Evaluation of the Patient with Fever
Fever = Temp > 38.3°C

1. Is the fever infectious or non-infectious?
   a. Infectious
      i. Bacterial
      ii. Viral
      iii. Fungal*
   b. Non-infectious
      i. Inflammatory: vasculitis, autoimmune, DVT
      ii. Malignancies: especially hematologic
      iii. Drug mediated: serotonin syndrome, neuroleptic malignant syndrome, meds (antibiotics [β-lactams, sulfa], anticonvulsants, allopurinol, others)
   c. * Risk factors include steroids, CVN, malignancies, prolonged neutropenia

2. If infectious, what is the likely source?
   a. Most common nosocomial infections are pneumonia, UTI, bloodstream infections from an IV or central line.
   b. Hospital acquired pneumonia/ventilator associated pneumonia; MRSA; VRE; Clostridium difficile; line associated bacteremia; urinary tract infection

3. What is the patient’s immune status?
   a. Recognize that some patients with altered immune systems may have difficulty mounting a febrile response to infection.
   b. Immune suppressed/Increased infection risk populations
      i. Medications (steroids, TNF-α inhibitors, others)
      ii. Hematologic malignancies
      iii. Elderly
      iv. Chronic liver disease/cirrhosis
      v. Chronic renal failure
      vi. Splenectomized patients (encapsulated organisms like pneumococcus, H. flu, meningococcus – ask about vaccinations)

4. What should the initial workup be?
   a. Rule out infectious causes
      i. CXR, U/A with micro and culture, blood cultures (including one form any indwelling lines)
      ii. Target other areas for workup per clinical suspicion based on history and physical exam

Neutropenic Fever
- Neutropenia = < 500 – 1000 neutrophils (PMNs + bands)
- Neutropenic fever = Temp > 38.0°C for more than one hour or single temp > 38.3°C
  o Indication for admission for IV antibiotics
  o Work-up with CXR/panculture, clinical suspicion as above
  o Always get cultures before starting antibiotics
  o Select/tailor antibiotics to target known infection
In absence of obvious source need to empirically treat with broad spectrum coverage (IDSA guidelines suggest cefepime, ceftazidime, meropenem, or imipenem ± vancomycin
If still febrile after 48 hours of antibiotics, empirically add Vancomycin (if not started already)
If still febrile after five days, consider adding an anti-fungal agent
GCSF shown to shorten hospital stays, but does not change mortality

Fever of Unknown Origin (FUO)

- Definition:
  - Fever of 38.5°C on more than one occasion
  - Duration at least three weeks
  - No diagnosis despite one week of intensive evaluation

- Etiologies
  - 30% Infection (TB, endocarditis, intraabdominal abscess, osteomyelitis, viral/parasitic)
  - 30% Connective Tissue Disease (giant cell arteritis, Polyaeritis nodosa, RA, DLE, sarcoidosis)
  - 20% neoplasm (lymphoma, renal cell, hepatocellular, pancreatic, colon, atrial myxomas, leukemia, myelodysplasia)
  - 20% miscellaneous (drugs, factitious, hematoma, thyroid, adrenal insufficiency)

- Work-Up
  - Thorough Hx and PE
  - D/C unnecessary drugs
  - Labs (CBC, ESR, chem7, LFTs, ANA, RF, cryoglobulin)
  - Blood cultures X3
  - U/A, micro and culture
  - PPD
  - Consider HIV, CMV, heterophile antibody
  - Consider bone marrow
  - Imaging (CXR, CT, ?tagged WBC scan)

- Empiric antibiotics not indicated unless neutropenia

Antibiotics

1. Coverage
   a. Drugs that cover MRSA
      i. Vancomycin (IV)
      ii. Linezolid (PO)
      iii. Daptomycin (IV)
      iv. Bactrim (IV/PO)
      v. Clindamycin (IV/PO)
   b. Drugs that cover Pseudomonas
      i. Piperacillin-tazobactam (Zosyn – IV)
      ii. Cefepime (IV)
      iii. Ceftrazidime (IV)
iv. Ciprofloxacin (PO)

v. Gentamicin (IV)

vi. Meropenem (IV)

vii. Aztreoam (IV)

c. Drugs that cover anaerobes
   i. Metronidazole (IV/PO)
   ii. Clindamycin (IV/PO)
   iii. Amoxicillin-clavulanic acid (Augmentin – PO)
   iv. Piperacillin-tazobactam (Zosyn – IV)
   v. Ampicillin-sulbactam (Unasyn – IV)

2. 12% of MRSA infections may be community acquired. Community acquired infections most commonly cause cutaneous infections.

3. Dosing Vancomycin
   a. Standard starting dose: 1g IV q 12h but adjusted according to patient’s age, body mass, and renal function (generally 10 – 15 mg/kg)
   b. Check trough immediately prior to the 4th dose
   c. Goal trough in uncomplicated bacteremia is 10 – 15
   d. In hardware, bone, endocarditis, CNS goal of trough 15 – 20
   e. Dialysis patients and patients with chronic kidney disease should get single doses and then re-check levels over next few days to maintain levels > 15

4. Other considerations
   a. Antibacterial cross-reactivity
      i. Be aware that an allergic response to penicillins carries risk of allergy to other beta lactams like cephalosporins and carbapenems (imipenem and meropenem), but does not to monopenems (aztreonam)
   b. Bacterial colonization
      i. Growth on culture without inflammatory response (no WBCs on gram stain) suggests colonization rather than true infection
      ii. Beware of this type of interpretation in neutropenic patients
   c. Abscess/Closed Infection
      i. Treatment is drainage or removal (placement of drain or surgical removal)
      ii. Antibiotics can slow progression/suppress bacteremia but are NOT curative

SIRS: Systemic Inflammatory Response Syndrome

- Defined as patients having two or more of the following
  - Temp > 38.0°C or < 35.0°C
  - RR > 20 or pCO2 < 32
  - HR > 90
  - WBC > 12,000 or < 4,000 or with > 10% band forms

- Sepsis = SIRS + documented infection as the cause

- Estimated mortality
- SIRS: 7%
- Sepsis (not severe sepsis or septic shock): 16%