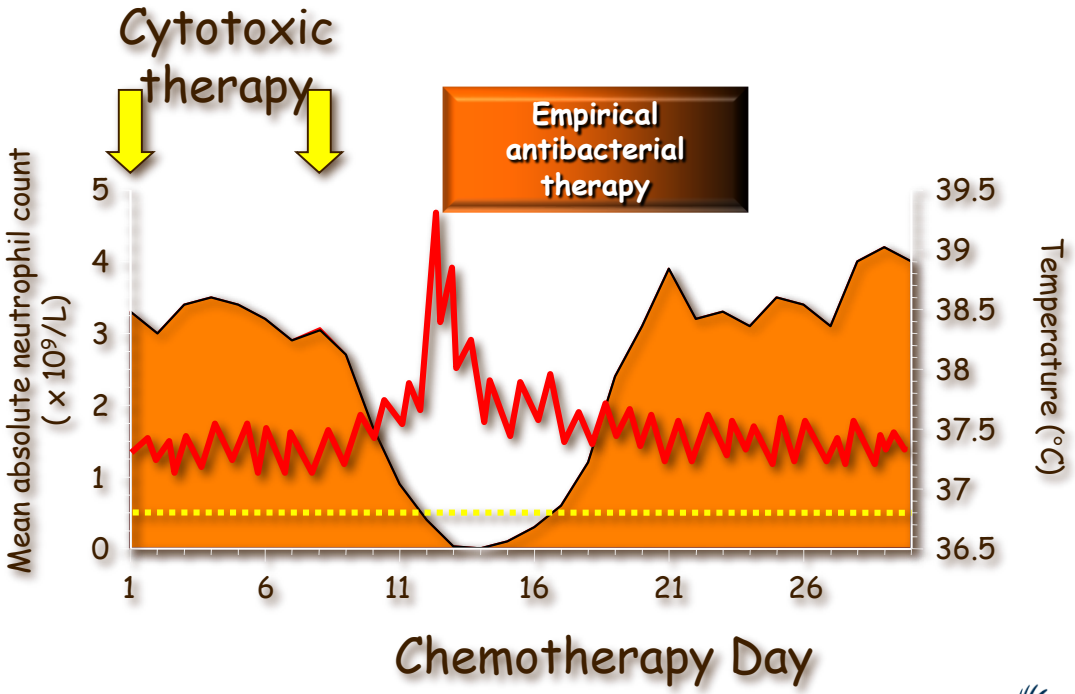


van Vliet MJ, Harmsen HJ, de Bont ES, Tissing WJ. The role of intestinal microbiota in the development and severity of chemotherapy-induced mucositis. PLoS pathogens **2010**; 6(5): e1000879.

INFECTION IN FEBRILE NEUTROPAENIC PATIENTS

Profile for "Low-risk" Solid Tumour Patients

Bow E.J. Semin Hematol 2009;46(3):259-68



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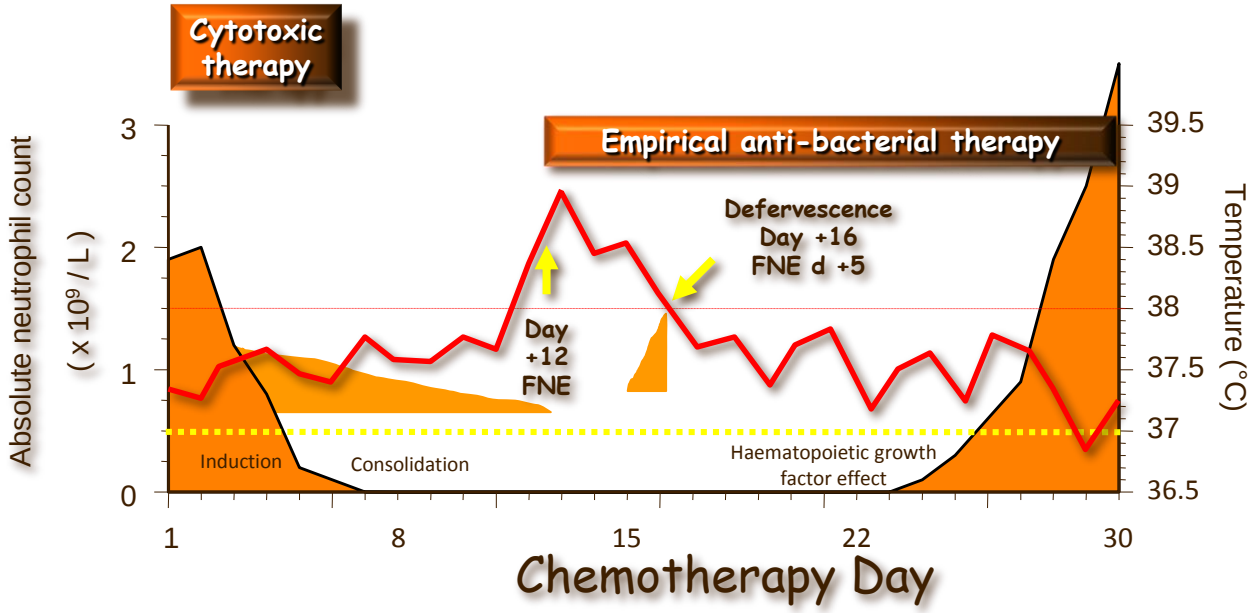
FEVER AND INFECTION IN NEUTROPAENIC CANCER PATIENTS

The "1st Fever" Profile: "High-risk" . . .

Bow E.J. Semin Hematol 2009;46(3):259-68



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Filgrastim

- Natural G-CSF is 175 amino acid glycoprotein
- produced by monocytes, fibroblasts, endothelial cells
- Binds to hematopoetic cell surface receptors
- Stimulates production by the marrow of neutrophils
- Recombinant Granulocyte Colony Stimulating Factor (G-CSF)+ N-terminal methionine = Filgrastim
- Elimination half life of 3.5 H

Filgrastim

- Not for the management of acute febrile neutropenia
- Exception: septic shock; ICU admission

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CCMB FNE Protocol: Risk Assessment

Risk - for developing medical complications that may require admission to hospital or prolong hospitalization.

"**Low-risk**" patients have the following characteristics:

- i) Out-patient status at the time of development of fever
- ii) No associated acute active co-morbidities
- Anticipated duration of severe neutropenia of < 7 days

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Risk Assessment, cont.,

- iv) Good performance status (ECOG 0-1)
- v) Normal serum creatinine
- vi) Liver function tests less than 3x the upper limit of normal
- vii) MASCC score of ≥ 21

MASCC Score (maximum = 26)

- **Burden of Illness: no or mild symptoms.....5**
- **Systolic greater than 90.....5**
- **No COPD.....4**
- **Solid tumor OR no previous invasive fungal infection..4**
- **No dehydration.....3**
- **Outpatient at onset of fever.....3**
- **Burden of illness – moderate symptoms.....3**
- **Age less than 60.....2**
- **TOTAL..... _____**

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IV Access & Fluids

- CVAD or 18 gauge in peripheral vein
- Normal (0.9%) saline
- Is patient hypotensive (systolic blood pressure < 90 mmHg or mean BP < 65 mmHg)?
- 500 millilitre “fluid challenge”
- 30 millilitres/kilogram/3 hours) over 30 min
- otherwise IV infusion of 125-150 millilitres/H to maintain
- urine output of > 0.5 millilitres/kilogram/hour

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Blood cultures

- before antibiotic administration.
- 2 sets (1 set = 1 aerobic + 1 anaerobic bottle) from separate anatomic sites
- 10 millilitre **aerobic** blood sample from each lumen of an existing CVAD
- plus an **aerobic and** an **anaerobic** bottle from a peripheral site; or
- one set each from at least two peripheral sites

Blood work

- CBC & diff
- Electrolytes (Na+ , K+ , CL- , total CO2)
- Glucose
- BUN/Cr
- Venous blood gases
- Lactate
- INR, PT
- AST, ALT, LDH, GGT, Alk Phos, Bilirubin (t & d)

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FNE: Initial Antimicrobial Therapy

- oral fluoroquinolone* (levofloxacin 750 mg od or ciprofloxacin 750 mg BID
- plus amoxicillin/clavulanate** (500/125 TID)
- Contact by telephone within 24 hours
- Clinic visit within 48-72 hours, and every 2nd day
- until defervescence and myeloid reconstitution

***unless given as primary prophylaxis**

**** if penicillin allergic give clindamycin**

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FNE: Initial Antimicrobial Therapy

- hospitalize for IV initial empirical antibiotic therapy
- monotherapy with anti-pseudomonal β-lactam agent, such as cefepime, a carbapenem, or piperacillin-tazobactam
- Piperacillin/tazobactam 4.5 grams IV Q 8 hours (CCMB)

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Barriers to Practice Change?

- In what settings do you practice?
- Have you encountered FNE in your practice?
- How does your approach to FNE differ from the updated CCMB recommendations?
- What barriers exist to adopting these recommendations?
- How might you address those barriers?

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Thank You!

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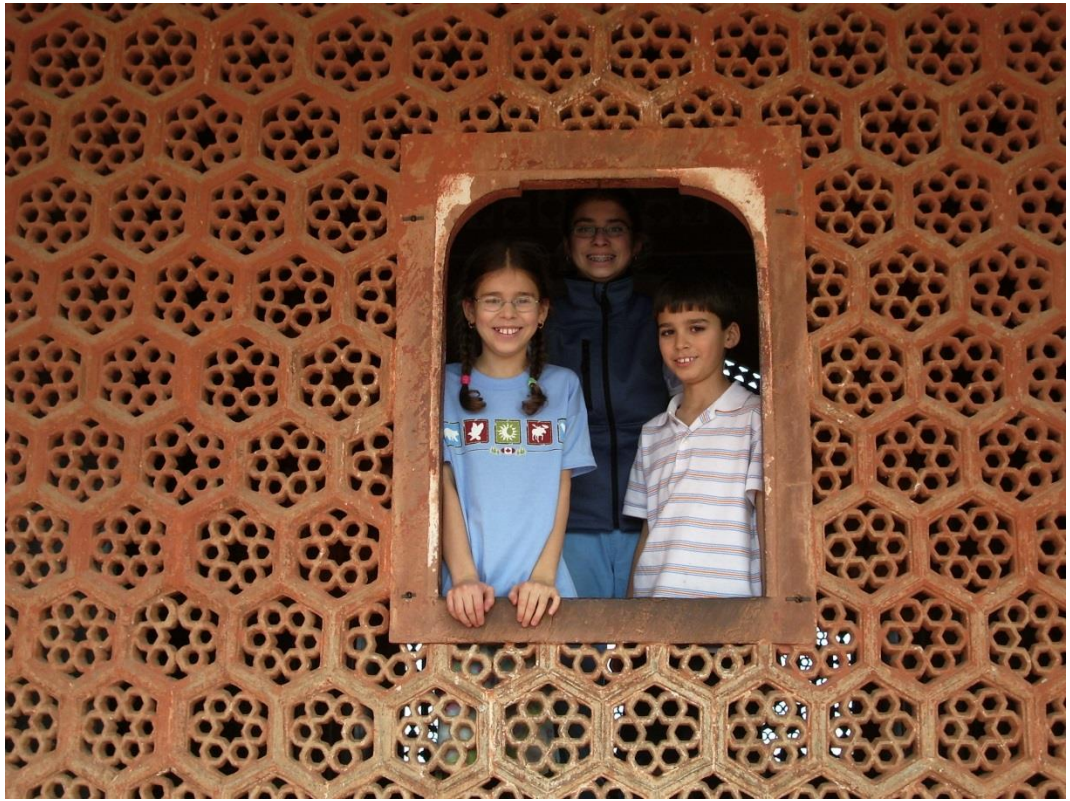
My Other Monkeys…..11 years ago



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Immediate or Accelerated Penicillin Allergy: Low Risk

- ciprofloxacin 750 milligrams PO every 12 hours or
- levofloxacin 750 milligrams PO every 24 hours plus
- clindamycin 600 milligrams PO every 8 hours

Delayed Penicillin Allergy: Low Risk

- ciprofloxacin 750 milligrams PO every 12 hours **or**
- levofloxacin 750 milligrams PO every 24 hours

+

- clindamycin 600 milligrams PO every 8 hours **or**
- cefixime 400 milligrams PO every 24 hours **or**
- cefuroxime 500 milligrams PO every 12 hours
- **or**

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Delayed Penicillin Allergy: Low Risk

- ceftriaxone 2 grams IV every 24 hours
- **+**
- amikacin 15-20 milligrams per kilogram IV every 24 hours
- **or**
- Monotherapy with moxifloxacin 400 milligrams PO OD

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Immediate or Accelerated Penicillin Allergy: High Risk

- meropenem 1 gram IV every 8 hours or
- Ciprofloxacin* IV + vancomycin** IV

- *400 mg Q 12H
- **15 mg/k Q 12H

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Severe Sepsis/Septic Shock

- consider adding an aminoglycoside such as:
- gentamicin or tobramycin 7 milligrams per kilogram IV daily or
- amikacin 15-20 milligrams per kilogram intravenously daily in one or more divided doses.

MRSA

- If skin/soft tissue MRSA infection or
- CVAD-related infection due to MRSA or a coagulase-negative Staphylococcus spp.
- **add** vancomycin 15 milligrams per kilogram per dose IV every 12 hours.
- If CVAD- related bloodstream infection due to S. aureus or a Candida spp., remove the CVAD

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VRE

- If vancomycin-resistant Enterococcus colonization
- consider adding linezolid 600 milligrams IV every 12 hours

Duration of Treatment

- The average time to defervescence:
- low-risk ~ 2-3 days*
- high-risk patients ~ 5 days*

- *Regimen modification is not recommended before this time in the absence of clinical deterioration or progression or unless antibacterial susceptibility testing suggests that the spectrum of antibacterial activity is suboptimal.

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Failure to Defervesce?

- Deterioration or failure to defervesce after 5 days of initial therapy?
- Consult Infectious Diseases
- Suggested modifications:
- i) Vancomycin if MRSA skin/soft tissue infection
- ii) Metronidazole 500 mg PO/IV Q 8 Hif necrotizing gingivitis or intra-abdominal focus
- iii) Empirical anti-fungal therapy may be considered if neutropenic & febrile despite 7 days of broad-spectrum antibacterial therapy

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