Chapter 183 – The Immunocompromised Patient

Episode Overview:

1) What are the three primary defense systems of the body?
2) What disease states produce impaired cell-mediated immunity? List 10 common infectious organisms in these patients and describe the expected infection syndrome.
3) What disease states produce impaired humoral / B-cell immunity? What are the most common bacteria?
4) List specific factors that may lead to an immunocompromised state in Cancer
5) Define neutropenia and list common pathogens associated with neutropenia
6) List 6 clinical findings in neutropenic patients and the suspected pathogens
7) Describe the management of febrile neutropenia in BC – low risk / high risk
    a. What are high-risk features mandating admission in febrile neutropenia? Low risk features?
8) What is Typhlitis? And how is it treated?
9) List 6 causes of:
    a. Diffuse bilateral pulmonary infiltrates in the immunocompromised patient
    b. Focal or patchy pulmonary infiltrates in the immunocompromised patient
10) What are 4 reasons diabetics have impaired immune function?
11) What are 8 reasons renal failure patients have impaired immune function? What type of immunocompromise do they have?
12) List 6 causes of functional asplenia
13) How does splenectomy or functional asplenia cause immunocompromised? And what are the most common infections?
14) Describe acute and preventative components of management of the asplenic patient
15) List 10 complications of steroid therapy + 4 typical infections

Key Points:

- Immunocompromised persons who present with acute infections, especially those that are neutropenic, may appear deceptively benign only to deteriorate rapidly if they are not evaluated and treated urgently. Early use of broad-spectrum antibiotics is indicated after obtaining appropriate cultures of all potential sites of infection, including intravascular catheters.
- Immunocompromised patients can have serious local or systemic infections without fever, which may be manifested by unexplained tachypnea or tachycardia, mental status changes, metabolic acidosis, increased volume requirements, rapid changes in serum glucose or sodium concentration, or acute abdominal pain.
- In neutropenic cancer patients, most severe infections and almost all instances of bacteremia occur when the neutrophil count is less than 100 cells/mL.
- In neutropenic patients, the temperature should be measured orally or tympanically, not rectally.
- In neutropenic cancer patients, pneumonia and anorectal infection are more likely to be associated with bacteremia than other localized Infections.
- Gram-positive organisms are responsible for most serious infections in neutropenic cancer patients, but infections due to gram-negative organisms are more rapidly lethal.
- Neutropenic cancer patients with chemotherapy-induced oral mucositis can develop rapid onset of fever with shock, acute respiratory distress syndrome and rash due to viridans streptococci.

- If the chest radiograph is normal or inconclusive but there is still suspicion for pneumonia, CT of the chest without contrast should be obtained because pneumonia is often detected by chest CT in febrile neutropenic patients with normal findings on the chest radiograph.
- Broad-spectrum intravenous antimicrobial therapy with cefepime, meropenem, imipenem, or piperacillin-tazobactam, should be initiated promptly in the febrile neutropenic patient, with an aminoglycoside added for the more seriously ill patient. Aztreonam plus vancomycin should be administered to those with serious penicillin-allergy. Empirical fluoroquinolone therapy should be avoided except for specific indications.
- Some low-risk febrile neutropenic patients may not require admission to the hospital
- Patients with cell mediated immune deficiency including those on high dose corticosteroids may develop life-threatening infections with intracellular bacteria (Listeria, Salmonella, tuberculosis), fungi (Cryptococcus, Coccidioides, Histoplasma), herpes simplex virus, and varicella-zoster virus.
- Patients with end stage renal disease on hemodialysis who develop pneumonia, C. difficile disease, or infections of dialysis access sites have high mortality.
- Functional or surgical asplenia predisposes to fulminant infection with pneumococci and other encapsulated organisms (H. influenzae, N. meningitidis, and Capnocytophaga canimorsus after dog bites) and, when seen early, may be misdiagnosed as a viral illness, gastroenteritis, or food poisoning.
- High doses of corticosteroids cause profound dysfunction of neutrophils and mononuclear cells and impair cell-mediated immunity (CMI), resulting in an increase in infections caused by pyogenic bacteria, varicella-zoster and herpes simplex viruses, tuberculosis, and a wide variety of other bacteria, fungi, and parasites.

Rosen's in Perspective

Which groups of patients are immunocompromised?

Patients with:

- Cancer, organ transplantation, diabetes, renal failure, cirrhosis, asplenism, human immunodeficiency virus (HIV) infection, and other immunosuppressive conditions. Including infectious complications of immunosuppressive and immunomodulating medications used for a wide variety of disorders.

(Not microbe specific)

- Surface barriers
- Innate immunity
  - Initial inflammatory response
  - Reticuloendothelial system

(Microbe-specific)

- Acquired immunity
  - Humoral immunity
    - Antibodies
    - Immunoglobulins
    - Complement
  - Cell-mediated
  - Granulocytic phagocytes

Box 187.1 shows immune system defects predisposing to infection and the most common pathogens associated with each - This FIGURE IS HUGE! KEEP coming back to it.

1) What are the three primary defense systems of the body?

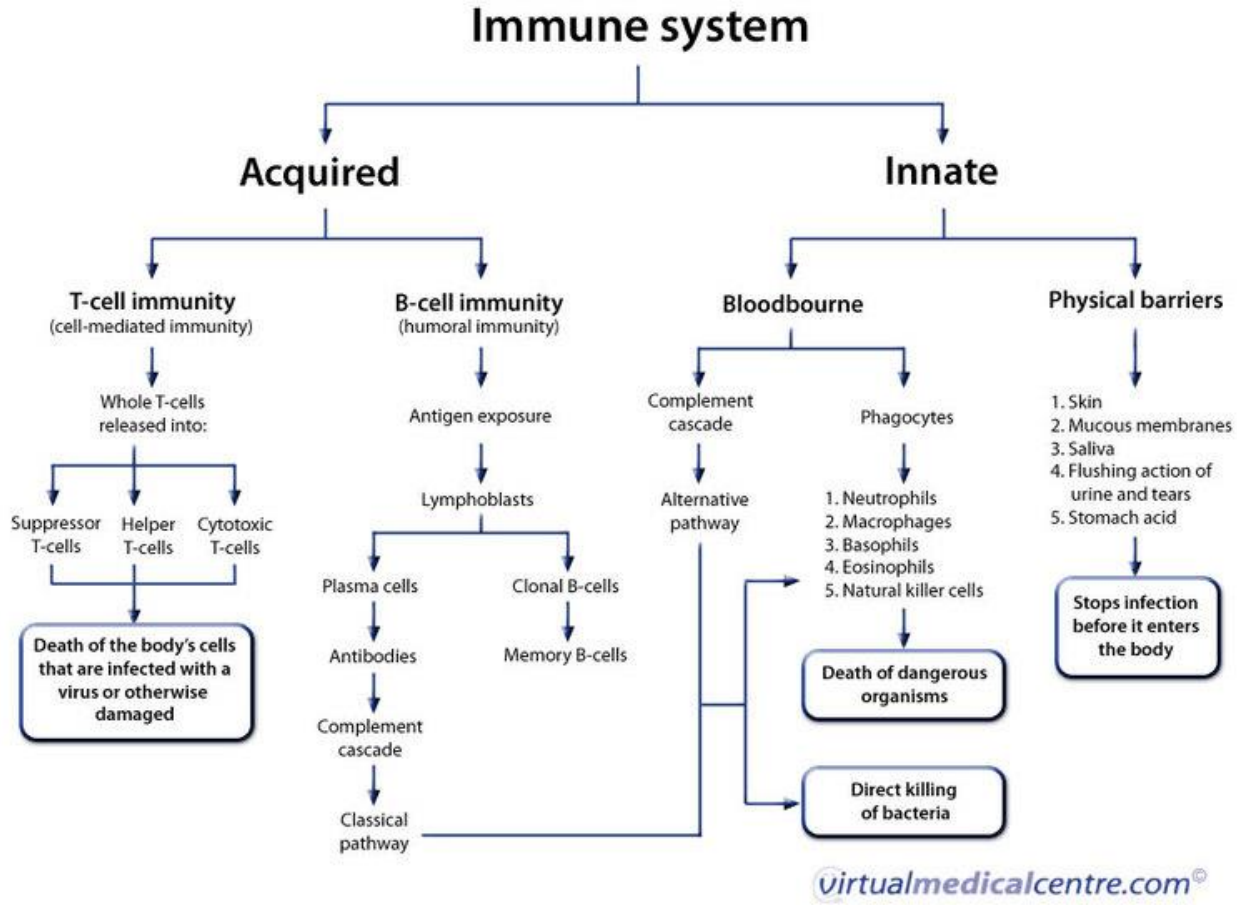
Hold on to your drawers… this is going to be a wild ride...

The body's defense mechanisms =

- **Surface barriers**, such as skin, enzymes, and mucus,
  - First line of defense against microorganisms, consist of intact skin, gastrointestinal and respiratory mucosa, cilia, bio film, gastric acid, antibacterial substances in pancreatic and biliary secretions, antimicrobial peptides and proteins on skin and mucous membranes, and resident micro-flora
- **Innate (natural)**
  - Innate responses occur to the same extent regardless of how often the body encounters the infectious agent
  - Innate immunity is activated immediately on exposure to an infecting agent, rapidly controlling replication and allowing the requisite
  - Complement (alternative pathway)
  - Phagocytes (neuts, basophils, eosinophils, natural killer T-Cells)
- **Acquired (adaptive) responses**
  - Humoral response
  - acquired responses improve on repeated exposure
    - 3 to 5 days for the adaptive component to clone sufficient T (cell mediated immunity) and B (antibody production) cells to respond more specifically
    - Antibodies
    - Immunoglobulin
      - Immunoglobulin M (IgM)
        - 1st to appear
        - provides some recognition of antigens
        - begins B-cell proliferation
        - 1st detectable in serum over IgG
      - Secretory immunoglobulin A (IgA)
        - gastrointestinal fluids, nasal and oral secretions, tears, and other mucous fluids
        - inhibits cell adherence of viral, bacterial, and protozoan pathogens = prevents invasion by organisms through the respiratory or gastrointestinal tract.
      - Immunoglobulin E (IgE),
        - surface of mast cells and basophils
        - responsible for immediate-type hypersensitivity reactions
        - important in defense against helminthic pathogens.
      - IgG
        - widely distributed in tissues
        - accounts for 75% of the total immunoglobulin mass.
        - It crosses the placenta and provides fetal immunity during the first 6 months of life

- ❏ Congenital or acquired deficiencies of IgG lead to infection with encapsulated organisms

- ❏ Complement
  - ❏ complex interaction of 30 proteins
  - ❏ crucial component of humoral response
  - ❏ produces inflammation and leukocytosis
  - ❏ also neutralizes viruses, enhances opsonization of bacteria, and produces bacterial cell wall and membrane lysis.
  - ❏ provide opsonization and modulate the response of lymphocytes (CMI)
  - ❏ Opsonization is important in defense against infection with S. pneumoniae, Streptococcus pyogenes, H. influenzae, and Staphylococcus aureus
  - ❏ The terminal leg of the cascade, C5 through C9, forms the membrane attack complex, which inserts into cell walls and membranes and leads to cell death.
- ❏ Cell-mediated
  - ❏ T lymphocytes, natural killer (NK) cells, and mononuclear phagocytes
  - ❏ 2 major forms of T-Cells = CD4 (helper) and CD8(suppressor)
  - ❏ CMI = vitally important in intracellular pathogens, including most viruses and some bacterial (obligate and facultative intracellular types), fungal, and protozoan pathogens
- ❏ Granulocytic phagocytes
  - ❏ Neutrophils and macrophages
  - ❏ Eat up all the bad cells
  - ❏ Improved function through opsonization (eg CRP, C3b, IgG)
  - ❏ Present antigens to lymphocytes, thus activating acquired / adaptive
    - ❏ Eosinophils destroy parasitic helminths via toxic proteins Normally only 3% of total granulocytes, this cell type can reach 20% during times of high parasite load.
    - ❏ Basophils (rare in circulation) and their tissue counterparts, mast cells, have high affinity for IgE. On exposure to antigens, they release granules with histamine, prostaglandins, and leukotrienes, which affect the allergic-inflammatory response with increased vascular permeability, bronchospasm, and vasodilation.



2) What disease states produce impaired cell-mediated immunity? List 10 common infectious organisms in these patients and describe the expected infection syndrome.

Punch line =

- ❑ Cancer chemotherapy or corticosteroid treatment
- ❑ The cancer itself impairs CMI in patients with Hodgkin's disease, non-Hodgkin's lymphoma, and hairy cell leukemia
- ❑ HIV

*** Remember***

CMI = Cell-mediated

- ❑ T lymphocytes, natural killer (NK) cells, and mononuclear phagocytes
- ❑ 2 major forms of T-Cells = CD4 (helper) and CD8(suppressor)
- ❑ CMI = vitally important in intracellular pathogens, including most viruses and some bacterial (obligate and facultative intracellular types), fungal, and protozoan pathogens
- ❑ So defects anywhere here will cause problems (HIV/AIDS, blood neoplasms etc)

- Patients with defects in CMI = increased risk for disseminated infection with intracellular bacteria
    - Mycobacterium tuberculosis
    - Listeria monocytogenes
    - Salmonella species.
    - The DNA viral infections, such as cytomegalovirus, herpes simplex, and varicella-zoster,
    - fungal infections with Candida, Cryptococcus, Mucor, Aspergillus, and Pneumocystis
    - protozoa such as Toxoplasma gondii.
    - Some infections are seen only below a certain CD4 cell count.
    - Pneumocystis pneumonia
        - Eg only seen w/ counts below 200 cells/mL (2 × 105 cells/L),
        - toxoplasmosis or cryptococcal meningitis = counts below 100 cells/mL (1 × 105 cells/L)
    - NK cells, closely related to lymphocytes but neither B nor T cells
        - important in the innate immune response and are found in high concentrations in blood and spleen
        - recognize infected cells and respond by directly killing these cells
        - secrete cytokines that activate macrophages to destroy phagocytosed microbes
        - important in defense against intracellular microbes
            - particularly viruses and intracellular bacteria such as L. monocytogenes.

- CELLULAR IMMUNE DYSFUNCTION
- Bacteria
    - Listeria monocytogenes
    - Salmonella sp.
    - Mycobacterium tuberculosis Mycobacterium avium-intracellulare Legionella sp.
    - Nocardia sp.
- Fungi
    - Cryptococcus neoformans Histoplasma capsulatum
    - Coccidioides immitis
    - Candida sp.
    - Aspergillus sp.
    - Pneumocystis jiroveci (formerly carinii)
- Viruses
    - Herpes simplex
    - Varicella zoster
    - Cytomegalovirus
    - Epstein-Barr
    - Less common: Measles, adenovirus
- Parasites
    - Toxoplasma gondii Cryptosporidium sp. Strongyloides stercoralis

3) What disease states produce impaired humoral / B-cell immunity? What are the most common bacteria?

- ❑ Inherited complement deficiencies = frequent and recurrent infections
- ❑ The risk of meningococcal infection is increased s**everal thousandfold**
- ❑ Bacteria
    - ❑ S. pneumoniae
    - ❑ Haemophilus influenzae
    - ❑ Neisseria meningitidis
    - ❑ S. aureus

NOTE: All patients diagnosed with meningococcemia should be tested for complement deficiencies, and if positive should undergo regular vaccination

4) List specific factors that may lead to an immunocompromised state in Cancer

- ❑ Neutropenia
- ❑ impaired function of T and B cells
- ❑ induced by cancer chemotherapy or by the disease process itself
- ❑ defects in physical barriers (skin and mucous membranes), think mucositis/gastritis/proctitis etc
- ❑ splenic dysfunction or splenectomy
- ❑ use of long-term intravascular catheters
- ❑ frequent use of complex invasive diagnostic and therapeutic procedures
- ❑ toxic effects of radiation therapy
- ❑ frequent colonization with antimicrobial-resistant pathogens are predisposing factors to immune system compromise.
- ❑ increasing resistance to antimicrobials
- ❑ new opportunistic pathogens
- ❑ acute leukemia and lymphoma (75% of patients) and multiple myeloma (50% of patients) than in those with solid tumors

5) Define neutropenia and list common pathogens associated with neutropenia

Neutropenia = count of less than 500 cells/ mL (5 × 105 cells/L), including band forms, or less than 1000 cells/ mL (1 × 106 cells/L) and expected to fall to less than 500 cells/mL

- ❑ Bacteria
    - ❑ Gram-negative bacilli Escherichia coli
        - ❑ Klebsiella pneumoniae Pseudomonas aeruginosa Enterobacter sp.
        - ❑ Serratia sp.
        - ❑ Citrobacter sp.
        - ❑ Proteus sp.
        - ❑ Acinetobacter sp. Stenotrophomonas maltophilia
    - ❑ Gram-positive cocci
        - ❑ Staphylococcus epidermidis

- ❑ Staphylococcus aureus including methicillin-resistant strains Viridans streptococci
- ❑ Streptococcus pneumoniae
- ❑ Streptococcus pyogenes
- ❑ Enterococcus sp., including vancomycin-resistant strains
- ❑ Gram-positive rods Corynebacterium sp.
- ❑ Less common: Bacillus sp.

❑ Fungi
- ❑ Candida sp.
- ❑ Aspergillus sp.
- ❑ Less common: Mucor sp., Rhizopus sp., Trichosporon beigelii, Fusarium
- ❑ sp., Pseudallescheria boydii

6) List 6 clinical findings in neutropenic patients and the suspected pathogens

Table 187.1 Characteristic Clinical Findings in Neutropenia That May Be Associated with Infection with Specific Pathogens

Characteristic Clinical Finding	Suspect Pathogens
Ulcerative lesions in the mouth	Viridans streptococci, herpes simplex, Candida, anaerobes
Necrotizing skin lesions	Pseudomonas aeruginosa, Aeromonas hydrophila, Aspergillus, Mucor
Nontender subcutaneous nodules	Nocardia, Cryptococcus
Nontender pink skin papules	Candida
Black eschar of nose or palate	Aspergillus, Mucor
Generalized macular red rash	Viridans streptococci

7) Describe the management of febrile neutropenia in BC – low risk / high risk

a. What are high-risk features mandating admission in febrile neutropenia? Low risk features?

See Box 187.1 for Evaluation and Management of Adult Cancer Patient with Febrile Neutropenia in the ED

See Table 187.2 for Selected Antimicrobial Agents Useful in the Immunocompromised Patient

See Table 187.3 Multinational Association for Supportive Care in Cancer Scoring System to Identify Patients with Cancer and Febrile Neutropenia at Low Risk of Medical Complications

Also see Box 187.3 and 187.4 for considerations for outpatient management of febrile neutropenia, for both adults and children, respectively

Summary:

- ❏ High risk patients = Admit =
  - ❏ Comorbid medical conditions
  - ❏ cute leukemia
  - ❏ Central line infection
  - ❏ Pneumonia
  - ❏ HD instability
  - ❏ Evidence of organ failure / ALOC

8) What is Typhlitis? And how is it treated?

Typhlitis = neutropenic enterocolitis

- ❏ caused by Pseudomonas aeruginosa, Escherichia coli, Clostridium septicum

As per Uptodate:

MANAGEMENT — A general approach to patients with neutropenic enterocolitis can be suggested, although care should be individualized. In patients without complications (ie, peritonitis, perforation, or severe bleeding), nonsurgical management with:

- ❏ bowel rest
- ❏ nasogastric suction
- ❏ intravenous (IV) fluids
- ❏ nutritional support
- ❏ blood product support (packed red blood cells and fresh frozen plasma as needed)
- ❏ broad-spectrum antibiotics is a reasonable initial approach
- ❏ Surgery for free perforation or another process that cannot be controlled medically (eg, persistent bleeding despite correction of coagulopathy and cytopenias)

Antimicrobial therapy

● Piperacillin-tazobactam (for adults: 4.5 g IV every six hours; for infants <9 months: 80 mg/kg of piperacillin component IV every eight hours; for infants and children ≥9 months and ≤40 kg: 100 mg/kg of piperacillin component IV every eight hours; for children >40 kg: 3 g of piperacillin component IV every six hours or 4 g of piperacillin component IV every six to eight hours; the maximum daily dose of the piperacillin component is 16 g/day)

● Cefepime (for adults: 2 g IV every eight hours; for children: 50 mg/kg IV every eight hours up to a maximum of 2 g per dose) or ceftazidime (for adults: 2 g IV every eight hours; for children: 50 mg/kg IV every eight hours up to a maximum of 2 g per dose) PLUS metronidazole (for adults: 500 mg IV every eight hours; for children: 30 to 40 mg/kg IV per day in divided doses every six to eight hours, maximum daily dose 1500 mg/day).

● Imipenem-cilastatin (for adults: 500 mg IV every six hours; for children: 25 mg/kg IV every six hours up to a maximum of 1 g per dose for infants older than one month of age and children) or meropenem (for adults: 1 g IV every eight hours; for children ≥3 months of age: 20 mg/kg IV every eight hours up to a maximum of 1 g per dose). We reserve the carbapenems for patients who are allergic to the other options or who are infected or colonized with an organism that is resistant to the other recommended agents (eg, extended-spectrum beta-lactamase–producing Enterobacteriaceae).

9) List 6 causes of:

A) Diffuse bilateral pulmonary infiltrates in the immunocompromised patient

- Viruses (CMV, RSV, Influenza, etc.)
- Pneumocystis jiroveci
- Fluid overload and pulmonary edema
- Acute lung injury due to transfusion of blood products
- Radiation damage
- Chemotherapy-induced toxicity

B) Focal or patchy pulmonary infiltrates in the immunocompromised patient

- Bacterial pneumonias
- Fungi
- TB
- Nontuberculous mycobacteria
- Nocardiosis
- PE

10) What are 4 reasons diabetics have impaired immune function?

- ❑ Neutrophil and monocyte-macrophage functions= impaired
- ❑ excess substrate for fungal and bacterial growth
- ❑ vascular insuf ciency related to microangiopathy and atherosclerosis
- ❑ sensory neuropathy that leads to wound neglect.

Note:

“Infections seen with increased frequency in diabetic patients include rhinocerebral zygomycosis (formerly mucormycosis) caused by Rhizopus and Mucor species; malignant (or necrotizing) otitis externa caused by P. aeruginosa; pneumonia caused by S. aureus and gram-negative bacilli; tuberculosis, emphysematous cholecystitis, and urinary tract infections including emphysematous cystitis and pyelonephritis; polymicrobial necrotizing fasciitis involving the perineum (Fournier’s gangrene) and lower extremities; and psoas abscess, spinal epidural abscess, foot infections with osteomyelitis, and postoperative surgical site infections. Diabetics who inject insulin are frequently colonized in the nares and skin with S. aureus that may predispose to skin infections with transient bacteremia, which can seed distant sites. Women diabetics with hyperglycemia are predisposed to vulvovaginal candidiasis. Diabetics are not more likely to have pneumococcal pneumonia but are more likely to become bacteremic and to have a higher mortality rate.”

11) What are 8 reasons renal failure patients have impaired immune function? What type of immunocompromise do they have?

- ❑ Often diabetic (see above)
- ❑ Decrease barrier =
    - ❑ Disruption of cutaneous barriers at vascular access sites and peritoneal dialysis catheter sites
    - ❑ Uremic pruritus with excoriation
    - ❑ epidermal and sweat gland atrophy
    - ❑ Dryness

- ❑ Vesicular eruptions

- ❑ Reduced renal clearance of unknown toxins
- ❑ nutritional deficiencies
- ❑ immunosuppressive medications
- ❑ Chronic kidney failure = chronic state of immune hyporesponsiveness
- ❑ Neutrophils dysfunction =
  - ❑ reduced mobility /chemotaxis/adherence/phagocytosis/intracellular bactericidal activity, and leukopenia is commonly present.
  - ❑ CMI is severely impaired
  - ❑
  - ❑
- ❑ humoral immunity= deficient production of certain IgG subclass antibodies
- ❑ Poor response to vaccines
- ❑ Additional factors:
  - ❑ low serum albumin, iron overload, increased intracellular calcium, circulating low-molecular-weight uremic toxins, metabolic acidosis, circulating inhibitors to chemotactic factors, decreased production of endogenous pyrogens, and invasive vascular procedures for dialysis access.

Punch line: They can be sick! Watch out for pneumonia (esp legionella), UTI, MRSA and line infections, as well as SBP in PD patients.

12) List 6 causes of functional asplenia

6 causes:

- ❑ sickle cell disease
- ❑ including sickle cell–hemoglobin C disease
- ❑ ulcerative colitis
- ❑ celiac disease
- ❑ Sarcoidosis
- ❑ Amyloidosis
- ❑ rheumatoid arthritis
- ❑ SLE

13) How does splenectomy or functional asplenia cause immunocompromised? And what are the most common infections?

The spleen is not vestigial!!!

- ❑ The primary site for IgM synthesis
- ❑ Opsonin production used for phagocytosis of bacteria by intracellular macrophages
- ❑ Patients without a spleen also have decreased production of neutrophils, NK cells, and immunomodulating cytokines

- ❑ Bacteria
  - ❑ S. pneumoniae
  - ❑ H. in uenzae
  - ❑ N. meningitidis
  - ❑ Capnocytophaga canimorsus
  - ❑ Bordetella holmesii
- ❑ Parasites
  - ❑ Babesia sp. (causing fatal hemolysis)

14) Describe acute and preventative components of management of the asplenic patient

Acute = blood culture x 2 & “nuke em”

- ❑ ceftriaxone or cefotaxime @ meningitis doses
- ❑ PLUS vancomycin IF MRSA CONCERN
- ❑ Pen allergy = Clindamycin, levofloxacin, or moxifloxacin

Chronic = Vaccinate

- ❑ Use of pneumococcal vaccine
- ❑ PLUS: H. influenzae type b
- ❑ N. meningitidis
- ❑ influenza virus.
- ❑ Children should receive prophylaxis with oral penicillin or amoxicillin up to the age of 5 years and for at least 1 or 2 years after splenectomy (but this is not evidence-based)
- ❑ These patients should have standby oral antibiotics at home (amoxicillin- clavulanate, levofloxacin, or moxifloxacin) with instructions to self-administer at the first sign of infection

15) List 10 complications of steroid therapy + 4 typical infections

This list is a Doozy!

- ❑ Impaired immune function / increased risk of infection
- ❑ Hyperglycemia
- ❑ iatrogenic Cushing’s syndrome
- ❑ peptic ulcer disease
- ❑ Pancreatitis
- ❑ benign intracranial hypertension (pseudotumor cerebri)
- ❑ Psychosis
- ❑ Glaucoma
- ❑ Posterior subcapsular cataract
- ❑ Poor wound healing
- ❑ Sodium retention
- ❑ Hypertension
- ❑ Vascular thrombosis
- ❑ Diabetic ketoacidosis / hyperosmolar hyperglycemic state
- ❑ avascular necrosis of bone (especially the femoral and humeral heads)
- ❑ myopathy and osteoporosis
- ❑ adrenocortical insufficiency may occur on withdrawal of therapy