Infections in immunocompromised children

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Objectives

• What it means to be immune compromised

• Management of
  – Fever and neutropenia
  – Fungal infections

• Travels of a blood culture bottle
  – Mechanics of the microbiology lab
Purpose of immunity

• Surveys and fight “non-self” particles
• In the context of infectious disease
  – The immune system recognizes infections
    • Bacteria
    • Viruses
    • Fungus
Components of immunity

• Innate immune system
  – Structural: skin (broken with central line)
  – Cells
    • Neutrophils, macrophages, eosinophils
    • Innate immune cells: “fast but stupid”

• Adaptive immune system
  – Cells
    • Lymphocytes “slow but deliberate”
      – B cells: produce antibodies
      – T cells: provide help to other immune cells, can also directly kill
Defining immune compromise

• Quantitative
  – Lacking the appropriate number of cells
  – Neutropenia – low number of neutrophils
    • Low ANC translates to increased risk of bacteria and fungus
  – Lymphopenia – low numbers of lymphocytes
    • Low ALC translates to increased risk of viral disease
Defining immune compromise

• Qualitative
  – Lacking the expected function
  – Examples
    • CGD – the neutrophils race to the site of infection, then just hang around
    • Following bone marrow transplantation – lymphocytes are a bit stunned for up to 12 months, so viral infections can reactivate
Immune-compromised children

- Congenital
- Acquired
  - HIV
  - Chemotherapy
  - Following bone marrow transplantation
- In Heme-Onc, acquired immune deficiencies are both quantitative and qualitative
Acquired immunodeficiency

• When do we induce immunodeficiency?
  – Cancer chemotherapy
  – Pre-transplant regimens (prior to HSCT)
  – Post-transplant regiment (HSCT, SOT)

• Purpose/benefits of immunosuppression (IS)
  – Eradication of malignant cells
    • To induce remission
    • To prepare for HSCT
  – To allow cells to accept foreign host
    • Prevention of graft-versus-host disease (GVHD)
  – To allow body to accept foreign tissue
    • Reduce rejection of solid organ by host

• Risk of immunosuppression
  – Decreased ability to combat infection
Risks of immune compromised patients

• Infections
  – 1970s – when giving chemotherapy to oncology patients, **they could die of infection**
    • Usual infections: but more severe and rapid
      – Bacteria
    • Opportunistic infections: otherwise not seen in healthy patients
      – Pneumocystic pneumonia
      – Fungus: yeast and mould
Acquired immunodeficiency

• In immunocompromised patients, where do the pathogens come from?

Endogenous flora (colonization)

Nosocomial exposure (sick contacts)

Reactivation of latent pathogens (latent viruses, TB)
What should we be afraid of?

• **Fever** in immunocompromised child
  – If neutropenic, lack of WBCs causes less inflammation in affected site
  – Fever may be (only) sign that something is wrong
    • May be only sign of infection...

• **Fever in neutropenic child is oncologic emergency**
  – Rapid evaluation
  – Administration of appropriate antibiotics
Fever and neutropenia

• Fever
  – Single fever of >38.3°C (101°F)
  – Sustained temperature >38.0°C (100.4°F)

• Neutropenia
  – Absolute: <1500 cells/mm³
  – PHO world: <500 cells/mm³
  – Profound: <200 cells/mm³
How common is fever?

• Once neutropenia is induced
  – Solid tumors: 10-50% of neutropenic patients will have fever
  – Hematologic malignancies: >80% of neutropenic patients will have fever

• Of all F&N: 20-30% will have documented infections
  – The vast majority of documented infections are bacteremia
    • Of all F&N: 10-25% will have bacteremia
Causes of fever

• In pediatric oncologic patients who are neutropenic:
  – Infection (only 1/3 of the time!)
    • But it is treatable...
  – Medications (chemotherapy, antibiotics)
  – Cancer itself
  – Tumor lysis
Identifying source of infection

• History (what does the patient tell you)
  – Specific complaints
  – Exposure to ill contacts
  – Duration of neutropenia
  – Underlying malignancy
  – Chemotherapeutics used
  – Previous antimicrobials
  – Previous infectious pathogens
F&N: what to look for

• Physical exam
  – Evidence of mucositis
    • Inspection of oral cavity
    • Inspection of peri-rectal region
  – Any localizing signs
    • Chest
    • Abdomen
    • Skin – areas of line insertion or biopsy sites
    • Etc...
F&N: what to test

• Blood
  – All ports of multi-lumen line
  – Utility of peripheral blood cultures?
• Urine

• Other sites (at your clinical discretion)
  – CXR: only with signs or symptoms
  – Skin swabs
  – Respiratory culture
  – Stool
  – CSF
F&N: how to treat

• Antibiotics
  – Watch and wait? **NO!**
    • Children with untreated bacteremia (particularly GNR) can **decompensate faster than the time it takes for the pathogen to be identified**
    • So start empiric antibiotic(s): **within 1 hour**
      – Don’t wait for CBC result

– What **EMPIRIC** anti-bacterial meds to use?
  • Coverage for Gram-negatives
    – Single antibiotic: 3\textsuperscript{rd}-4\textsuperscript{th} generation CEPH or carbapenem: **CEFEPIME (OHSU)**
Empiric antibiotics in F&N

• Criteria for a good antibiotic
  – Bactericidal
  – Anti-pseudomonal coverage
  – Minimal toxicity (above all – do no harm!)
  – Offer coverage of a site-specific infection
Bacterial infections in febrile neutropenic patients

- Epidemiology (over past 40 years)
  - Early 1960-70’s: mostly gram-negatives
    - Predominately Pseudomonas
  - Since 1980’s
    - Gram positives
    - Why: use of indwelling plastic venous catheters
      - Colonization of plastic by gram-positive skin flora
      - Subsequent entry into blood stream

- Trends in 3 decades
  - Gram positives – more common, likely LESS mortality
    - Coagulase-negative Staph
  - Gram negatives – less common, associated with increased mortality
Empiric antibiotic choices in F&N

- Monotherapy
  - Anti-pseudomonal beta-lactam drug
    - **Cefepime** meropenem zosyn
      - Ceftazidime has fallen out of favor (decreasing effectiveness against today’s GNR, poor streptococcal coverage)
  - For B-lactam-allergic children:
    - Ciprofloxacin + clindamycin (latter for α-hemolytic strep)
    - Aztreonam + Vancomycin
What bacteria worry us during F&N?

- >2000 (adult) patients
  - 23% of F&N had bacteremia
    - 57% were Gram-positive: of these – 5% died
    - 34% were Gram-negative: of these – 18% died
    - 10% were polymicrobial: of these – 13% died

Wait a minute!

• **Predominance of gram-positive** organisms as cause of bacteremia during neutropenic fever

• Rationale for **NOT** using Vancomycin in empiric antibiotics?

• Randomized studies (4) showed **NO** significant reduction in duration of fever nor overall mortality

• Coagulase-negative staphylococci are **WIMPS**
  – Weak pathogens which rarely cause rapid clinical deterioration
  – No urgent need to treat such infections at time of febrile presentation

• Over-use of Vancomycin may lead to emergence of VRE and VISA
When **to use** Gram-POSITIVE coverage at the onset?

- Clear line-associated infection
  - Cellulitis or pus around an exit-site
- Pneumonia
- Hemodynamic instability
- Worsening clinical picture after initial dose(s) of cefepime
- Initial blood culture with +GPCs
  - Draw a repeat blood culture PRIOR to vancomycin
Case

• 10 y/o male, ALL s/p chemo 10 days ago
• Presents with 1 day of F&N, otherwise looks well
• Blood cultures obtained
• CEFEPIME started
• Now what?
Outcomes of F&N cases

• Depends on
  – Results of work-up (ie the blood culture)
  – What happens to the fever
  – Whether the ANC rises
Outcome 1

• Blood culture (before antibiotics) grows bacteria (Klebsiella)
  – Subsequent blood cultures are negative
• Fever resolves within 48 hours

• Recommendation?

  Determine final antibiotic
  Determine duration of therapy for syndrome (bacteremia)
  Duration should be until neutropenia resolves
Clinical infections in children with cancer

• “Ya wahoo!” – *ID attending*
  – Only 1/3 of children with F&N have identifiable infection

• Bacteremia
  – Usually catheter associated (CVL)
    • Single organism
      – Coagulase negative Staph is most common
      – GNR generally cause greater mortality
Outcome 2 (most common)

- Blood cultures grow nothing (sterile)
- Fever resolves within 48 hours on abx

- Recommendation?

If ANC <500, then have neutropenic patient who “improved” on abx. Perhaps a cryptogenic infection?

*Could recommend given 7-10 day course of original abx.*

If ANC rose >500, then have non-febrile patient who “improved” on either abx or recovery of WBCs.

*Could recommend stopping original abx.*
Case – outcome 3

• Blood cultures grow nothing (sterile)
  – Blood cultures take 5 days to finalize
• Fever continues...
• Recommendation?

If ANC rose >500, then have febrile patient who has recovered some neutrophil numbers (but not all). Still a little worrisome...

*No strong recommendations on what to do*

If ANC <500, then have neutropenic patient who is persistently febrile despite abx.

*What are you starting to worry about?*
Another illustrative case

• 4 year old female, AML, recent chemotherapy finished 2 weeks ago.
  – Staying in hospital until her counts recover.
• Has had daily **fevers x 5 days**
• No change with anti-bacterial agents: cefepime
• No bacteria isolated from blood cultures
• VS: **T39** P130 R 20 BP 90/50 100% on RA
• Exam: well-appearing, alopecia, no mucositis, no peri-rectal abscess, no skin changes
• Labs: **ANC 10**
Persistent/prolonged F&N > 4-5 days

- Unique problem
  - Multiple studies show, in patients with prolonged F&N x 5 days...

- **FUNGUS!**
  - High morbidity
  - High mortality 😞
Deaths from invasive mould infection

• Literature review (n=1941 patients)
  – Reports >10 patients (mostly tx’d with AmphoB)
  – Articles published between 1995-2000
  – Outcome: case fatality rate (58%)

![Image of bar chart showing case fatality rates for patients with aspergillosis, according to underlying diseases or conditions (as determined from patient-level data)]
What it means to be a fungus

• Fungus
  – Two broad groups

• Yeast (uni-cellular)
  – Solitary rounded forms
  – Reproduce by making more rounded forms (budding)
  – Examples: Candida

• Mould (multi-cellular)
  – Reproduce through spores
  – Examples: Aspergillus
Another illustrative case (cont’d)

• Clinical diagnosis: *Prolonged neutropenic fever*

• What infections are you worried about: *Untreated infection, particularly fungus*

• What to do diagnostically: *Look for deep-seated source of infection*

• What to do therapeutically: *Add coverage for fungus*
What happens to a blood culture bottle

- Purpose: to support growth of bacteria from blood
  - Adequate volume
  - Received in central lab (on campus)
  - Transported to microbiology (off campus)
- Placed in 37°C incubator and watched for 5 days
  - Clinically significant bacteria usually grows in 1-2 days
Mechanics of microbiology

• Any changes in turbidity of liquid in bottle sets off alarm (anytime in the 24 hour period)
  – This suggests bacterial growth, which turns the liquid (more) cloudy
  – At time of alarm, bottle is pulled from incubator by technician
  – Fluid is extracted from the bottle for fluid is extracted for 2 purposes...
    • Gram stain
    • Plating
Gram stain

- To determine color and shape of bacteria
- To guide initial antibiotic choice

- Fluid is extracted from a bottle that is turbid
  - Onto slide: blue dye, red dye
    - Results in 1 hour
    - Called into patient unit

- Note: a gram stain is used to either confirm or expand the initial antibiotic choice
  - If on cefepime, and gram-stain has GPCs, would ADD vanco.
    - Would NOT stop cefepime to add vanco
Plating

• To determine name of bacteria
• Fluid is extracted from a bottle that is turbid
  – Onto 4 petri dishes: each with different purposes
• Once fluid is plated, the culture dishes are placed at 37oC and observed for growth for 5 days
  – Clinically significant bacteria usually grows in 1-2 days
• Growth on solid plates allows microbiologist to assign name and test for antibiotic susceptibilities
The life-time of a blood culture bottle

1 hour

5 days

1-2 days
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