Infectious Diseases

Lesson 14

INFECTIONS IN THE IMMUNOCOMPROMISED HOST

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Objectives, learning goal and contents

Objective

- To understand the principal mechanisms of infection in the immunocompromised host
- To know the clinical presentation of infection in the most common immunodeficiency states

Learning goal

To develop enough skills to recognize and properly manage the principal infections related to immunodeficiency states, in the most prevalent clinical scenarios

Contents

The immunocompromised host: general concepts

General causes of immunodeficiency

- Treatment of leukemia, lymphoma, or solid tumors with:
  - Chemotherapy
  - Bone marrow transplant (including stem cell transplant), or solid organ transplant
- Splenectomy
- Treatment with immunosuppressive agents and immune modulators of inflammatory disorders
- HIV infection
- Genetic, mainly of pediatric interest

General causes of immunodeficiency

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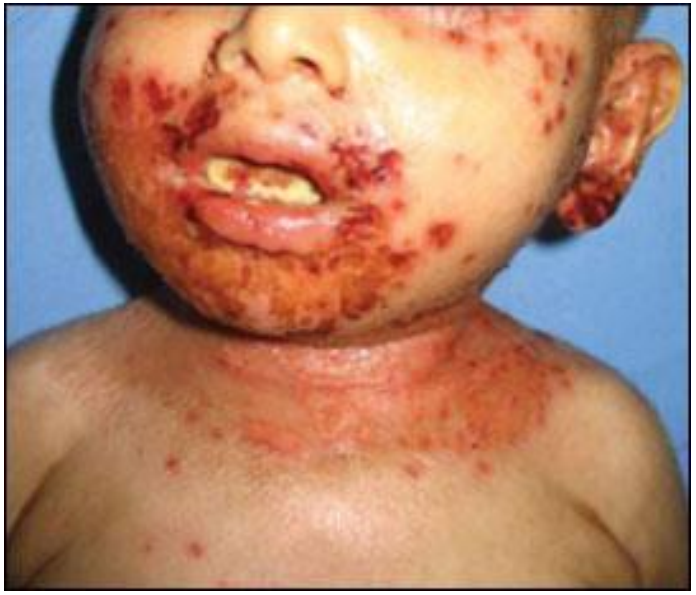
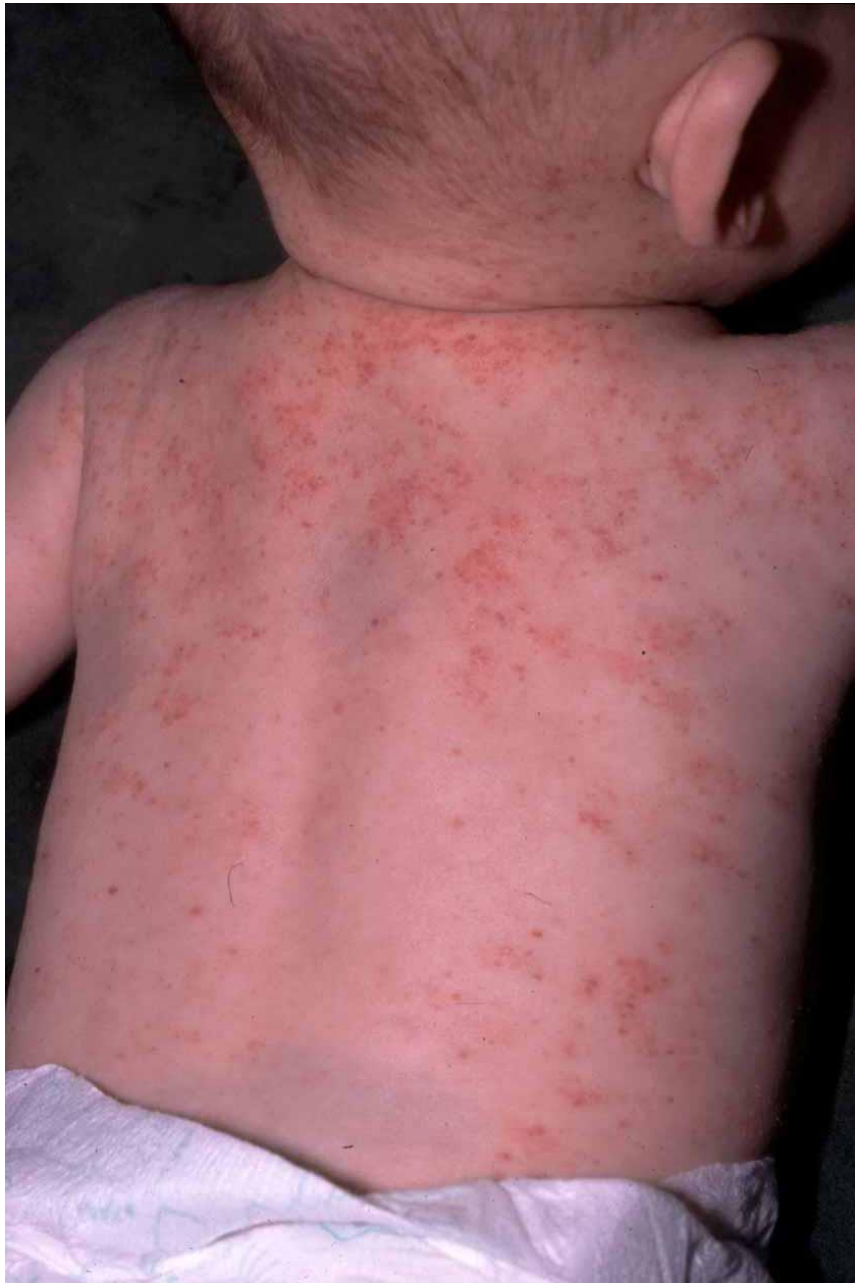




Wiskott-Aldrich syndrome:

- Eczema
- Thrombocytopenia
- Recurrent infections

General consequences of immunodeficiency

- Major host defense mechanisms are not functioning optimally
- Immune system failures result in infection by:
  - Usual human pathogens
  - Human saprophytes
  - Environmental organisms of low intrinsic virulence

Classification of immunodeficiencies - I

- The immunodeficiency type guides
  - The diagnostic approach
  - The decision to initiate empiric therapy
  - The empiric regimen to be used
- Immunodeficiencies may be:
  - Temporary, until repair mechanisms return to full functionality (e.g., the bone marrow recovers)
  - Lifelong (e.g., immunosuppression may be permanently required to control inflammation)

Classification of immunodeficiencies - II

- The major defect is caused by cytotoxic therapy or irradiation, or both, → **neutropenia** and **mucosal barrier** damage
- The major defect is caused by immunosuppressive agents used to control organ rejection or inflammation → suppression of **cell-mediated immunity**
- Both previous defects may present at the same time

Neutropenia and mucositis - I

- Normal host: any bacteria passing through the mucosa are phagocytosed and killed by:
  - Toxic oxygen byproducts
  - Proteases
  - Small bactericidal cationic proteins within the phagolysosome
- **Neutropenia** = absolute neutrophil count < 500/mm^3, often accompanied by **mucosal damage** → bacteria from the mouth and lower gastrointestinal tract pass through the damaged mucosal barrier → blood and organs

Neutropenia and mucositis - II

- Lack of protection against device-related vascular infection
- Risk of infection increases…
  - …as cell number decreases
  - …as duration of neutropenia prolongs: > 10 days → high risk

Cell-mediated immunodeficiency

- Caused by T cell (= T lymphocyte) deficiency or dysfunction
- T cell plays a central role in immunity
- T cell defects associates with:
  - **A wide range of infections**
  - Autoimmune diseases
  - Chromosomopathies
  - Cancer

Pathogenesis and microbiology of infection in patients with neutropenia and mucositis

Infecting organisms

- In most cases those found in:
  - **Skin (coagulase-negative staphylococci and *S. aureus*)**
  - Oral cavity (*Streptococcus viridans* and anaerobes)
  - Gastrointestinal tract (gram negative rods and anaerobes)
- Sometimes those introduced by contamination from environment, for example in ingested food
- Generally **bacteria** and fungi

Bacteria: gram-positive pathogens

- The most frequent cause of infection in neutropenic patients
- They usually originate in vascular catheter or other devices
- Incidence has ↑ in recent years, probably as a consequence of
  - Use of long-lasting indwelling venous catheters
  - Overuse of fluoroquinolones
- Mainly:
  - **Coagulase-negative staphylococci**
  - ***Staphylococcus aureus***
  - *Streptococcus viridans*
  - Enterococci
  - *Corynebacterium* spp.

Bacteria: gram-negative pathogens

- Second in frequency
- They usually originate from the gastrointestinal tract
- Polymicrobial sometimes
- Mainly
  - *Escherichia coli*
  - *Klebsiella* species
  - *Pseudomonas aeruginosa*
  - Less commonly, *Enterobacter* spp., *Proteus* spp., *Acinetobacter* spp., *Stenotrophomonas* spp., and *Citrobacter* spp.

Bacteria: anaerobes

- Despite their presence in large numbers in the gastrointestinal tract, anaerobic gram-negative rods such as *Bacteroides* spp. are not frequent causes of bacteremia in neutropenic patients
- Occasionally seen in association with severe mucositis

Fungi

- Generally after 7 days of febrile neutropenia, when antibiotics have ↓ bacterial flora, so “superinfections”
- If patient has received antibiotics recently and fungal colonization in the gut is high, they may produce infection earlier
- Some fungi are acquired by inhalation, and become symptomatic later, after they have multiplied and invaded lung parenchyma and blood vessels, thus appearing a superinfection
- ***Candida* spp.** (*albicans*, *tropicalis*, *krusei*, *glabrata*, and others), occasionally *Aspergillus* spp. and rarely *Mucor* spp or other

Pathogenesis and microbiology of infection in patients with cell-mediated immunodeficiency

Causes of cell-mediated immunodeficiency

- Prevalence of infections related to suppression of T lymphocyte function is progressively increasing
- Those infections affect:
  - Patients with autoimmune disease, receiving cytokine antagonists: corticosteroids → new cytokine antagonists
  - **Organ transplant recipients**, receiving agents directed against T lymphocytes

Post-transplant infections occurring during the **first** postoperative month - I

- The same hospital-acquired pathogens as other hosts
- Gram-negative bacilli such as *P. aeruginosa*, etc.
- Gram-positive cocci, such as vancomycin-resistant enterococci and methicillin-resistant *S. aureus*
- Fungi, such as *Aspergillus* spp. and azole-resistant *Candida* spp.
- *Clostridium difficile*

Post-transplant infections occurring during the **first** postoperative month - II

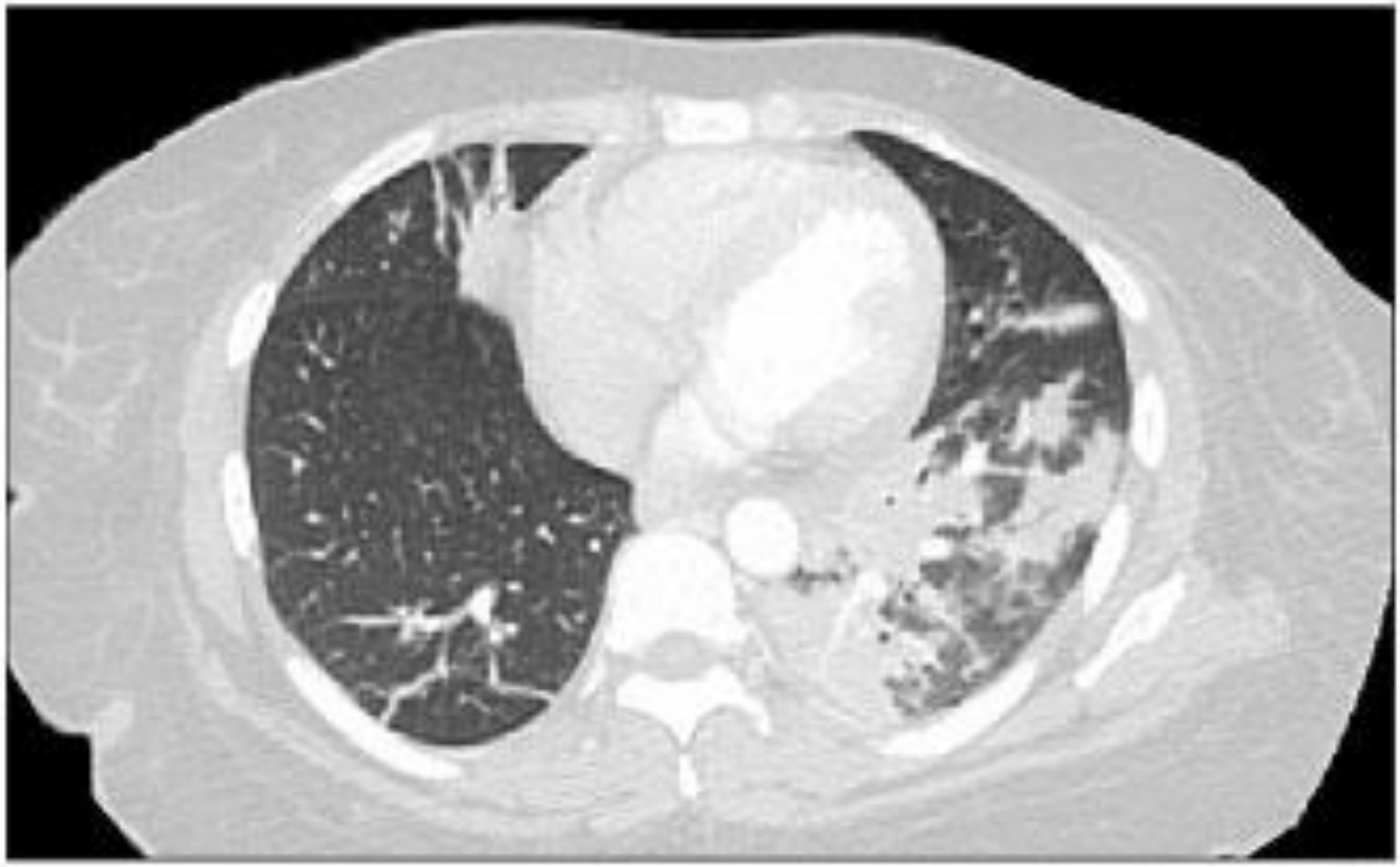
- Before organs are harvested, adequate therapy is provided, but **bacteria** can **survive** in a vascular aneurysm or other protected sites
- Infections transmitted by the **donor** organ: *S. aureus* or pneumococci or gram-negative rods
- Asymptomatic **low-grade infection** in the donor that becomes apparent only when the organ is transplanted; examples: West Nile virus, lymphocytic choriomeningitis virus, rabies, leishmaniasis, and Chagas disease

Post-transplant infections occurring **one to six** months after transplantation

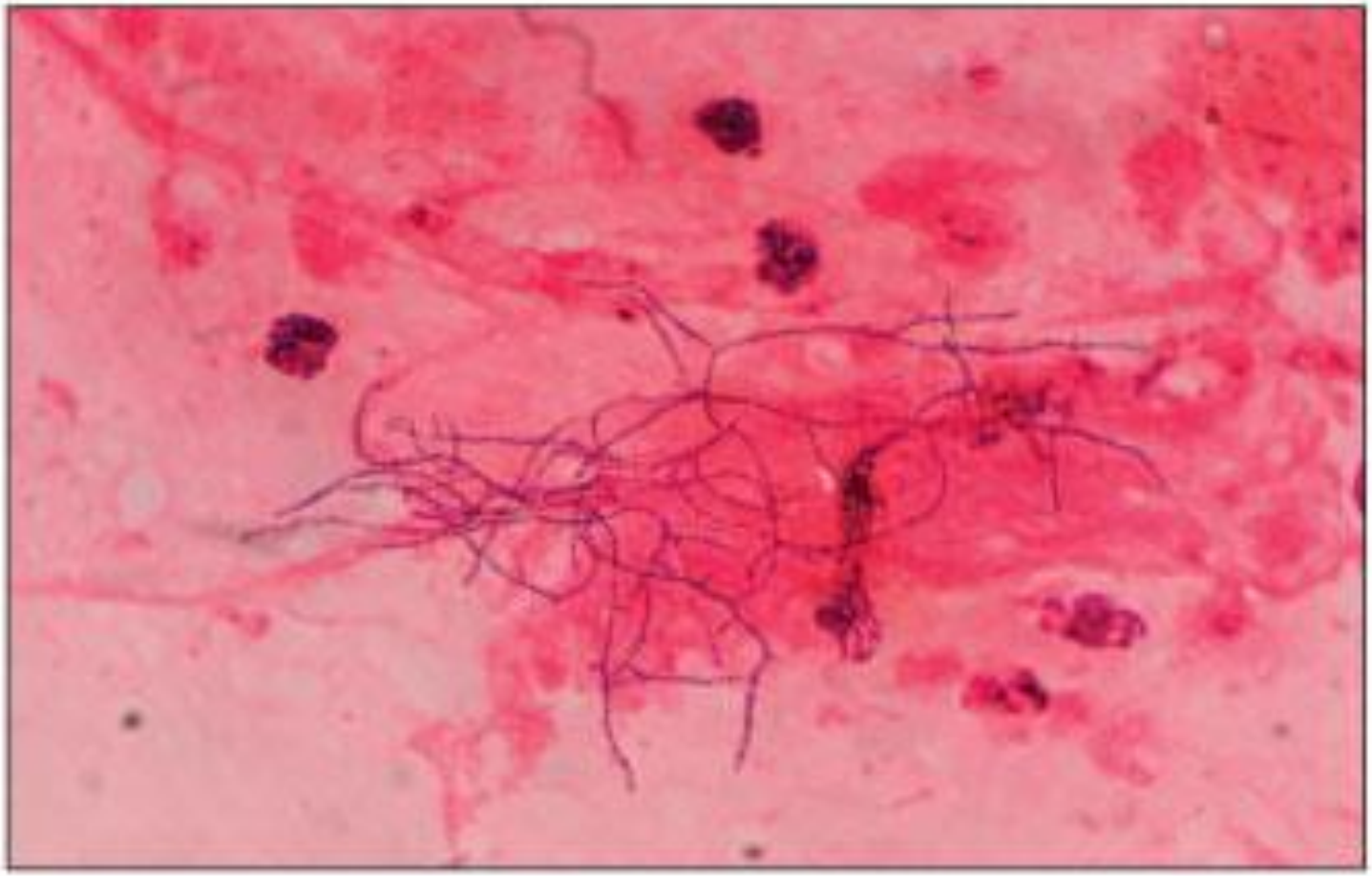
- Immunosuppression is highest to prevent acute rejection
- The widest variety of potential opportunistic infections:
  - Bacteria
  - Fungi
  - Viruses
  - Other pathogens

Post-transplant infections occurring one to six months after transplantation: **bacteria**

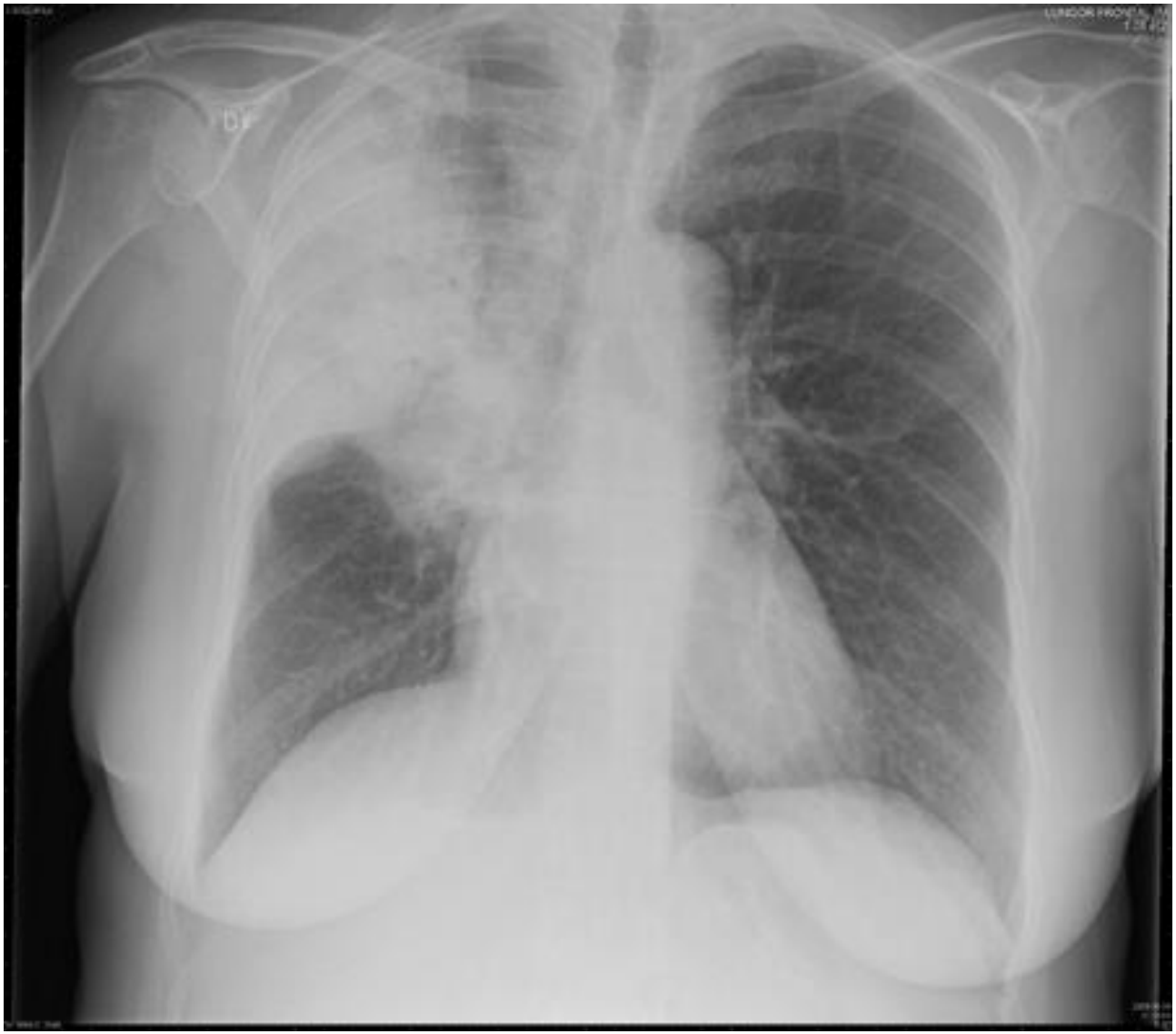
- Patients harboring latent ***Mycobacterium tuberculosis*** can develop miliary tuberculosis
- Atypical mycobacteria may become more invasive and cause symptomatic infection
- *Listeria monocytogenes*, by eating contaminated foods, community-acquired bacterial meningitis
- *Nocardia* spp., cavitary or nodular pulmonary infections, brain abscess
- *Legionella pneumophila*



Nocardia asteroides pneumonia



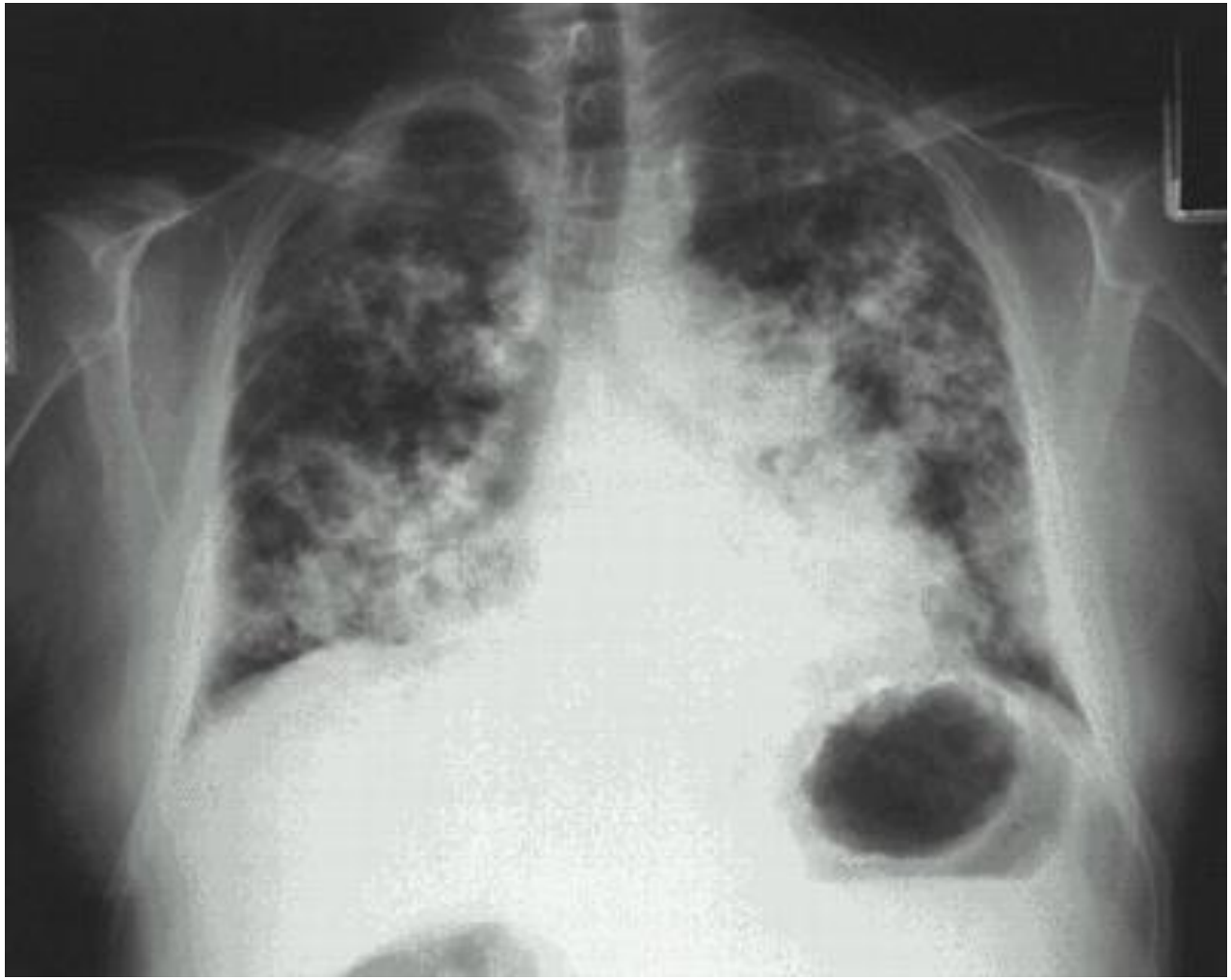
Gram stain of a sputum revealing
gram-positive filamentous rods



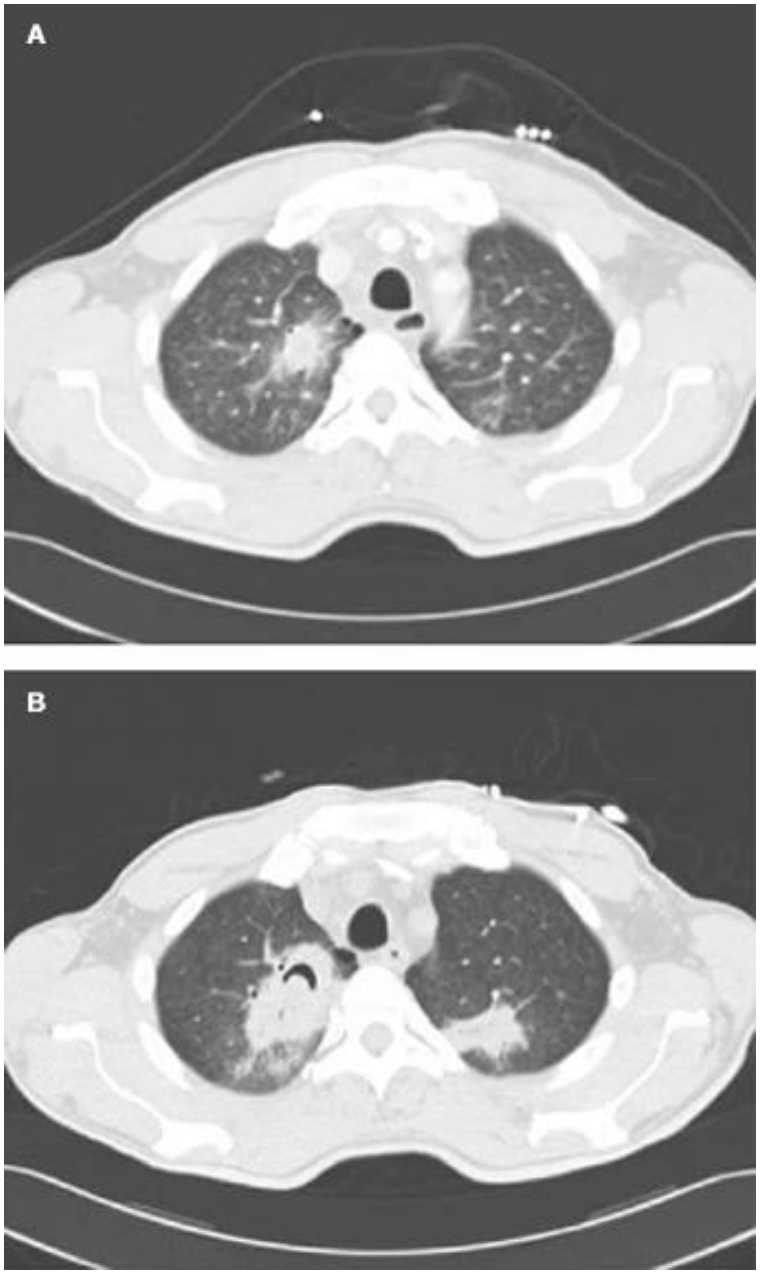
Legionella pneumophila pneumonia

Post-transplant infections occurring one to six months after transplantation: **fungi**

- Often life-threatening and difficult to diagnose infections
- ***Cryptococcus neoformans* the most common**, pneumonia and lymphocytic meningitis
- **Filamentous** fungi: ***Aspergillus***, *Fusarium*, *Mucor* and *Rhizopus* spp.: **cure extremely difficult**
- *Histoplasma capsulatum* and *Coccidioides immitis*
- Dematiaceous (“black”) fungi
- *Candida* spp. rarely, probably because they are controlled by neutrophils



Cryptococcus neoformans pneumonia



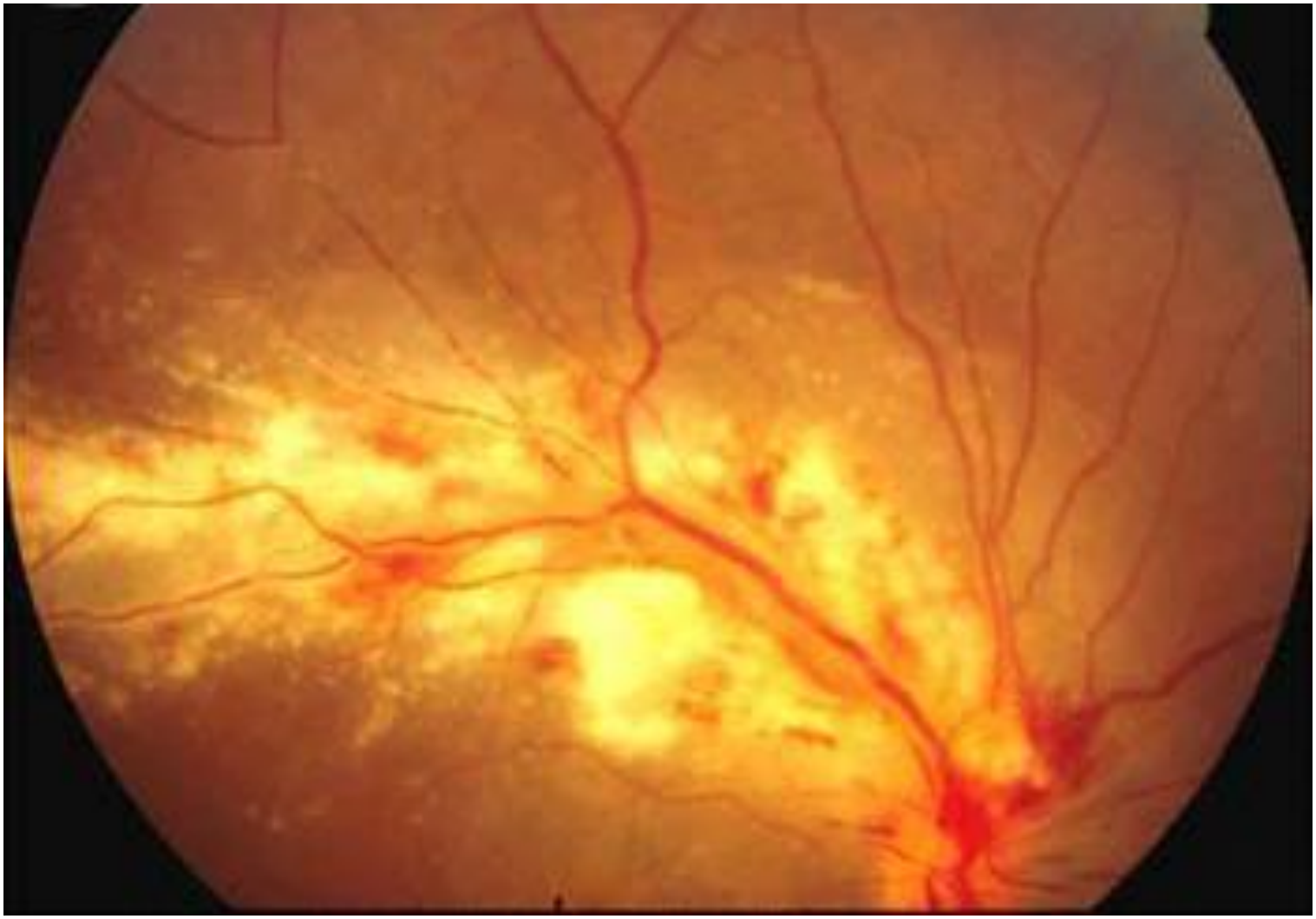
Invasive pulmonary aspergillosis: halo sign (A) and air-crescent sign (B) after recovery of neutropenia

Post-transplant infections occurring one to six months after transplantation: **viruses** - I

- **Viruses** that are **latent** in the body of the recipient
- Infections with new viruses, through:
  - Transfusion
  - Transplanted organ

Post-transplant infections occurring one to six months after transplantation: **viruses** - II

- Cytomegalovirus (CMV) the most common, **reactivated** or acquired; risk of infection depends on antibody status:
  - Recipient -, donor + → high risk
  - Recipient +, donor - → intermediate risk
  - Recipient -, donor - → lowest risk
- General symptoms, gasteroenteritis, and retinitis
- Tests to diagnosis and monitor response to therapy in CMV infection:
  - Antigen test, correlates with active replication
  - PCR test, can detect latent and active infection (high copy number indicate active invasive infection)



Cytomegalovirus retinitis

Post-transplant infections occurring one to six months after transplantation: **viruses** - III

- Epstein-Barr actively replicates in 20-30 % of transplant recipients and can cause a lymphoproliferative syndrome
- Other viral infections:
  - Herpes simplex
  - Herpes zoster
  - Human herpesvirus-6
  - Hepatitis B and C viruses

Post-transplant infections occurring one to six months after transplantation: **other pathogens**

- *Pneumocystis jiroveci*, pneumonia, that should be prevented with trimethoprim-sulfamethoxazole during the period of peak immunosuppression
- Toxoplasmosis, brain abscesses and encephalitis
- Disseminated strongyloidiasis, often fatal, patients with unexplained eosinophilia should undergo stool sampling to exclude *Strongyloides stercoralis* before transplant

Pathogenesis and microbiology of infection in patients with mixed deficits found in bone marrow transplantation

Phases of immunosuppression - I

- I (days 0–30 post-transplant), neutropenic
- II (days 30-100 post-transplant), primarily compromised cell-mediated immunity, infection with CMV particularly common; acute graft-versus-host disease also frequent

Phases of immunosuppression - II

- III (beyond day 100 post-transplant), defects in cell-mediated immunity, plus depressed humoral immunity from:
  - Functional hyposplenism after total body irradiation
  - Chronic GVHD * → dysfunctional B lymphocytes →
    - → ↓ production of IgG2
    - → ↓ production of specific pneumococcal antibodies

**

* GVHD = graft-versus-host disease

** Infections with encapsulated bacteria:
- *Haemophilus influenzae*
- *Streptococcus pneumoniae*

Management of infection in patients with neutropenia and mucositis

The febrile neutropenic patient

- Tª > 38.3 °C in neutropenia after chemotherapy warrants emergent:
  - Diagnostic studies
  - Antibiotic therapy, within 60 minutes
- Differential infectious/noninfectious causes challenging
- The usual manifestations of infection are often absent:
  - Skin infections may lack erythema, warmth, and purulence
  - Chest X-ray may appear normal in bacterial pneumonia
  - Cerebrospinal fluid may contain minimal polymorphonuclear leukocytes in bacterial meningitis

Initial workup

- Physical examination looking for sites of infection in lungs, skin, mucous membranes, perirectal area, etc.
- Biopsy and culture of any skin lesions
- Blood tests: blood cell count, serum creatinine, electrolytes, hepatic transaminases, serum bilirubin, etc.
- Blood cultures, from peripheral vein and central line
- Cultures from other sites: urine, any other suspicious site
- Chest X-ray for patients with respiratory symptoms

Low severity indicators

- Tª < 39 °C and nonseptic appearance
- Neutropenia < 7 days duration
- Normal or nearly normal liver and renal function
- Normal chest X-ray
- No evidence for intravascular device infection
- Malignancy in remission
- No neurologic deficits, no abdominal pain
- No comorbid conditions: hypotension, vomiting, diarrhea, etc.
- Low-severity score, > 21, in Hughes index (next slide)

Hughes' scoring index[a] for identification of low-risk febrile neutropenic patients at the time of presentation of fever*

Characteristic	Score
Extent of illness[b]	
No symptoms	5
Mild symptoms	5
Moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no fungal infection	4
No dehydration	3
Outpatient at the time fever onset	3
Age below 60 years	2

[a] Highest score is 26; > 21 indicates low risk for complications and morbidity.
[b] Choose one item only.

* Hughes WT et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002; 34: 730-51.

Antimicrobials election

- Low-severity score: oral ciprofloxacin plus amoxicillin-clavulanate is recommended
- More severely ill patients, intravenous: imipenem, or cefepime, or piperacillin-tazobactam:
  - Monotherapy
  - With aminoglycosides or vancomycin
  - With antifungals: caspofungin, amphotericin B, voriconazole
- Regimen must take into account:
  - Antibiotic resistance patterns of the local institution
  - Patient's prior history of infections and antibiotic treatment

Choosing antibiotics - I

- Monotherapy and dual therapy comparable results
- Vancomycin:
  - Should not be routinely administered as empiric therapy
  - Should be added if:
    - Intravascular device infection is suspected
    - Colonization with methicillin-resistant *S. aureus*
    - Blood cultures grow gram-positive cocci before final identification and sensitivity testing
    - If the patient is hypotensive or has other evidence of cardiovascular compromise

Choosing antibiotics - II

- **Linezolid** equivalent to vancomycin in the neutropenic patient, however, with selective serotonin-reuptake inhibitors → severe myelosuppression in bone marrow transplant patients
- Blood cultures may guide adjustments in treatment
- Broad-spectrum coverage should be generally maintained at least **7 days** or until the **neutrophil > 500/mm^3**, to prevent breakthrough bacteremia

Choosing antibiotics - III

- If fever persists after 3-5 days, reevaluation is needed:
  - Complete physical examination repeated
  - Additional imaging, such as computed tomography of the chest
  - Bronchoscopy if lung infiltrates
  - Cultures should be repeated
- If fever persists for more than 5 days, and…
  - …the patient is **improving his condition** and neutrophil count is expected to recover quickly → continue the same antibiotics
  - …sepsis **persists or worsens** → antibiotic changed and antifungal added

Duration of antibiotic treatment - I

- Afebrile patient after 3–5 days of therapy, and neutrophil count has been > 500/mm3 for 2 days → discontinued after the patient has been afebrile for 48 hours
- Afebrile for 5 to 7 days, neutrophil count < 500/mm3, initially low risk and not currently septic → can be discontinued
- Afebrile, initially at high risk, neutrophil count < 100/mm3, or the patient has mucositis or is clinically unstable → continued

Duration of antibiotic treatment - I

- Persistently febrile and neutrophil count is > 500/mm3 for 4-5 days → can be discontinued but patient should be reassessed
- Persistently febrile and neutrophil count < 500/mm3, → continued for 2 weeks, with reassessment at that time; then, if no infection is evident and the patient is clinically stable → discontinued

Prevention

- Antiviral therapy is not indicated in neutropenic patients unless a specific viral infection is documented
- Fluoroquinolone prophylaxis indicated in high-risk patients who are expected to have a **prolonged** duration of **profound** neutropenia, < 100 cells/mm3 for > 7 days, despite the concern of development of widespread antibiotic resistance

Management of infections in patients with cell-mediated immunodeficiency

Patient evaluation - I

- List of organisms that can cause infection is so large that empiric therapy is not recommended unless…
  - …a specific site of infection is identified
  - …a specific pathogen is the most likely cause
- Cellulitis may have a nonbacterial origin
- Empiric therapy may be given for central catheter or urinary tract infections, because the usual organisms continue to cause these infections
- Complete clinical and social history required to assess community-acquired infections

Patient evaluation - II

- Living in certain geographic areas predisposes to specific infections (reactivation or new infection), such as
  - Histoplasmosis and coccidioidomycosis in the US
  - Visceral leishmaniasis in Spain
- Certain sites of infection do require urgent action:
  - Headache or other central nervous system complaint → lumbar puncture if not contraindicated, as **cryptococcal** or **listerial** meningitis are possible and require immediate treatment
  - Blood, urine, and any suspicious sites should be cultured

Patient evaluation - III

- Certain sites of infection do require urgent action (contd.):
  - Inflamed central line → treatment for gram-positive cocci
  - Chest radiograph abnormal or patient producing sputum → gram, acid-fast, silver staining and culture of sputum; if no sputum produced, bronchoscopy etc. may be needed

Preventive measures in graft recipients - I

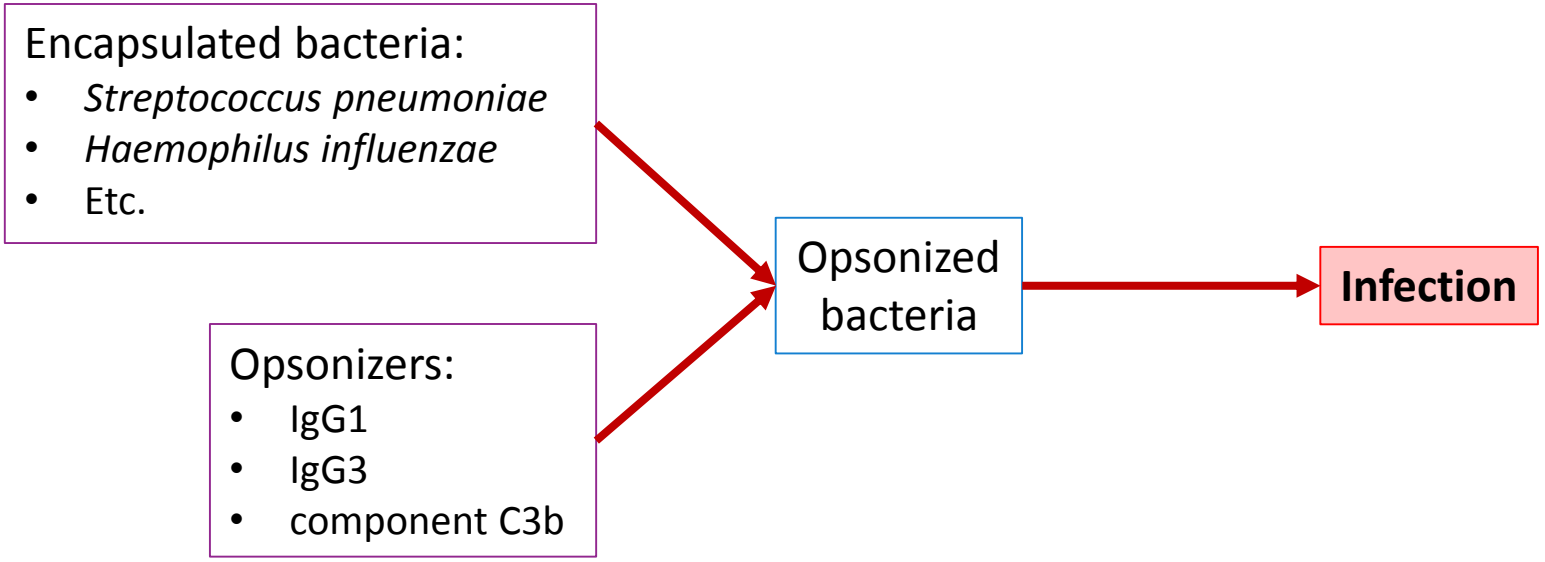
- IgG level < 400 mg/dL, IV IgG to prevent *S. pneumoniae* sinus and lung infections
- Recipient and donor **without CMV antibodies**: all blood product transfused to recipients should be CMV negative or cleansed of all leukocytes
- Both **recipient and donor**, or just **donor**, **with CMV antibodies**: the recipient should receive prophylaxis for the first 100 days with oral valganciclovir
- **Recipient** with **CMV antibodies** and donor without them: **preemptive** therapy with intravenous ganciclovir or oral valganciclovir, based on quantitative PCR for CMV

Preventive measures in graft recipients - II

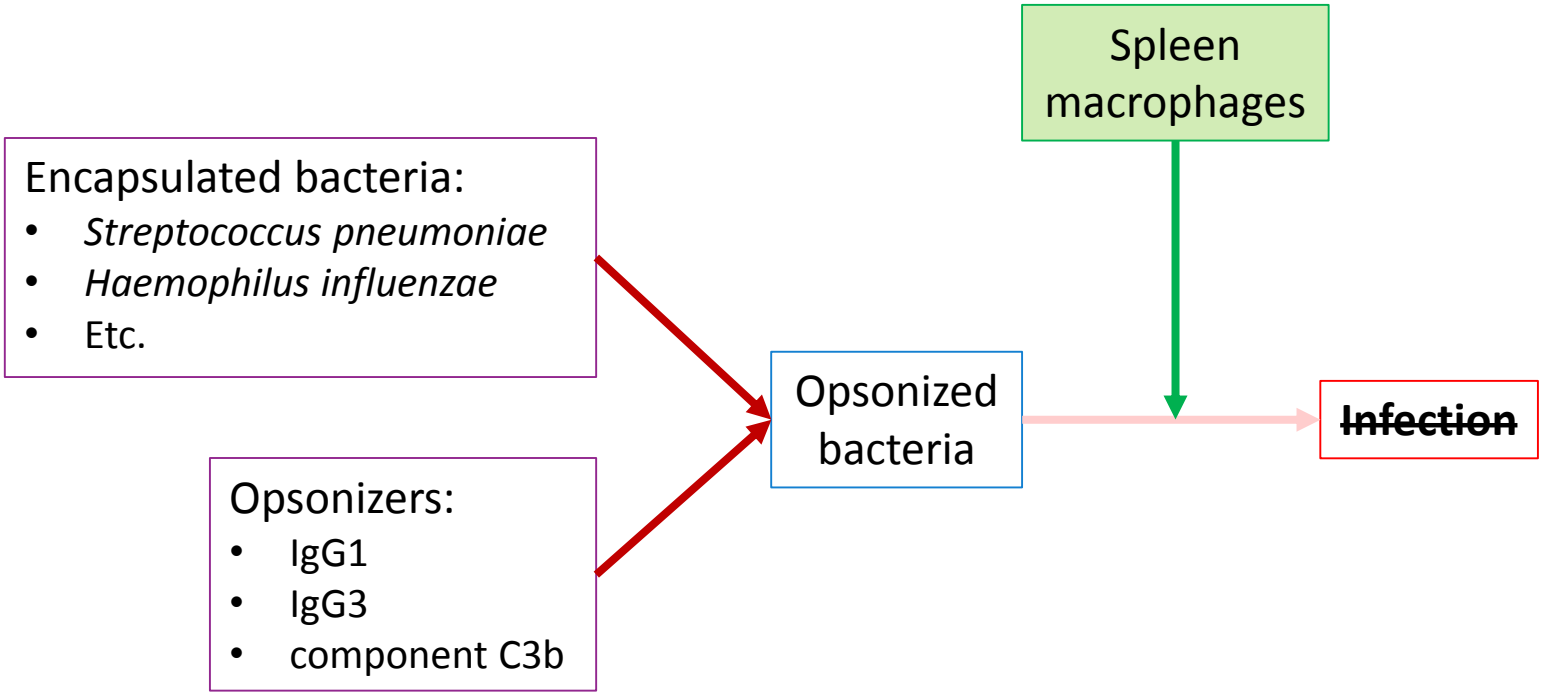
- Bone marrow recipients with antiherpes simplex IgG antibodies should receive prophylaxis during the induction phase and during the first 30 days after transplant
  - Oral valacyclovir or
  - Oral valganciclovir, if the patient also requires CMV prophylaxis

Infections related to splenectomy

Infection by encapsulated bacteria



Role of spleen in infection control



Overwhelming infection in asplenic patients

- ***S. pneumoniae***, *S. typhi*, *N. meningitidis*, *E. coli*, *H. influenzae*, etc.
- Highest risk the first 2 years after splenectomy
- Short prodrome, severe sepsis with 50 % mortality rate
- Treatment ceftriaxone + vancomycin
- Prevention
  - Prophylactic antibiotics
  - *S. pneumoniae*, *N. meningitidis*, *E. coli*, and influenza vaccines

Infections related to immunosuppressive agents and immune modulators used in inflammatory diseases

Corticosteroids

- Decreasing function and/or numbers of:
  - Neutrophils
  - Lymphocytes, both B cells and T cells
  - Monocytes and macrophages
  - Anatomical barrier function of the skin
- Risk of infection related to **dose** and the **duration** of therapy
- Most common pathogens:
  - Pyogenic bacteria
  - Intracellular pathogens such as *Listeria* spp., fungi, and herpes viruses

Biologic therapy

- Increasingly used to treat many systemic inflammatory conditions
- Antibodies or other peptides that:
  - Inhibit inflammatory cytokine signaling
  - Inhibit T-cell activation
  - Deplete B-cells
- Increased risk of:
  - Respiratory, intestinal and other common infections
  - Atypical and opportunistic infections by *Mycobacterium tuberculosis*, herpes zoster virus, *Legionella* spp., and *Listeria* spp.

Key messages

To remember…

- In the immunodeficient patient, high-grade life-threatening infection is common, therefore rapid evaluation and empiric antibiotics are frequently required in this population
- Clinical presentations of these infections is protean, so a high index of suspicion must be kept when attending the immunodeficient patient

Further reading

Used references

- Southwick F. Infectious disease. A clinical short course. 3rd Edition. New York: McGraw-Hill, 2014. Chapter 15.
- Tolan RT Jr, MD et al. Infections in the Immunocompromised Host. Available at: http://emedicine.medscape.com/article/973120-overview#aw2aab6b3.

Preparing the exam

- Southwick F. Infectious disease. A clinical short course. 3rd Edition. New York: McGraw-Hill, 2014. Chapter 15.
- These slides !!!.