



Pneumonia in the Immunocompromised Host

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Outline

- Definitions and clinical criteria
- Epidemiology
- Risk factors
- Etiologic agents
- Diagnostic methods
- Biomarkers
- Treatment
- Prevention



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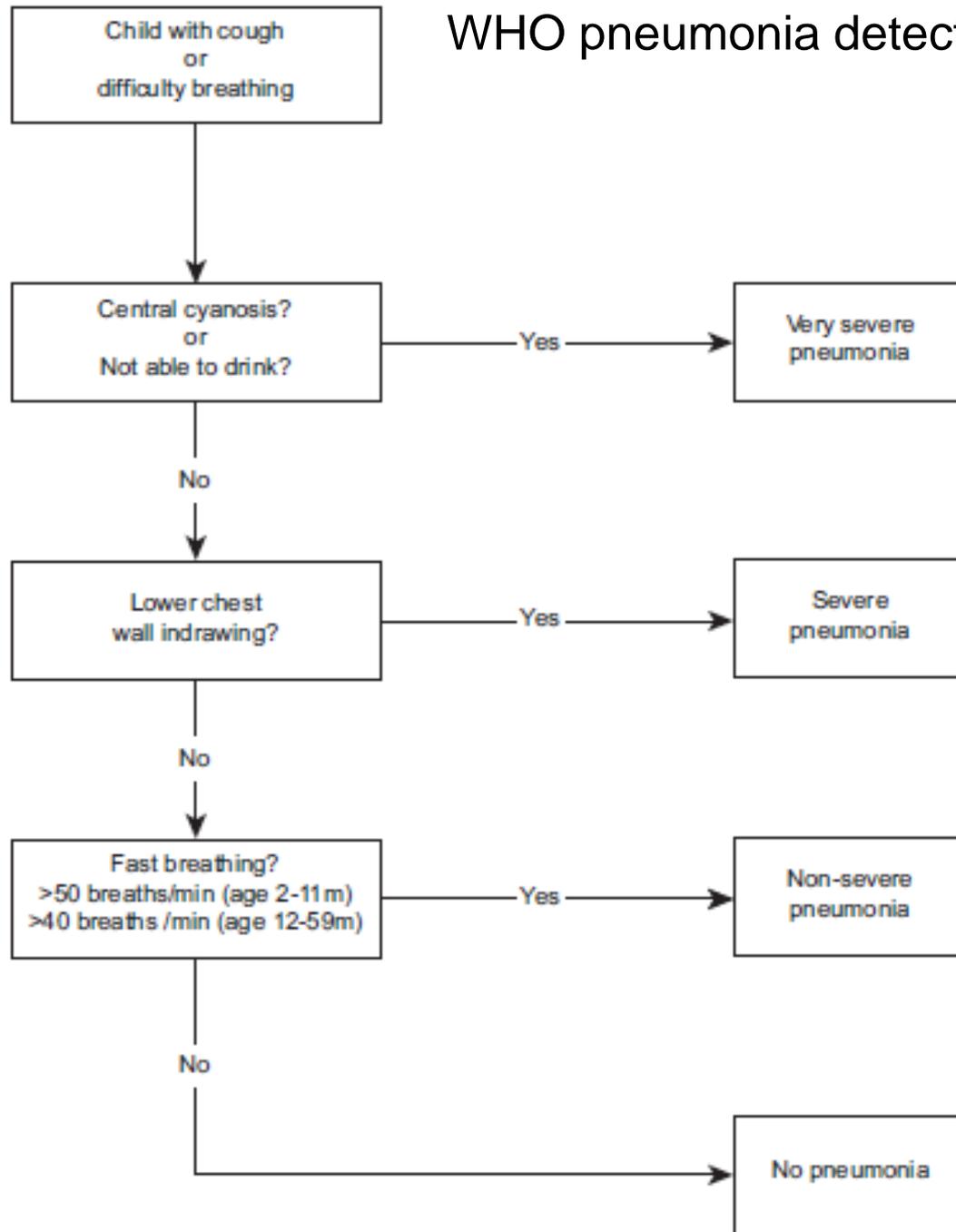


Definitions and Clinical Criteria

- Pneumonia is an infection of the lower respiratory tract, involving the lung parenchyma.
- The WHO clinical case definition of pneumonia takes into consideration clinical symptoms and signs in children 2 – 59 months of age:
 - History of cough or breathlessness; inability to feed; raised respiratory rate; lower chest indrawing; fever; and tachycardia.



WHO pneumonia detection guidelines





WHO clinical definition: Issues

- WHO clinical case definition had a low specificity and low negative predictive value
 - ↑ RR is observed in many other diseases;
 - Lower chest wall indrawing may be observed in any condition that leads to tachypnea;
 - The danger signs of very severe pneumonia apply to the “final common pathway” of a variety of processes.
- In clinical practice, low negative predictive value was simply overtreatment.



Radiographic Clinical Criteria

- A case definition with higher specificity was needed when assessing the effect of vaccines on pneumonia produced by *Haemophilus influenzae type b* (Hib) and pneumococcus.
- The WHO produced a case definition that was specific for pneumonia caused by these 2 bacteria. The definition selected was based on a common interpretation of chest radiographs.

Primary end-point pneumonia:

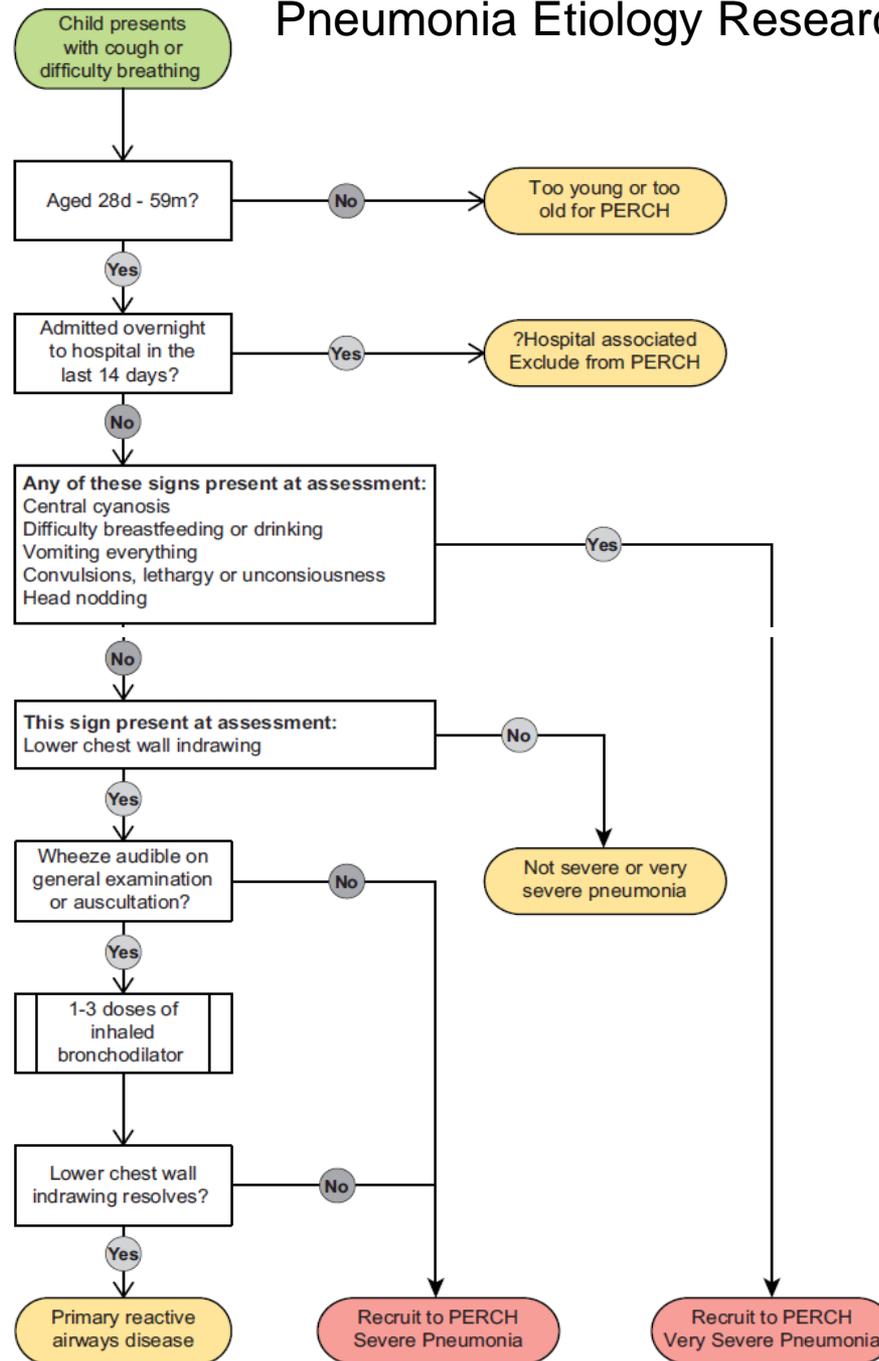
- The presence of end-point consolidation or pleural effusion that in the lateral pleural space and was spatially associated with pulmonary parenchymal infiltrate OR the effusion obliterated enough of the hemithorax to obscure an opacity.



Definitions and Clinical Criteria

- The PERCH (Pneumonia Etiology Research for Child Health) project adopted the WHO criteria focusing on an age group (1–59 months) that bears the brunt of pneumonia mortality.

Pneumonia Etiology Research for Child Health (PERCH) project



Scott et al. CID 2012:54
(Suppl 2)



Immunocompromised Children

- Because the neutropenic child was thought to be less likely to exhibit signs and symptoms of pneumonia than the immunocompetent child, a CXR had been recommended as part of the routine, initial assessment of pediatric FN.
- But, in the review of 4 studies which examined the value of routine CXR in FN, it was found that in a asymptomatic child pneumonia was $\leq 5\%$.
- Currently, routine CXRs are not recommended in asymptomatic children in the initial evaluation of FN.



Immunocompromised Children

In patients with persistent fever, beyond 96 hours, on broad spectrum antibacterials, and high risk for invasive fungal disease, it is recommended to perform studies looking for fungal infections:

- Serial galactomanann studies (twice a week)
- Imaging studies include, computed tomography (CT) of the lungs.
- CT detects pneumonia earlier than CXR and CT allow earlier diagnosis of invasive pulmonary aspergillosis.



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Epidemiology

- The WHO estimates that there are 150.7 million cases of pulmonary infection each year in children younger than 5 years, with as many as 20 million cases severe enough to require hospital admission.
- Pneumonia is still the number one cause of childhood mortality in developing countries.



Epidemiology of pneumonia in the immunocompromised host

- Incidence of pneumonia in 844 children with ALL treatment
- 310 episodes in 239 patients
- Peak incidence in the periods of 0 – 20 days, and 40 – 80 days after starting antileukemic therapy.
- Bacterial pneumonias occurred during the first 20 days after diagnosis.
- No Pneumocystis before 40 days.
- In 80% causative organisms were not detected.



Epidemiology of pneumonia in the immunocompromised host

Predictors of respiratory failure and death

- Retrospective chart review of children with acute leukemia diagnosed with pneumonia or ARDS (1991 – 1994)
- 174 admissions, 36 admission had pneumonia (20%)
- Mean age 9.2 ± 1.1 years.

Results: higher mortality associated with extension of pneumonia, sepsis, shock, high oxygen requirements and mechanical ventilator support.



Pathogens and Mortality Rates

Table 2—Likely Causative Organisms of Pneumonia

Organism	Admissions (% of 36 Admissions)	Source
Bacterial		
<i>Klebsiella</i>	4	BAL(2), blood(2)*
<i>Staphylococcus aureus</i>	3	BAL, blood(2)
<i>Streptococcus pneumoniae</i>	1	Blood
<i>Fusobacterium</i>	1	Blood
<i>Enterobacter agglomerans</i>	1	Blood
<i>Legionella pneumophila</i>	1	BAL
Total	11 (31)	
Viral		
Cytomegalovirus	4	BAL(4)
Herpes	2	BAL, Tr Asp, [†] and autopsy
Influenza A	1	BAL
Influenza B	1	BAL
Total	8 (22)	
Fungal		
Aspergillosis	1	BAL
Total	1 (3)	
At least one organism identified	16 (44)	
No organisms identified	20 (56)	

*Blood=blood culture.
[†]Tr Asp=tracheal aspirate.

Table 3—Mortality Rate of Children With Acute Leukemia and Pneumonia

Characteristic	Deaths/Total No. of Children (%)
Overall	11/30 (37)
Acute leukemia no BMT	4/18 (22)
Acute leukemia and BMT	7/12 (58)*
Required mechanical ventilation	9/10 (90) [†]

*p<0.05 vs acute leukemia no BMT.
[†]p<0.001 vs overall.



Etiologic Agents

- Same agents that cause pneumonia in the normal host
 - *Streptococcus pneumoniae*
 - *Haemophilus influenzae* type b
 - Respiratory syncytial virus
- Several opportunistic agents
 - depending on the type and severity of immunodeficiency
 - temporal pattern after chemotherapy or transplant.



Abscess / Necrotizing Pneumonia

- The most common causes of lung abscess in cancer are:
 - *Pseudomonas aeruginosa*
 - Other aerobic gram-negative bacilli
 - Gram positive bacteria
 - *Nocardia* spp, and fungi (*Aspergillus* and *Cryptococcus* spp).
- Opportunistic organisms can also cause lung abscess such as:
 - *Rhodococcus equi*, *Mycobacteria* spp, and *Aspergillus* spp



Etiology of FN

St. Jude

Etiology of fever, n (%)	
FUO	177 (53)
Proven infections	86 (25)
Bacteremia	41
Viral URI	10
GI infection	10
HSV mucositis	8
Pneumonia	7
Fungal infection	4
S/ST tissue infection	3
Other*	3
Probable Infections†	74 (22)
URI	37
GI infection	16
Culture-negative sepsis	14
S/ST infection	13
Fungal infection	8
Pneumonia	7



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Diagnostic Methods

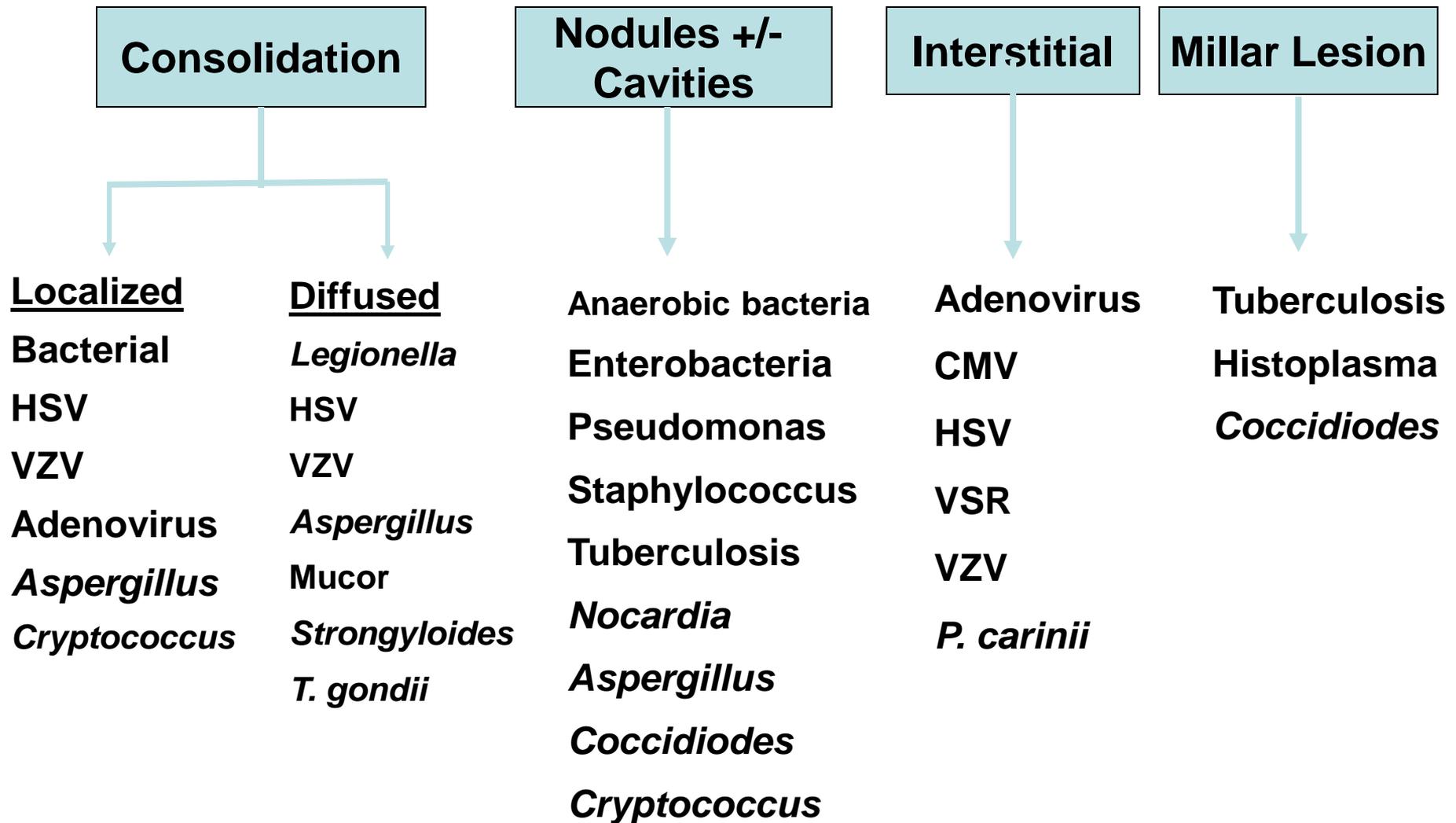
- Although the radiographic or CT appearance might not be specific for a pathogen, knowledge of the clinical setting in combination with the imaging studies might guide in the diagnostic presumption and treatment.



Diagnostic Methods

- Advantages of chest CT over chest radiographs:
 - The presence, pattern, and extent of the disease process are better visualized.
 - More than 1 pattern of abnormality may be detected, suggesting dual pathologic entities.
 - Invasive diagnostic procedures (eg, bronchoscopy or needle aspiration) can be more precisely planned.
 - CT also allows for increased sensitivity in assessment of the response to treatment.

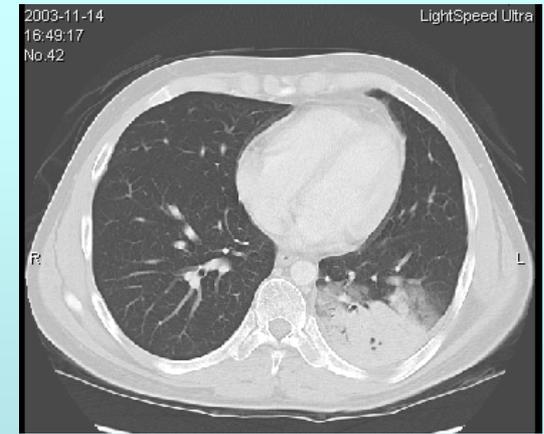
Pulmonary Infiltration Type and Etiology



Fungal Lung Infection



10/17/03



11/14/03

Imaging studies are essential for initial and progression of the disease diagnosis.



Infected pulmonary tissue with *Aspergillus*.
Aspergillus and *Zygomycetes*, are angioinvasive.

Courtesy of Dr. F. Pedrosa. Recife, Brasil



Diagnostic Challenges

- Diverse etiologies
- Blood culture
- Obtaining samples is difficult (BAL vs. Biopsy), know when ask such studies
- Reactivations of previous infectious processes
- Laboratories equipped for microbiologic studies (bacterial, viral, mycobacterial, fungal)
- Availability of early results



Diagnostic Challenges

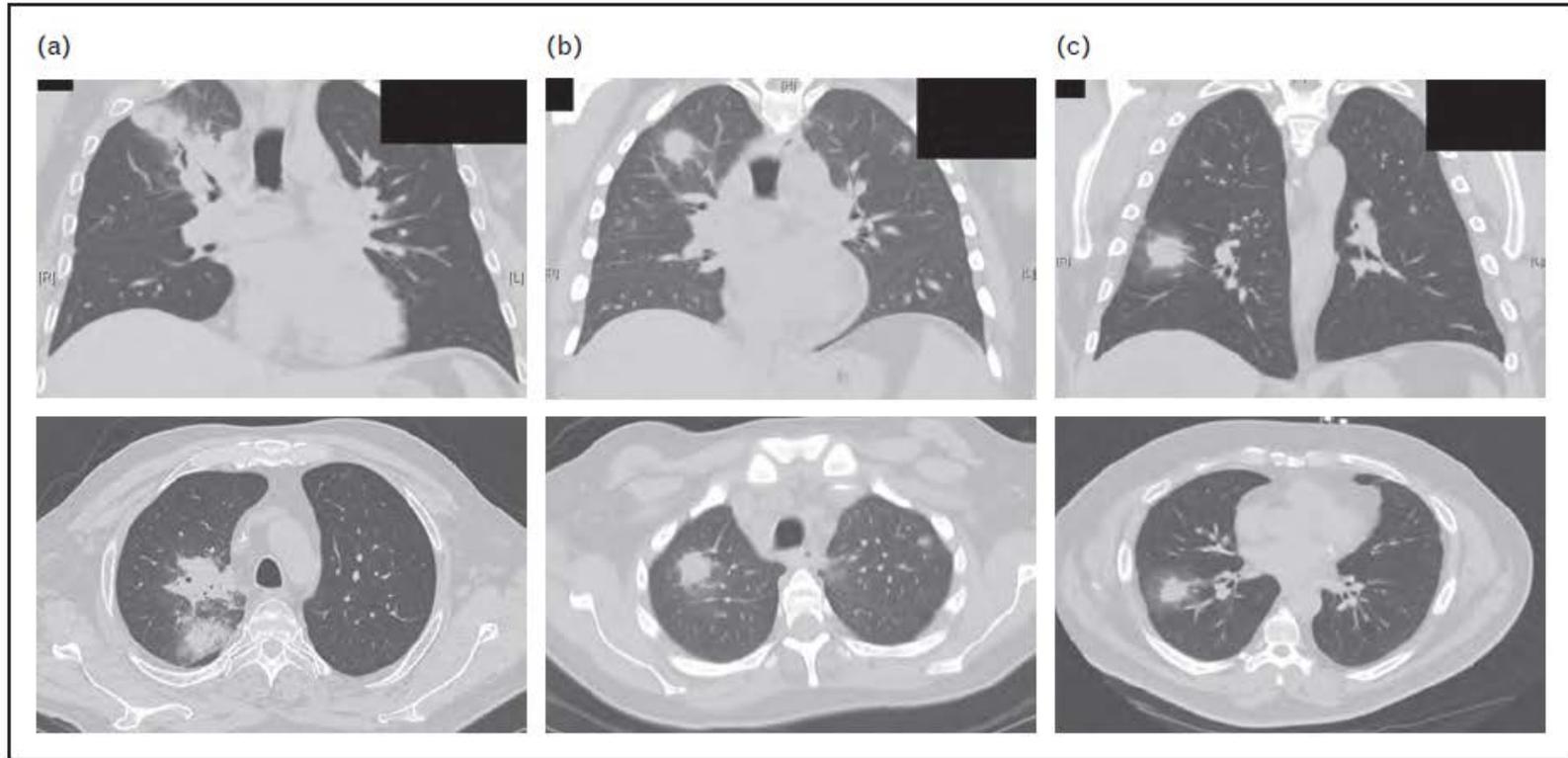


FIGURE 1. Challenges in interpreting radiography. Three patients undergoing treatment for hematologic malignancies developed new pulmonary nodules with surrounding ground glass opacities. (a) Sputum, bronchoalveolar fluid and fine needle aspiration cultures grew *Escherichia coli*. Eventual lung biopsy diagnosed mucor. (b) Serum (1-3)- β -D-glucan (BDG) and galactomannan antigen were positive. This patient received voriconazole for probable invasive aspergillosis and had a good clinical response. (c) Sputum cultures, BDG, galactomannan antigen and lung biopsy were negative. This patient was treated with antibacterials alone and made a full recovery.



Etiologic Agents

- **Bacterial:**

Pneumococcus, Staphylococcus, pseudomonas, legionela, listeria, capnocytophaga, bordetella, tuberculosis

- **Viral:**

Cytomegalovirus, varicella zoster y herpes simplex, HHV- 6, adenovirus and sincicial respiratory virus

- **Fungal:**

Aspergillus sp., Mucor sp., Candida spp., Histoplasma capsulatum, Blastomyces sp., Cryptococcus neoformans

- **Parasites:**

Pneumocystis carinii, Toxoplasma gondii, Cryptosporidium



Blood Culture

- In one study, blood cultures were positive in 5% of patients with pulmonary infections
- Pneumonia in the context of positive blood culture: the origin or the seeding of positive blood culture
- Look for additional source of infection, for example catheters



BAL vs. Biopsy

- Systematic literature review to describe the diagnostic yield and complication rate of BAL and lung biopsy for the evaluation of pulmonary lesions in patients with cancer and HSCT
- 72 studies of BAL and 31 studies of lung biopsy
- An infection dx was more common with BAL
- Lung biopsy result most likely to change treatment
- Transthoracic biopsies yield diagnosis most often than transbronchial
- Guidelines to promote consistency in the approach to the evaluation of lung infiltrates may improve clinical care of patients



Recommendations for diagnosis of IFD

- Standard diagnostic procedures:
 - Blood cultures for yeast and molds
 - Cultures and microscopic examination of appropriate liquids and solid diagnostic specimens
 - Imaging studies
- Early detection of IFD by non-culture assays for fungal antigens or NAA



Fungal Antigen Detection

- **Galactomannan (GM)**, cell wall component released by all *Aspergillus* spp, can be detected by an enzyme immunoassay with high specificity
- False-positive test
- GM positivity in serum, BAL, CSF accepted as criteria for invasive aspergillosis.
- 5 combined pediatric study:
 - Sensitivity: 0.76 (95%CI=0.62-0.87)
 - Specificity: 0.86 (95%CI=0.68-0.95)



Recommendation for GM

- Prospective screening of GM 2/week in high risk for IFD for early diagnosis of invasive aspergillosis (AII)
- Blood: Positive test ≥ 0.5 optical density index
Systemic mould active prophylaxis might decrease the dx performance of GM in serum in children (BIII)
- BAL GM (cut off optical density index of ≥ 1) for invasive pulmonary aspergillosis (microbiology + XR)



Fungal Antigen Detection

- **B-D-glucan (BDG)**, can be detected in patients with IFD due to *Aspergillus*, *Candida* spp, *Fusarium* spp, *Trichosporum* spp, or *Saccharomyces* spp, and *Pneumocystic jirovecii* and some bacterial infections.
- The Fungitell assay approved by FDA and shown that in adults as good diagnostic for early diagnosis of IFD; data in children is scarce.
- The optimal threshold for positivity of BDG in children is not known.



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Treatment and challenges

- Appropriate antimicrobial coverage
- Control, cure and eradication of infection



Antimicrobial Treatment

- Lobar pneumonia, cover for common community acquire pathogens + opportunistic pathogens (*Pseudomonas*)
 - Antipseudomonal, broad spectrum antimicrobials
 - pip/tazo; ceftazidime; cefepime; \pm aminoglycoside
 - During AML treatment, think about *Streptococcus viridans* (ARDS), usually resistant to penicillins, use vancomycin, 3rd gen cephalosporins, carbapenems
 - Rare pathogens, for example *Legionella*, use fluoroquinolones



Antimicrobial Treatment

- Necrotizing pneumonia and abscess, caused mostly by anaerobic bacteria, others aerobic bacteria such as microaerophilic streptococci (eg, *S. milleri*), *Staphylococcus aureus*, and *Klebsiella pneumoniae*, *Nocardia* (prolonged steroids)
- Antimicrobials: Clindamycin (preferred to penicillin more anaerobes beta-lactamase +); associate with other antibiotic appropriate for Enterobacteriaceae; carbapenem good for *Nocardia*



Empirical and Pre-emptive Therapy

- Empirical antifungal (FN on appropriate antibacterial therapy).
 - In 3 prospective RCT caspofungin was better tolerated than LAmB, and LAmB < nephrotoxic than dAmB. Caspofungin and LAmB were not different in the efficacy.
 - In patients receiving mould-active antifungal, switching to a different antifungal; patients receiving mould-inactive antifungal (fluconazole) give either caspofungin or LAmB.
- Pre-emptive (diagnostic driven) antifungal therapy
 - Using non-culture based microbiological and radiographic parameters to start or not antifungals.



Duration of therapy

The duration of therapy is based on:

- Control of infection, improvement of signs and symptoms
- Cure of infection:
 - Antimicrobials until the chest radiograph shows a small, stable residual lesion or is clear.
 - This generally requires several weeks of treatment (PO)
- Eradication of infection:
 - Secondary prophylaxis, frequently done for fungal infections.



Prevention

- Vaccination of patients and close contacts
- Avoidance of cross transmission during healthcare by adhering to best practices, specially hand hygiene
- Administration of prophylactic antimicrobials / immunoglobulins

Table 4. Immunization during chemotherapy for patients with acute lymphoblastic leukemia age 0–18 years.

Immunization status at diagnosis of ALL	Vaccination recommendation during ALL treatment		>3 months post chemotherapy finalization, no medication for immunosuppression, no HSCT
	Induction/consolidation	Maintenance	
Primary immunization series [†] was completed	None	<ul style="list-style-type: none"> • Influenza vaccine (IV) annually • DTaP (4th & 5th doses) between 4 and 6 years of age; and Tdap for those >7 years of age • Hib (4th dose) between 13 and 15 months • Meningococcal vaccine • PCV13 (4th dose) between 13 and 15 months • PPSV23 between 2 and 18 years[§] • HPV between 11 and 12 years (HPV2: female only; HPV4: female and male) 	<ul style="list-style-type: none"> • Influenza vaccine annually using either IIV or LIAV • MMR (2nd dose) • VAR (2nd dose)
Primary immunization series [†] was NOT completed	None	<p>Complete primary immunization series[†] avoiding live virus vaccine, follow the CDC recommendation. Priority <i>S. pneumonia</i> vaccination^{†,‡,§}</p> <ul style="list-style-type: none"> • Influenza vaccine (IV) annually • DTaP (4th & 5th doses) between 4 and 6 years of age; and Tdap for those >7 years of age • Meningococcal vaccine • HPV between 11 and 12 years (HPV2: female only; HPV4: female and male) 	<p>Complete immunization providing live virus vaccine (MMR, VAR)</p> <ul style="list-style-type: none"> • Influenza vaccine annually using either IIV or LIAV • MMR (2nd dose at least 4 weeks after 1st dose) • VAR (2nd dose at least 4 weeks after 1st dose)
Primary immunization series [†] NOT given	None	<p>Initiate primary immunization series[†] avoiding live virus vaccine, follow the CDC recommendation. Priority <i>S. pneumonia</i> vaccination^{†,‡,§}</p> <ul style="list-style-type: none"> • Influenza vaccine (IV) annually • DTaP (4th & 5th doses) between 4 – 6 years of age; and Tdap for those >7 years of age • Meningococcal vaccine • HPV between 11–12 years (HPV2: female only; HPV4: female and male) 	<p>Complete immunization providing live virus vaccine (MMR, VAR)</p> <ul style="list-style-type: none"> • Influenza vaccine annually using either IIV or LIAV • MMR (2nd dose at least 4 weeks after 1st dose) • VAR (2nd dose at least 4 weeks after 1st dose)

Table 5. Recommendations by the Infectious Diseases Society of America for vaccines for household members of immunocompromised patients.

Vaccines	Recommendations
Inactivated vaccines	Immunocompetent household individuals can receive inactivated vaccines according to the annually updated recommended vaccination schedules by the Advisory Committee on Immunization Practices (ACIP) of Centers for Disease Control (CDC) for children and adults or for travel [‡]
Influenza vaccines	<p>Household Individuals age ≥ 6 months should receive influenza vaccine annually[†]. These individuals should receive either:</p> <ul style="list-style-type: none">• Inactivated influenza vaccine (IIV)[†] or• Live attenuated influenza vaccine (LAIV), if they are healthy, not pregnant, and aged 2–49 years[§] <p><i>Exceptions:</i> Individuals living in a household with an immunocompromised patient, who was a hematopoietic stem cell transplant (HSCT) recipient within 2 months after transplant had graft versus host disease (GVHD) or was a patient with severe combined immune deficiency (SCID). In these household individual, LAIV should not be given^{§§} or, if administered, contact between the immunocompromised patient and household member should be avoided for 7 days^{§§}.</p>
Live virus vaccines	<p>Oral polio vaccine (OPV) should not be given to household individuals with immunocompromised patients[‡]. Healthy immunocompetent individuals who live in a household with immunocompromised patients should receive the following live vaccines according to the CDC annual schedule:</p> <ul style="list-style-type: none">• Combined measles, mumps, and rubella (MMR) vaccines[‡]• Rotavirus vaccine for infants aged 2–7 months[§]• Varicella (VAR) vaccine[‡]• Zoster (ZOS) vaccine[‡] <p>These individuals can safely receive the following vaccines for travel:</p> <ul style="list-style-type: none">• Yellow fever vaccine[‡]• Oral typhoid vaccine[§] <p><i>Notes:</i></p> <p>Immunocompromised patients should avoid handling diapers of rotavirus vaccinated infants for 4 weeks post vaccination[¶].</p> <p>Immunocompromised patients should avoid contact with persons who develop skin lesions after receipt VAR or ZOS until the lesions clear[§].</p>



Summary

- ❑ Be aware of the type of malignancy, and the neutropenia duration and depth.
 - Bacterial infection most frequent during the early cancer treatment, except in myelogenous leukemia.
 - Fungal infection is common in the context of prolonged neutropenia and use of broad spectrum antimicrobials.
- ❑ Obtain blood cultures, pneumonia could be part of a systemic infection, and patient might be bacteremic.
- ❑ Obtain samples (BAL, pulmonary biopsy) for microbiologic studies whenever the patient does not respond to treatment.
- ❑ Treat bacterial infection with broad spectrum antimicrobials.
- ❑ Fungal infection treatment duration is prolonged.