Pneumonia in the Immunocompromised child

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Immunocompromised child

- Primary immunodeficiency: Congenital
- Secondary immunodeficiency:
  - Malignancy and chemotherapy
  - Transplant
  - Steroids
  - Splenectomy
  - HIV/ AIDS
  - Biologic response modifiers (BRMs)

Case 1

3 year old Indian boy

Admitted for:

-cough x 3 wk (mild / productive)

-runny nose x 3 wk

-fever x 1 wk, T max 38.5 ^{0} C

No recent travel or contact history.

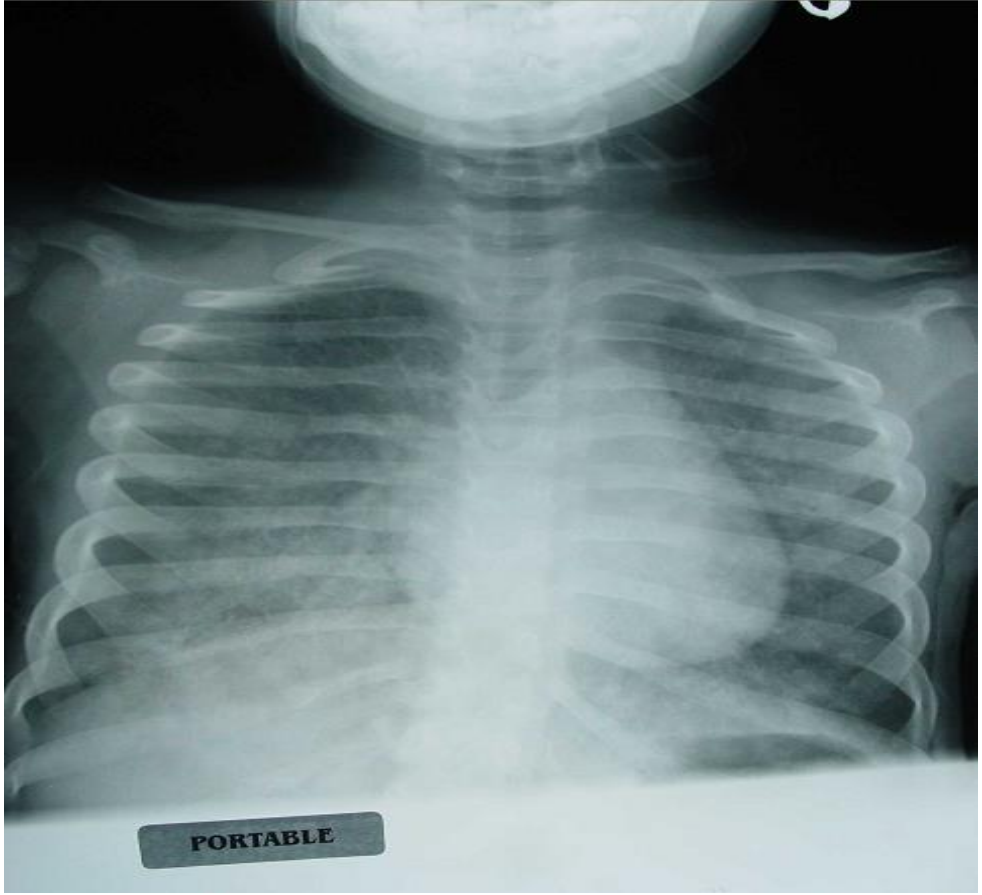
1 admission in India at 2 yrs old for pneumonia, treated with a 5 day course of IV antibiotics. No intubation required.

Wheezing and short of breath at 6 months of age. Given nebuliser. Told to have ? lactose intolerance. Changed to soy formula - no further wheezing noted.

Came to Singapore past 6 months and started on Nespray milk - developed frequent stools (4x / day)with abdominal pain. BO watery- loose, no blood. Diagnosed to have lactose intolerance and changed to soy formula but patient refused. Very picky eater.

- Significant Physical Findings
- Afebrile, weight 11.4 kg.
- B.P: 95/55 mm Hg, HR 160 /minute. RR 45-60/minute.
- Sp02: 98-100%
- Heart: S1S2
- Lungs: subcostal retractions. Breath sounds equal bilaterally with occasional bilateral coarse crepitations.
- Abdo: soft and non tender. Liver 1 spleen 1 cm, kidney 0
- Tone normal, reflexes 2+/ bilateral, plantar down bilateral, no clonus

- What is your diagnosis and differential diagnoses?
- What investigations would you perform?



How would you manage him?

FBC: Hb 12, tw 6.3, plt 503. P 25%, L 64%
U/E : U 1.9, Cr 34, Na 134, K 4.1, HCO3 24, Cl 102
CRP < 5, LFT : TP 61, alb 28, bil 7, ALT 10, AST 24, ALP 88

Blood culture neg, Mycoplasma serology negative
Blood CMV PCR negative
BAL: culture: P. aeruginosa 2 +, CMV PCR positive, neg for respi viruses fungal stain negative for *Pneumocystis jiroveci*, galactomannan negative, AFB smear negative, TB PCR negative, AFB culture and fungal culture pending, cytology pending

Stool tests neg for OCP, c/s
Urine neg FEME, c/s

How would you manage him?
Any other investigations?

Serum Immunoglobulins:

IgM 9.06 g/l	(0.37- 1.79)
IgA <0.25 g/l	(0.25- 0.62)
IgE <18 iu/ml	(18- 100)
IgG <1.4 g/l	(5.02- 18.1)

Flow cytometry for CD40 ligand on 8/1/04 - nil detected

CD3 54% (normal 56-68%), CD56 3% (9-19%), CD20 36% (18.5-28%).

CD 4 (absolute)	2278 (342-929 cells/uL)
CD 8 (absolute)	953 (103-717 cells/uL)
T cell CD 8 blood	18.7 (11.3-29.3%)
T cell CD 4 blood	44.7 (22.6-41.3%)
CD 4/CD 8 ratio	2.4 (1-2.2)

HIV Ab screen - non-reactive

What is your diagnosis and further management?

HyperIgM disease
CMV pneumonitis, P. aeruginosa pneumonia- IV ganciclovir, IV ceftazidime, BMT

Pathogens in immunocompetent patients

Age	Organisms	Salient clinical features
Birth to 20 days	GBS Gram negative enteric CMV Listeria	Early-onset, very severe, bilateral diffuse Nosocomial Part of systemic CMV Early-onset sepsis
3 wk- 3 mths	Chlamydia trachomatis RSV Parainfluenza 3 *S. pneumoniae* *B. pertussis* *S. aureus*	Afebrile, subacute interstitial Peak 2-7 mths, R/N profuse, wheeze Similar to RSV Most common cause of bact. Pneumonia Facial congestion, apnoea, cyanosis Less common
4 mth- 4 yrs	RSV, parainfluenza, influenza, adenovirus *S. pneumonia* *H. influenzae* *Mycoplasma pneumoniae* *M. tuberculosis*	Most common cause of pneumonia Most likely cause of lobar/ segmental Non-type b Subacute, walking pneumonia Chronic cough/ fever and positive contact
5-15 yrs	*Mycoplasma pneumoniae* *Chlamydophila pneumoniae* *S. pneumoniae* *M. tuberculosis*	Most common cause of pneumonia Controversial Most likely cause of lobar pneumonia Chronic cough/ fever and positive contact

McIntosh K, N Engl J Med 2002, 346: 429-437

Pathogens by Immunological defect

Defects	Bacteria	Fungi	Viruses	Parasites
Phagocytes	*Staphylococcus aureus* *Pseudomonas aeruginosa* *Klebsiella pneumoniae* *Escherichia coli*	*Aspergillus* spp. *Candida* spp.		
B-cell	*Streptococcus pneumoniae* *S. aureus* *Haemophilus influenzae* *P. aeruginosa*			
T-cell	*Legionella* spp. *Nocardia* spp. *Mycobacteria* spp.	*Pneumocystis jirovecii* *Cryptococcus neoformans* *Histoplasma capsulatum* *Coccidioides immitis* *Candida* spp.	Cytomegalovirus Varicella-zoster virus Herpes simplex virus	*Toxoplasma gondii* *Strongyloides stercoralis*
Splenectomy	*S. pneumoniae* *S. aureus* *H. influenzae*			
Steroid therapy	*S. aureus* *Legionella* spp. *Nocardia* spp. *Mycobacteria* spp. *P. aeruginosa* Other gram-negative bacteria	*Aspergillus* spp. *Candida* spp. *C. neoformans* *H. capsulatum* *C. immitis*	Cytomegalovirus Varicella-zoster virus Herpes simplex virus	*T. gondii* *S. stercoralis*

Peck KR, Precision and Future Medicine 2018;2(3):95-108

Pathogens by phase of Stem cell transplant

Pre-engraftment (day 0–30)	Post-engraftment (day 31–100)	Late engraftment (day >100)
Neutropenia	Defect in CMI & humoral immunity	Community-acquired infection
Aspiration	CMV	*Streptococcus*
G (–) bacilli	*Pneumocystis jirovecii*	*Staphylococcus*
Aspergillus	Idiopathic pneumonitis	Varicella
	GVHD	GVHD
		Bronchiolitis obliterans
		BOOP

CMI, cell-mediated immunity; CMV, cytomegalovirus; GVHD, graft-versus-host disease; BOOP, bronchiolitis obliterans organizing pneumonia.

Peck KR, Precision and Future Medicine 2018;2(3):95-108

BRM

Biologic Response Modifier

Generic Name (Year[s] FDA Approved for Indications)	Trade Name	Mechanism of Action	Usual Route, Half-Life	FDA-Approved Indication[a]
Etanercept (1998)	Enbrel[20–22]	*TNF-α inhibitor* (soluble TNF-α receptor fusion protein)	SC, 70–132 hr	Juvenile idiopathic arthritis, rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis
Infliximab (1999, 2009)	Remicade[17–19]	*TNF-α inhibitor* (anti–TNF-α chimeric monoclonal IgG1κ antibody)	IV, 7.5–9.5 days	Crohn disease, rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis
Anakinra (2001)	Kineret[32]	Recombinant anti-IL1 receptor antagonist	SC, 4–6 hr	Rheumatoid arthritis
Adalimumab (2002)	Humira[23–27]	*TNF-α inhibitor* (anti-TNF-α humanized monoclonal IgG_1 antibody)	SC, 10–20 days	Juvenile idiopathic arthritis, rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn disease
Rituximab (2006)	Rituxan[33]	Anti-CD20 therapy	IV, 14–62 days	Rheumatoid arthritis, non-Hodgkin lymphoma
Abatacept (2005, 2009)	Orencia[31]	Anti-CTLA4 selective T-cell costimulation modulator protein (blocks *TNF-α*, IL-2, and interferon γ production)	IV or SC, 8–25 days	Juvenile idiopathic arthritis, rheumatoid arthritis
Rilonacept (2008, Orphan Drug)	Arcalyst[40]	IL-1 receptor fusion protein	SC, 8.6 days	CAPS
Golimumab (2009)	Simponi[28–29]	*TNF-α inhibitor* (anti-TNF-α IgG1κ antibody)	SC, 7–20 days	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis
Natalizumab (2008, 2013)	Tysabri[38]	Humanized anti-integrin alpha 4 subunit monoclonal antibody (reduces leukocyte adhesion and transmigration)	IV, 11 days	Crohn disease multiple sclerosis
Certolizumab pegol (2009)	Cimzia[30]	*TNF-α inhibitor* (PEGylated human Fab antigen binding)	SC, 14 days	Rheumatoid arthritis, Crohn disease
Canakinumab (2009, 2013)	Ilaris[36–37]	Anti–IL-1B human monoclonal antibody	SC, 26 days	CAPS, juvenile idiopathic arthritis
Tocilizumab (2010)	Actemra[34]	Anti–IL-6 humanized monoclonal antibody	IV, 8–14 days	Rheumatoid arthritis
Belimumab (2011)	Benlysta[39]	Human IgG1λ monoclonal antibody against soluble human B lymphocyte stimulator protein	IV, 19 days	Systemic lupus erythematosus
Eculizumab (2011)	Soliris	Humanized monoclonal antibody that inhibits terminal complement components C5a and the membrane attack complex C5b–9	IV, 11.3 days	Paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome
Tofacitinib (2012)	Xeljanz[41]	Small molecule protein kinase inhibitor of JAK-3 and JAK-1	Oral, 3 hr	Rheumatoid arthritis
Ustekinumab (2013)	Stelara[35]	Anti–IL-12 and anti–IL-23 humanized monoclonal antibody	SC, 20–24 days	Psoriatic arthritis, plaque psoriasis

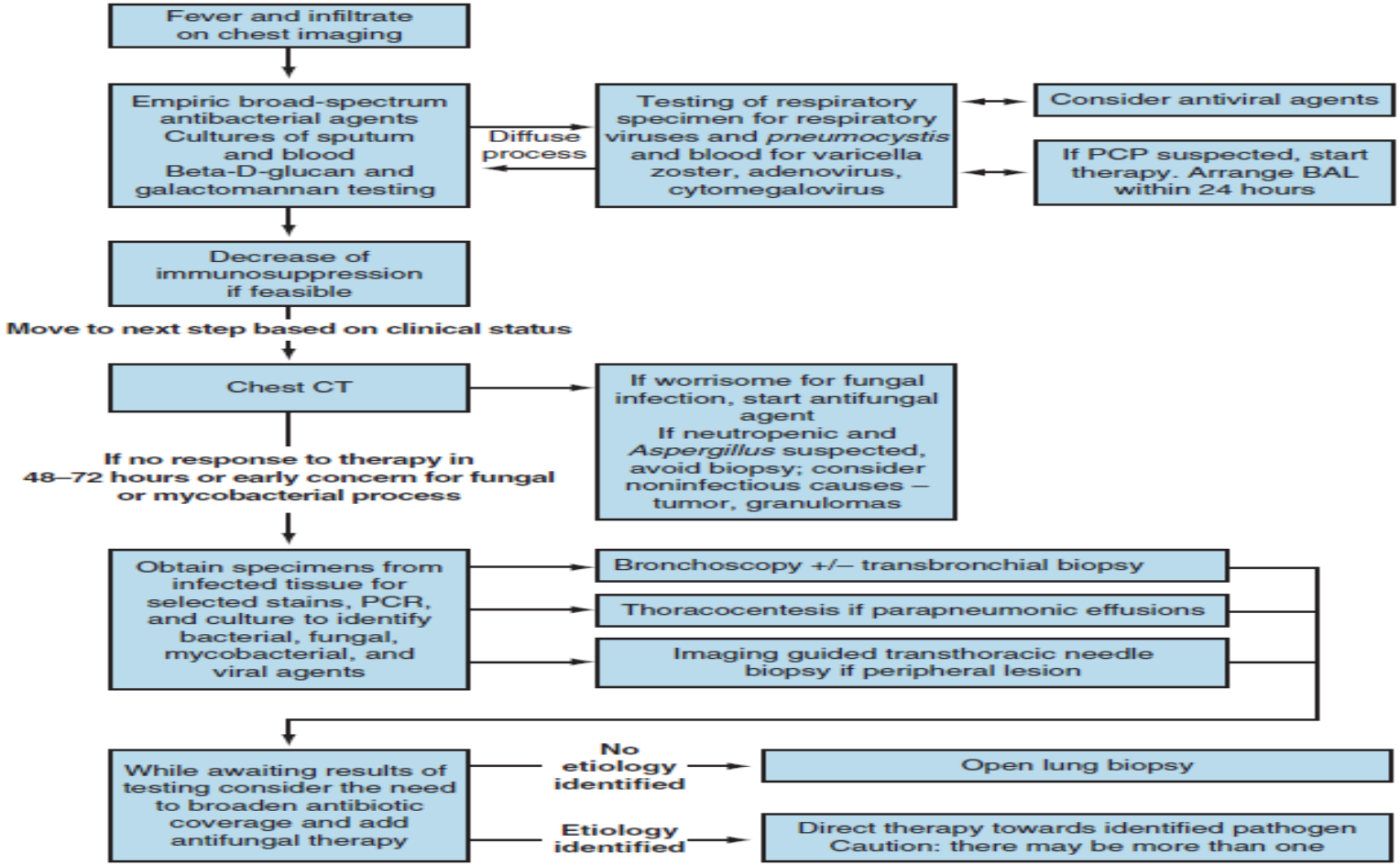
[a]FDA approved indication: for conditions in *purple*, safety and efficacy have been established in children <18 years; for indications in *red*, safety and efficacy have only been shown in adults. Infliximab, etanercept, and adalimumab have been used off-label for scleritis, but none is FDA approved for this condition.
CAPS, cryopyrin-associated periodic syndromes (consisting of familial cold autoinflammatory syndrome and Muckle-Wells syndrome); FDA, U.S. Food and Drug Administration; IV, intravenous; SC, subcutaneous.

Principles of Paediatric Infectious Diseases 2018, Sarah Long. Chapter 107

Biologic Response Modifiers

- Cytokines that are targeted include tumor necrosis factor α; interleukins (ILs) 6, 12, and 23; and the receptors for IL-1α (IL-1A) and IL-1β (IL-1B) as well as other molecules.
- Higher risk of infection or reactivation with mycobacterial infections
  - TB and nontuberculous mycobacteria
  - TNF antibodies (e.g., infliximab and adalimumab) associated with the highest risk, and soluble TNF receptor antibodies (e.g., etanercept) appear to have the lowest risk
- Viral : VZ, HSV, EBV, hepatitis B
- Fungal : PJP, histoplasmosis infections
  - Rituximab (which depletes B lymphocytes that are crucial to control *P. jirovecii*) particularly is associated with ↑ risk for PCP. No clear benefit of screening for PCP or of chemoprophylaxis for PCP in patients receiving rituximab.

Algorithm for Pneumonia in Immunocom-promised



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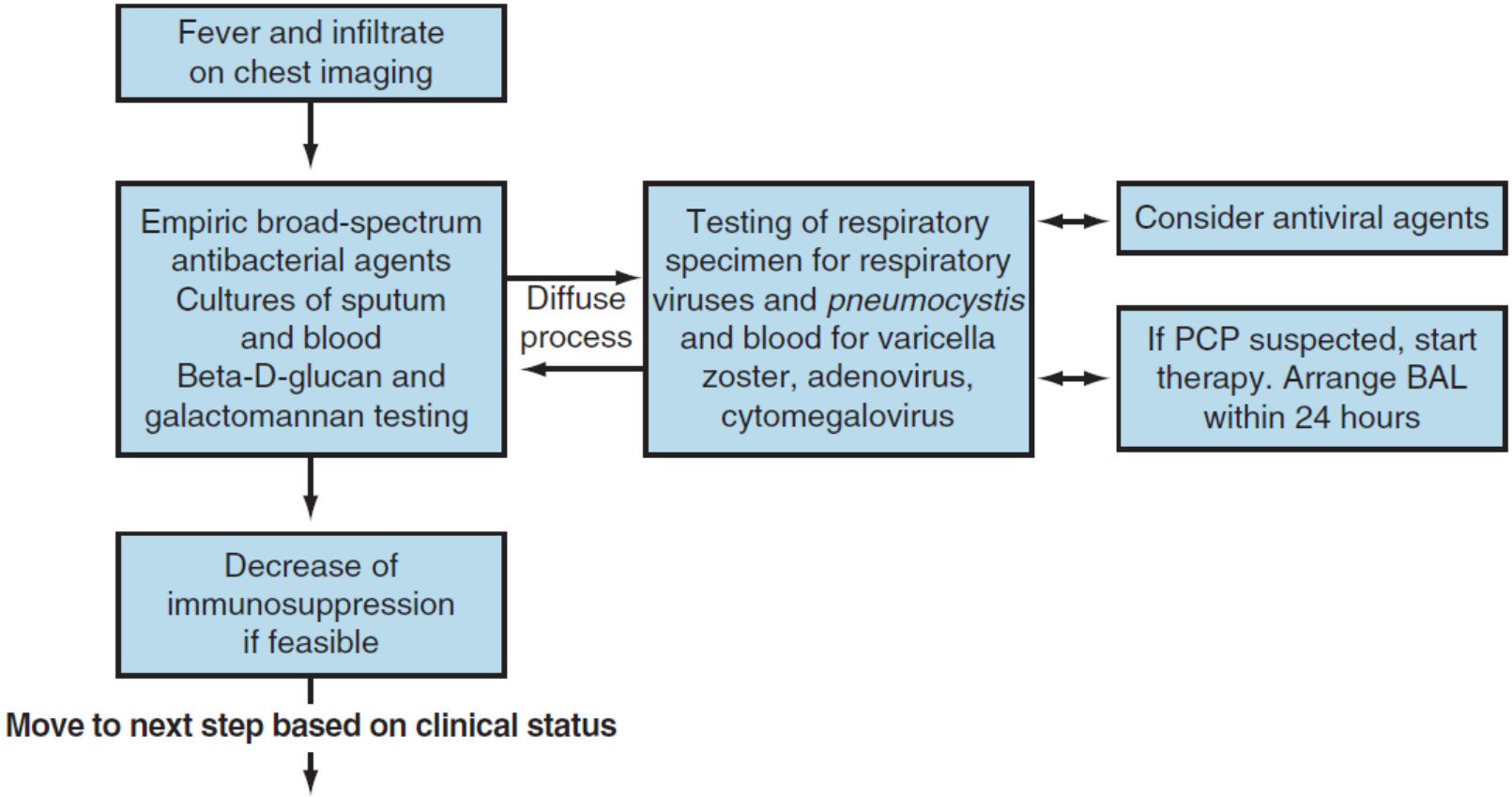

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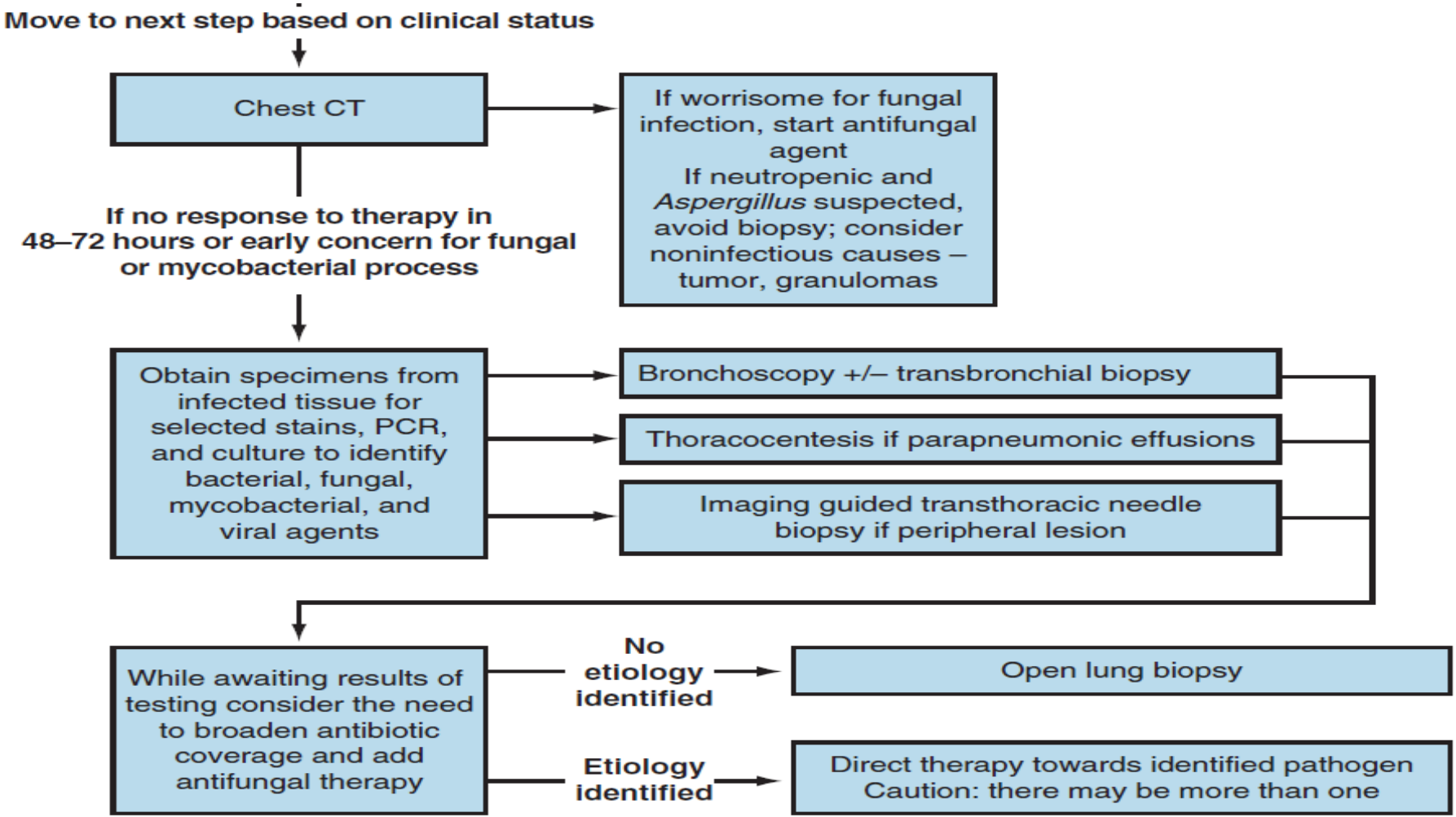


Case 2

13 yr old girl

ITP diagnosed 8 mths ago had pulse methlyprednisolone, rituximab,

prednisolone 30 mg BD x 1 wk then 20 mg BD x 1 wk

Fever x 2 days, SOB x 2 days with chest tightness, dry cough x 5 days.

Physical Examination:

RR 55 /min, SpO2 88%, HR 110/min, BP 90/56

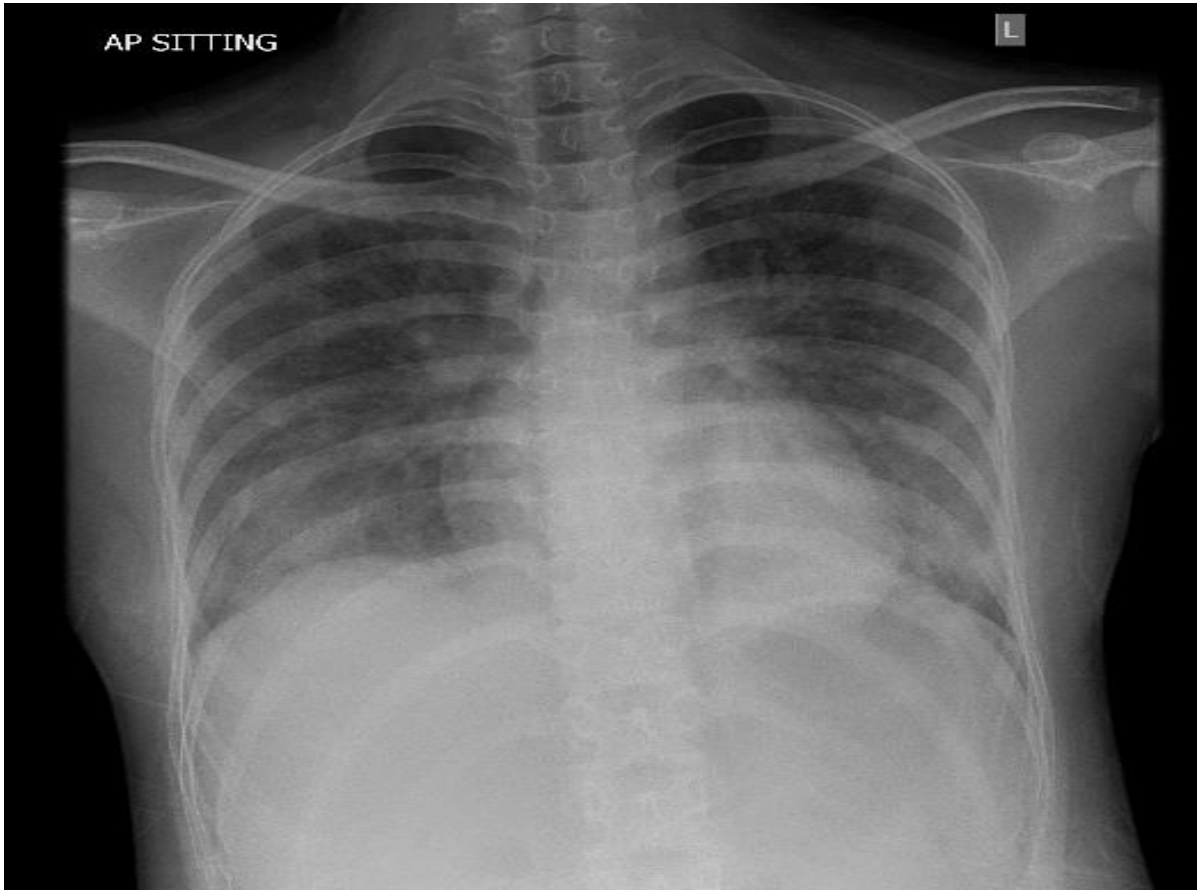
H/L basal crepitations, no rhonchi

Abd soft nontender no masses

Scattered petechiae. Cervical lymph nodes 0.5-0.8 cm

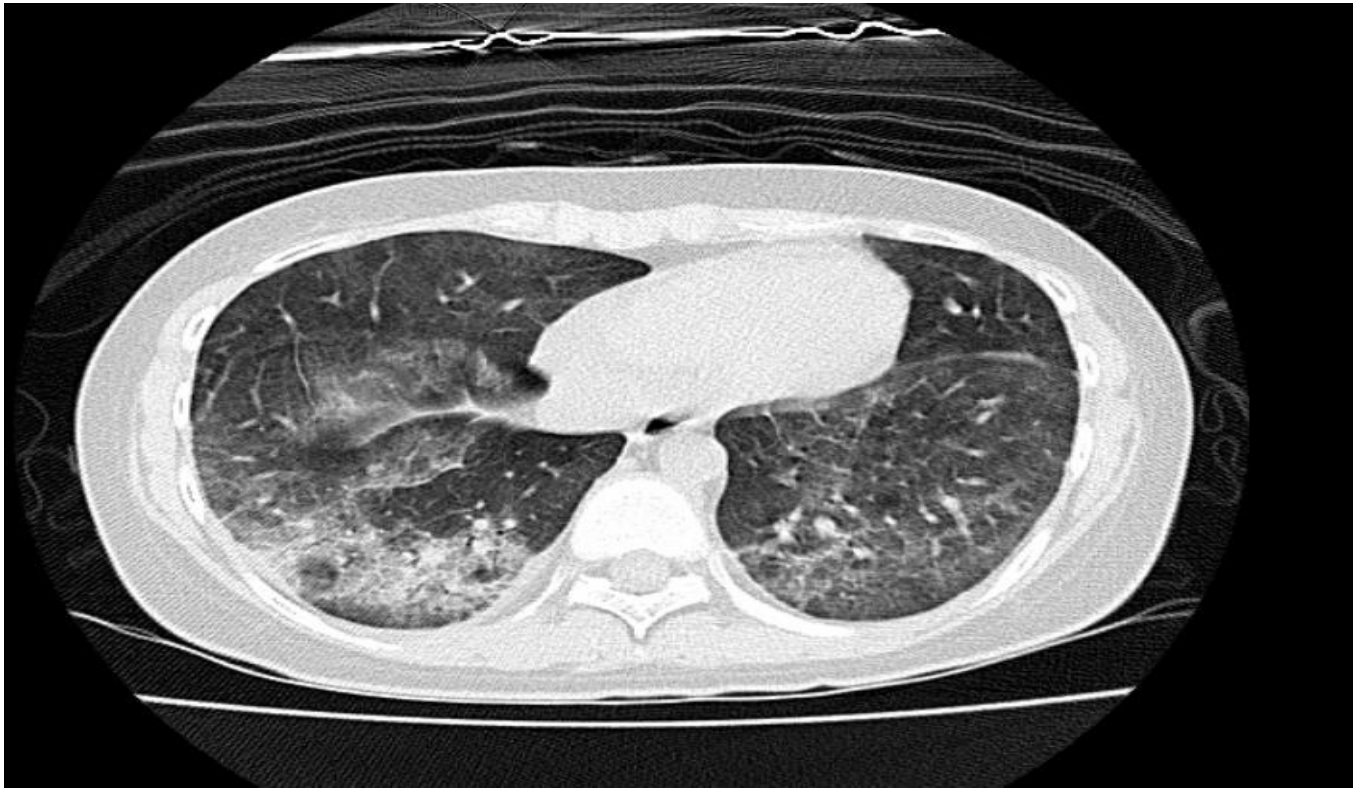
FBC: Hb 15.7, tw 4.7, plt 10

Interpret CXR



What is your diagnosis? What further investigations would you do?

CT thorax



What is your interpretation of the CT scan?

Unenhanced helical CT scanning of the thorax was performed. The chest radiograph performed earlier at 1651hrs was reviewed.

Diffuse ground-glass attenuation is evident in both lungs, with relative sparing of the right middle and lingular lobes. In addition, there is denser opacification superimposed on the ground glass opacities in both lower lobes, worse on the right. There are also increased peripheral interstitial markings seen in both lung bases. A small right pleural effusion is also present, measuring up to 7mm in depth.

There is no pneumothorax or pneumomediastinum. The tracheobronchial tree is patent.

No enlarged mediastinal, hilar, supraclavicular or axillary nodes are identified on this non -contrast study. A speck of calcification is seen in the aortopulmonary window attributable to ductus arteriosus closure (image 3/25).

The bones are unremarkable. Vascular structures cannot be accurate assessed in this unenhanced study.

Upper abdominal structures show no contour deforming abnormality.

IMPRESSION:
Diffuse ground glass attenuation in both lungs is non-specific but could represent pneumonitis / interstitial lung disease.
Small right pleural effusion.

What other investigations do you want to order?
How would you manage the patient?

- BAL
  - Bacteria culture negative
  - Respiratory Multiplex PCR -ve,
  - Pneumocystis jirovecii positive, fungal c/s pending, fungal smear -ve,
  - AFB smear -ve, AFB culture pending, TB PCR negative
  - CMV PCR +ve log 3.1
  - Galactomannan 0.13 (negative)

- Hb 12.7, TWC 3.4, Plt 25, Neut 78%, Lymp 13%
- Blood CMV PCR undetectable

How would you manage her ?

What is your management?

Complete IV bactrim x 2 wks then PO,

IV ganciclovir x 2 wks, then PO

Stop Clarithromycin if negative for mycoplasma,

complete 2 wks Augmentin

Tail down hydrocortisone

Wean respiratory support

Support plt via IVIG

PJP difference between HIV negative and positive

Difference	HIV-positive	HIV-negative
PCP may reveal the underlying disease	yes	exceptional (three cases of adult T cell leukaemia due to HTLV infection revealed by PCP)
Corticosteroids received before the diagnosis of PCP	no	yes (90%), mostly during tapering or after withdrawal
Onset	progressive	acute
Duration of symptoms before diagnosis	long (3–5 weeks)	short (4–8 days)
Hypoxaemia	mild	often severe
LDH elevation		
specificity and sensitivity	good	low
levels	high	moderate
Characteristics of BAL fluid	high number of cysts; few neutrophils	low number of cysts; many neutrophils
Mortality rate	17%–30%	28%–53%; especially high after HSCT

HTLV, human T cell leukaemia virus; LDH, lactate dehydrogenase.

Cordonnier C, J Antimicrob Chemother 2016; 71: 2379–2385

XR patterns and pathogens in immunocompromised

Radiographic Pattern	Likely Pathogens	Diagnostic Approach
Diffuse, interstitial	Viruses (CMV, RSV, parainfluenza, HSV) *Mycoplasma pneumoniae*[a] *Chlamydia* spp.[a] *Pneumocystis jirovecii*	Rapid viral, mycoplasmal, or chlamydial diagnostic tests on upper airway secretions; β-D-glucan for *Pneumocystis;* bronchoscopy with PCR or immunofluorescence for viruses, and methenamine silver stain for *Pneumocystis*
Focal, consolidative	Pyogenic bacteria (*Streptococcus pneumoniae, Haemophilus influenzae,* others) Nosocomial bacteria *Legionella* spp. (Also consider fungi and mycobacteria)	Blood cultures Gram stain and culture of deep respiratory tract secretions *Legionella* antigen in urine *Cryptococcus* antigen (blood) *Histoplasma* antigen (urine) Galactomannan (blood) Acid-fast smears Bronchoscopy Biopsy
Micronodular	Viruses (adenovirus, VZV, EBV [LIP]) Mycobacteria *Histoplasma, Candida, Cryptococcus* spp.	Rapid viral diagnostic tests on upper respiratory tract secretions Acid-fast smears, cultures of lower respiratory tract secretions *Histoplasma* antigen (urine) *Cryptococcus* antigen (blood)
Nodular	*Aspergillus* spp., other fungi, agents of mucormycosis *Nocardia* spp. EBV lymphoproliferative disease	Galactomannan (blood) *Histoplasma* antigen (urine) *Cryptococcus* antigen (blood) EBV PCR (blood) Bronchoscopy Biopsy (transbronchial, fine-needle, VATS, or open)

[a]Can also cause patchy infiltrate in less compromised individuals.
CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; LIP, lymphocytic interstitial pneumonitis; PCR, polymerase chain reaction. RSV, respiratory syncytial virus; VATS, video-assisted thoracoscopic surgery; VZV, varicella-zoster virus.

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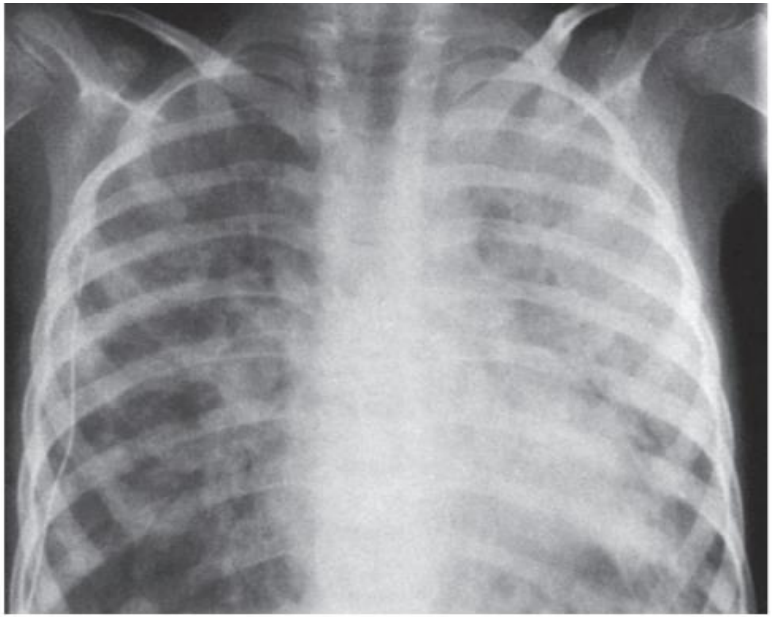

FIGURE 98.2 Chest radiograph showing bilateral interstitial and alveolar infiltrates in a child with acute lymphocytic leukemia and *Pneumocystis* pneumonia.

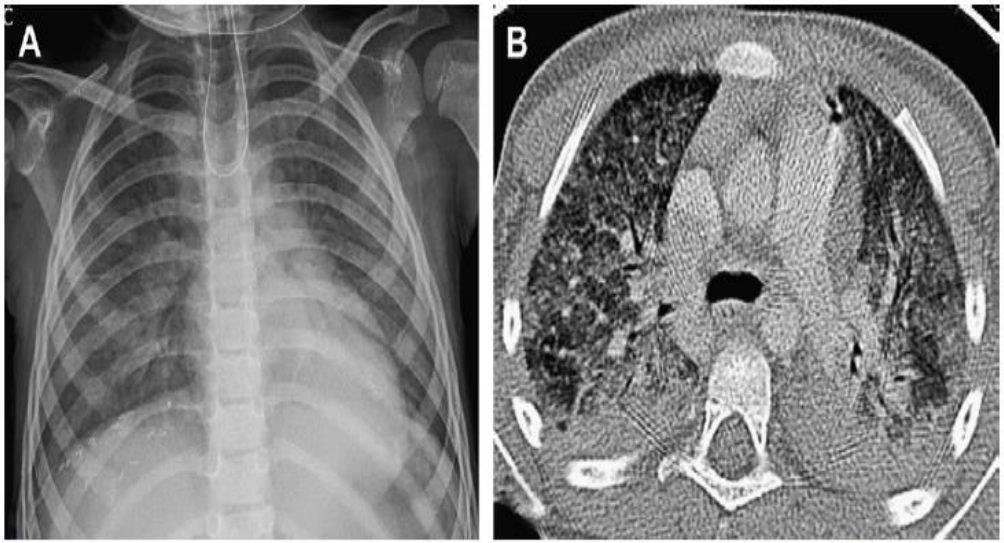

Fig. 23. *Pneumocystis jiroveci* pneumonia in a 4-year-old girl 2 years after liver transplant with known posttransplant lymphoproliferative disorder. *(A)* Frontal chest radiograph shows diffuse bilateral ground-glass opacities and malpositioned nasogastric tube coiled in the esophagus. *(B)* Axial contrast-enhanced CT shows bilateral diffuse ground-glass opacities and dependent atelectasis.

Eslamy HK, Radiol Clin N Am 49 (2011) 895–920

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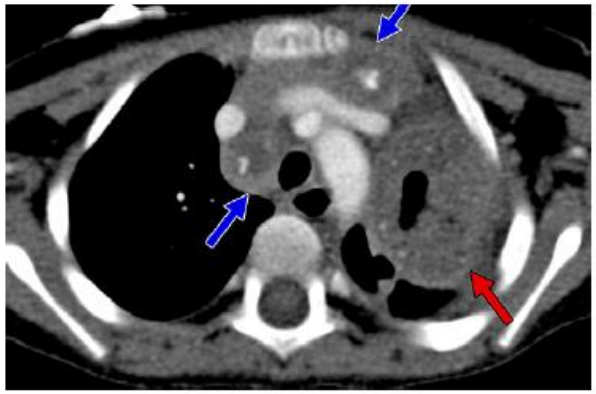

Fig. 7. Chronic pneumonia with lymphadenopathy caused by disseminated *Mycobacterium tuberculosis* in a 2-year-old boy. Axial contrast-enhanced CT shows mediastinal (*blue arrows*) and hilar (*not shown*) lymphadenopathy with central low attenuation, peripheral rim enhancement, and calcification. A left upper lobe mass with cavitation and punctuate calcification is consistent with a cavitating tuberculoma (*red arrow*).

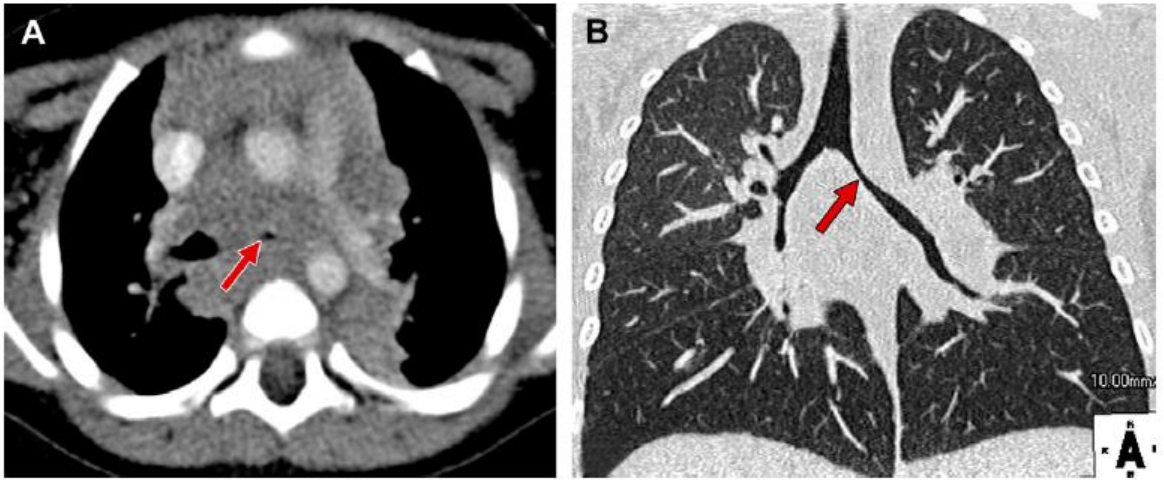

Fig. 8. *Mycobacterium tuberculosis* in an 11-month-old boy with 1.5-month history of intermittent stridor. *(A)* Axial contrast-enhanced CT shows low attenuation mediastinal and hilar lymphadenopathy with compression of the left mainstem bronchus (*arrow*). *(B)* Curved oblique multiplanar reformation (MPR) shows the extent and degree of left mainstem bronchial narrowing (*arrow*).

Eslamy HK, Radiol Clin N Am 49 (2011) 895–920

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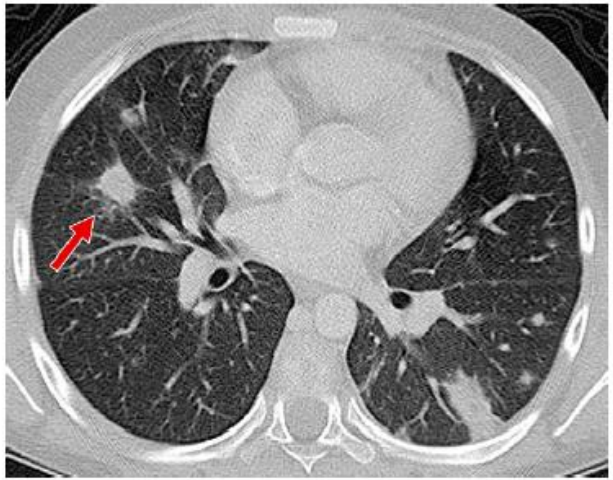

Fig. 22. Pneumonia in a febrile neutropenic patient caused by angioinvasive aspergillosis in a 7-year-old boy. Axial contrast-enhanced CT shows multiple bilateral pulmonary nodules, some have rims of ground-glass opacity (*arrow*), which is also known as the CT halo sign.

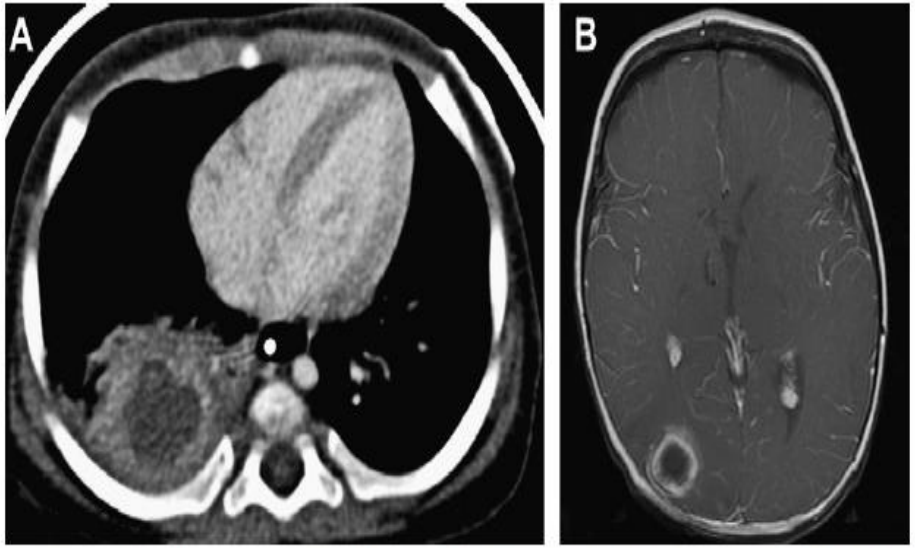

Fig. 25. Lung abscess in immunocompromised host caused by angioinvasive aspergillosis in a 6-month-old girl with acute myelogenous leukemia on induction chemotherapy. *(A)* Axial contrast-enhanced CT shows an air-filled cavity with a thick, definable enhancing wall in the right lower lobe and surrounding consolidation. *(B)* Axial contrast-enhanced T1-weighted MR image of the brain shows a rim-enhancing brain abscess in the right occipital lobe. The patient underwent right lower lobectomy and craniotomy for resection of these lesions.

Eslamy HK, Radiol Clin N Am 49 (2011) 895–920

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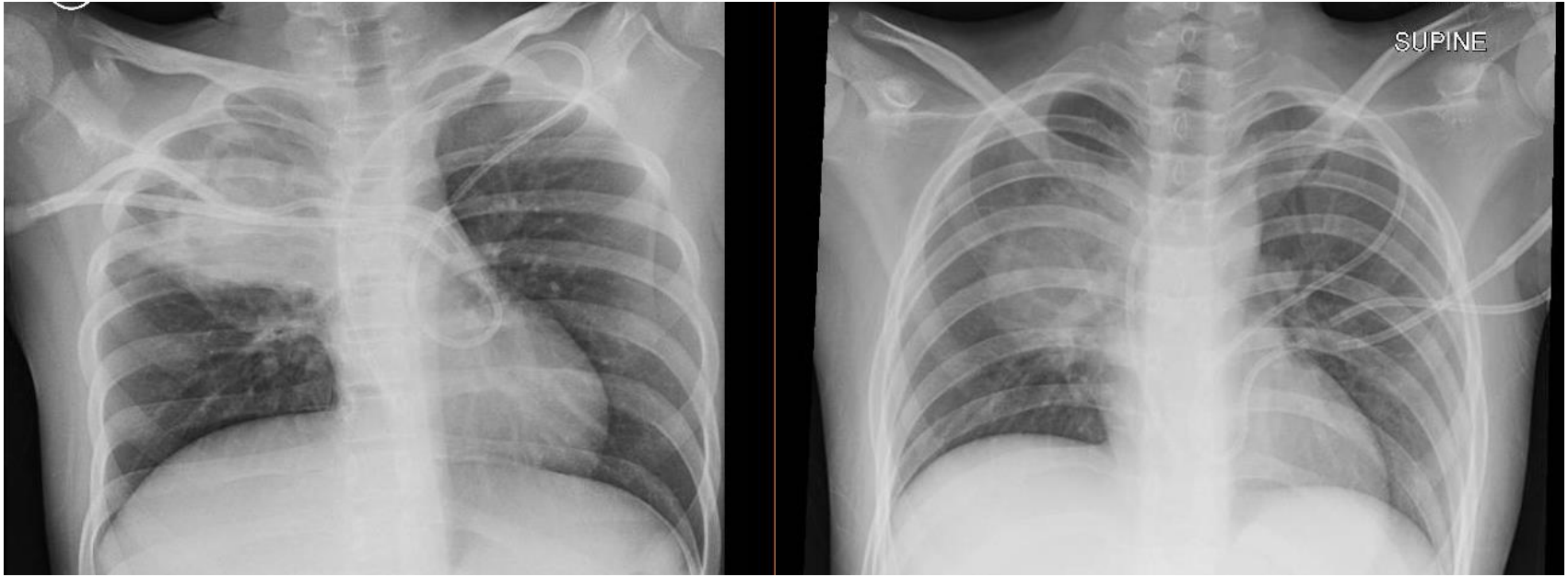
Diagnostic work-up

- Nasopharyngeal swab for multiplex PCR: Influenza A, B viruses, Parainfluenza 1, 2, 3, 4 viruses, Adenovirus, Respiratory syncytial virus, Human coronavirus, Rhinovirus/Enterovirus, Human metapneumovirus, *Bordetella pertussis, Mycoplasma pneumoniae, Chlamydophila pneumoniae*.
- Blood cultures
- Blood for galactomannan, Cryptococcal antigen
- Blood for CMV PCR
- Bronchoalveolar lavage for : Gram stain, culture, fungus smear/culture, PJP (Pneumocystis jiroveci/ carinii) stain/ PCR, galactomannan, Aspergillus PCR, AFB smear, AFB culture, TB PCR, CMV PCR, Multiplex PCR

- ± Mycoplasma serology, urine Legionella antigen/ BAL for Legionella IF antigen
- ± Blood Melioidosis PCR

Case 3: Mediastinal mass

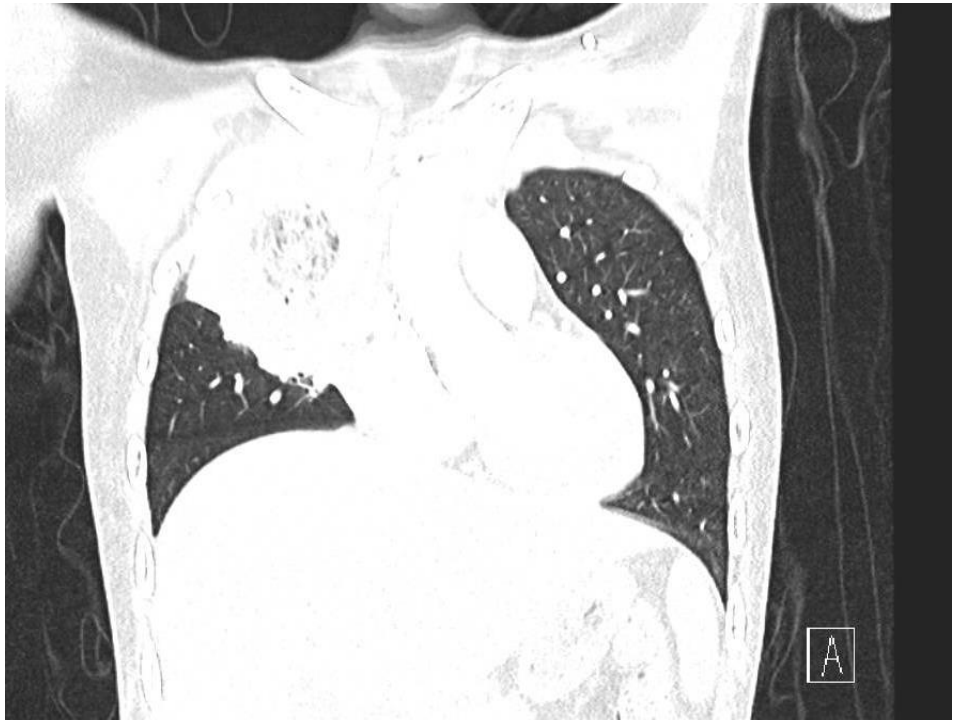


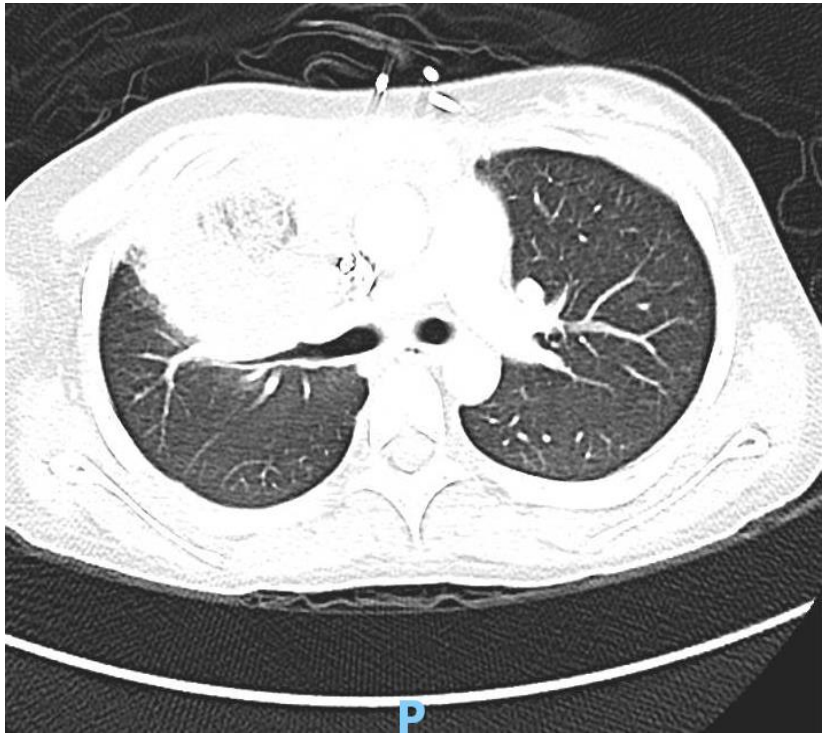
TW 0.1 CRP 239.8 procal 0.51 ESR 131, Blood negative for Cryptococcus antigen , Histoplasma Ab, galactomannan negative, blood culture, TB Quantiferon indeterminate

BAL positive for hyphae, non-septated, 90 degree branching suggestive of Rhizopus.

BAL negative for Aspergillus PCR, PCP Stain and PCP PCR neg, TB PCR neg, fungal cs, fluid cs, fungal smear, AFB cs, AFB smear neg, TB PCR neg, galactomannan antigen 0.85

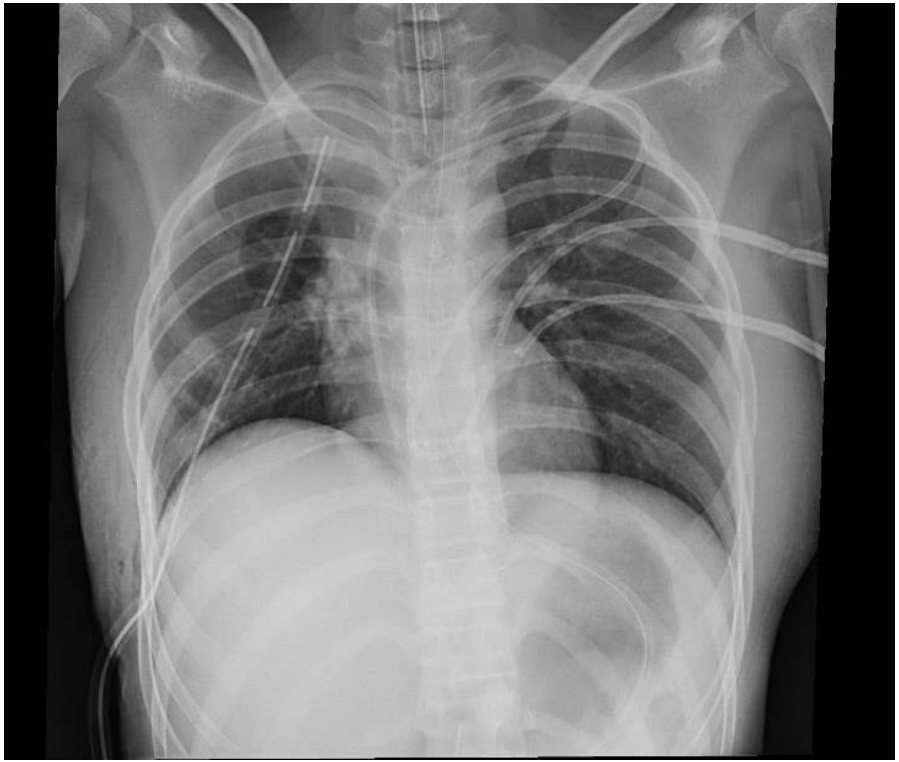
CTscan of thorax

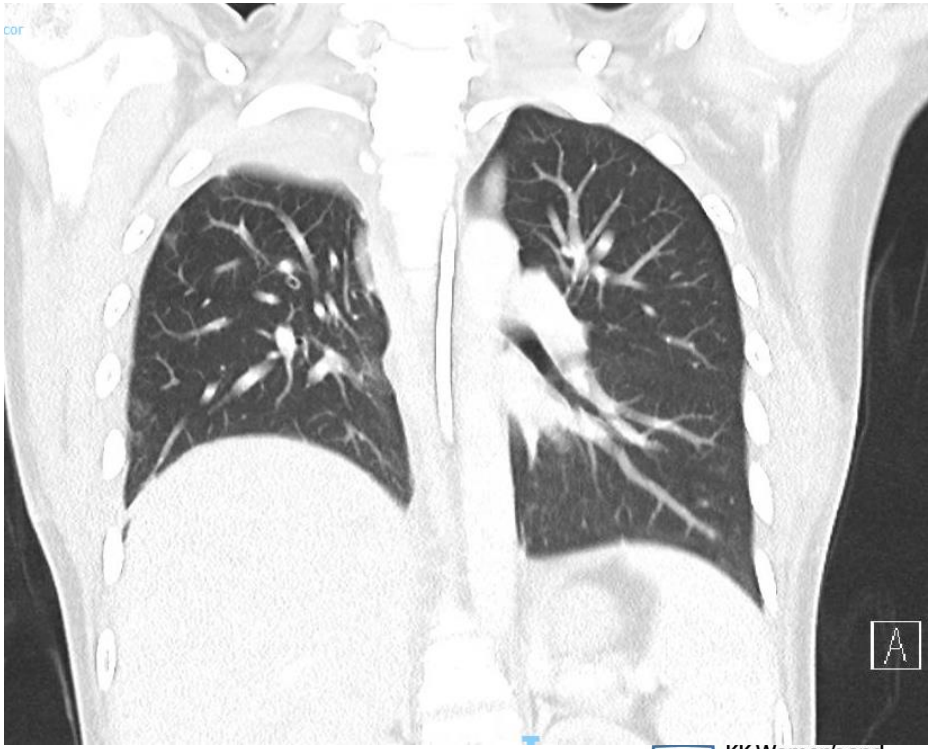




Mass in the right upper lobe , interim cavitation and anterior chest wall invasion.
There is also a new cavitating nodule in the right lower lobe

Lichtheimia hyalospora R lung cavitary nodule s/p right upper and middle lobectomy





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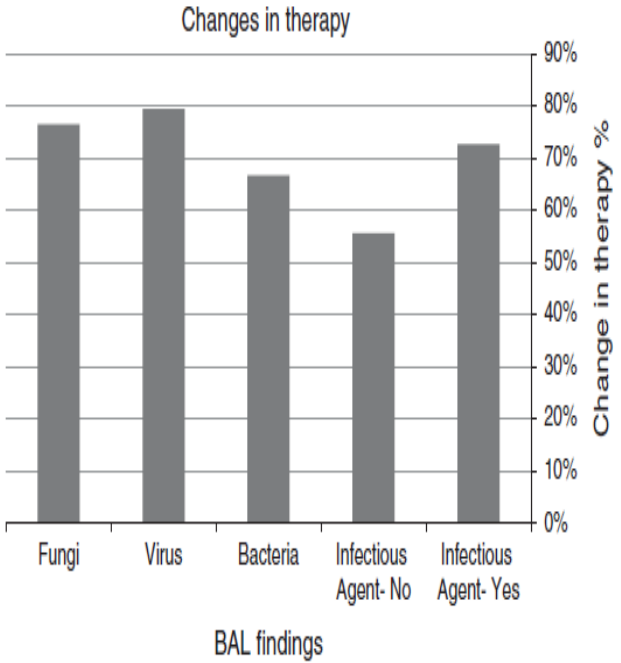
BAL results in Israel

2006 to 2014
117 pats in Heme-Onco underwent BAL.
47% (55/117) positive pathogen by BAL.
Treatment was changed in 63% of patients following BAL results :
73% when BAL result positive,
56% if negative .

TABLE 3. Pathogens Isolated From BAL Samples

Pathogen Types	No. Patients With Each Pathogen (n)
Bacteria	33
Haemophilus influenza	15
Streptococcus pneumoniae	10
Staphylococcus aureus	2
Escherichia coli	2
Pseudomonas	7
Virus	34
CMV	18
Adenovirus	5
hMPV	3
RSV	4
Influenza	4
Parainfluenza	3
HSV6	2
Fungi	17
PCP	4
Aspergillus	9
Candida nonalbicans	4



Rizik S, J Pediatr Hematol Oncol 2018

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Aetiology of CAP in immunocompromised

Clinical Infectious Diseases

MAJOR ARTICLE

Prevalence and Etiology of Community-acquired Pneumonia in Immunocompromised Patients

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Background. The correct management of immunocompromised patients with pneumonia is debated. We evaluated the prevalence, risk factors, and characteristics of immunocompromised patients coming from the community with pneumonia.

Methods. We conducted a secondary analysis of an international, multicenter study enrolling adult patients coming from the community with pneumonia and hospitalized in 222 hospitals in 54 countries worldwide. Risk factors for immunocompromise included AIDS, aplastic anemia, asplenia, hematological cancer, chemotherapy, neutropenia, biological drug use, lung transplantation, chronic steroid use, and solid tumor.

Results. At least 1 risk factor for immunocompromise was recorded in 18% of the 3702 patients enrolled. The prevalences of risk factors significantly differed across continents and countries, with chronic steroid use (45%), hematological cancer (25%), and chemotherapy (22%) the most common. Among immunocompromised patients, community-acquired pneumonia (CAP) pathogens were the most frequently identified, and prevalences did not differ from those in immunocompetent patients. Risk factors for immunocompromise were independently associated with neither *Pseudomonas aeruginosa* nor non–community-acquired bacteria. Specific risk factors were independently associated with fungal infections (odds ratio for AIDS and hematological cancer, 15.10 and 4.65, respectively; both $P = .001$), mycobacterial infections (AIDS; $P = .006$), and viral infections other than influenza (hematological cancer, 5.49; $P < .001$).

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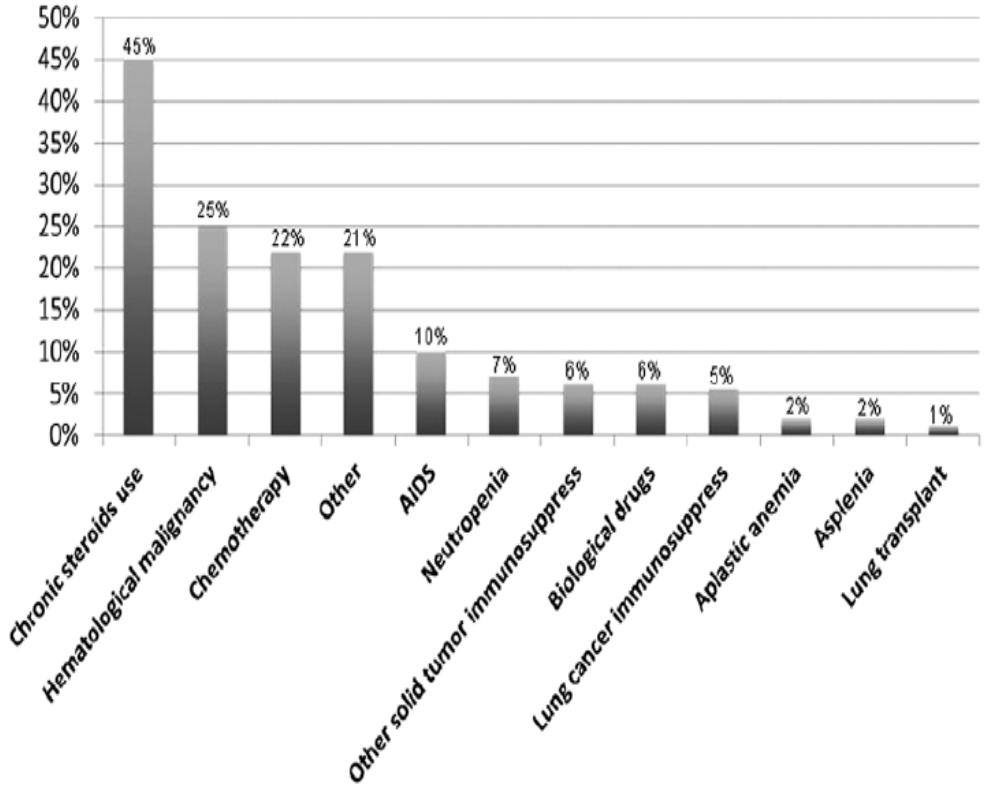
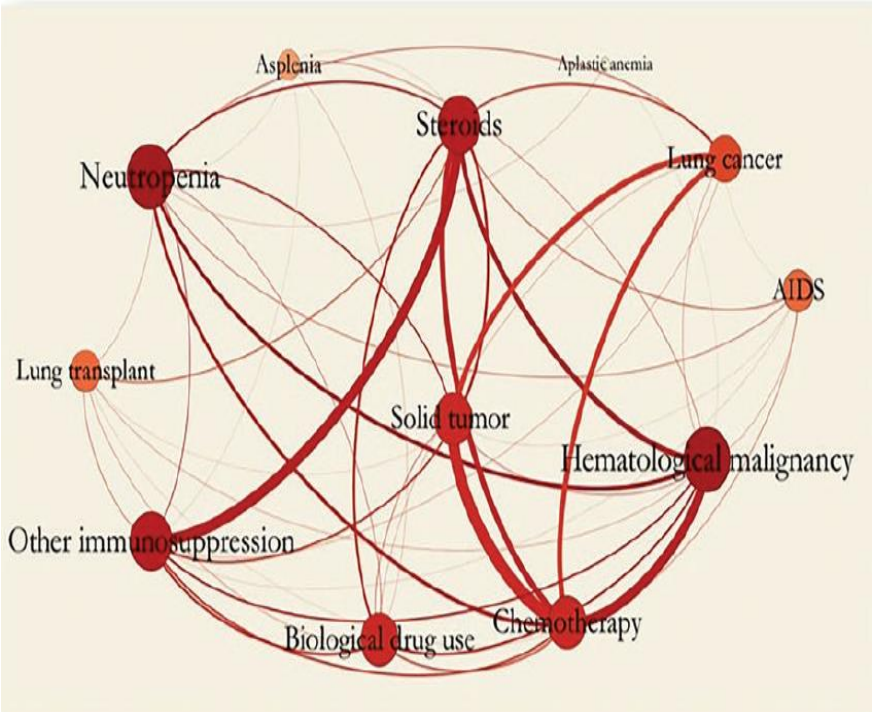
Prevalence of immunocompromising risk factor





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Pathogens

Pathogen	Patients, No. (%) Immunocompetent (n = 2626)	Immunocompromised (n = 596)	*P* Value
Pathogens covered by CAP therapy			
Streptococcus pneumoniae	218 (8.3)	50 (8.4)	>.99
Atypical	50 (1.9)	13 (2.2)	.78
Legionella	21 (0.8)	10 (1.7)	.08
MRSA	83 (3.2)	12 (2.0)	.17
MSSA	73 (2.8)	20 (3.4)	.53
Pseudomonas aeruginosa	98 (3.7)	35 (5.9)	.02
Haemophilus influenzae	65 (2.5)	10 (1.7)	.31
Klebsiella pneumoniae	89 (3.4)	22 (3.7)	.81
Influenza virus	126 (4.8)	28 (4.7)	>.99
Pathogens not covered by CAP therapy			
Non-CAP bacteria			
Acinetobacter baumanii	33 (1.3)	7 (1.2)	>.99
Nocardia spp.	0 (0.0)	4 (0.7)	<.001
Mycobacteria			
Mycobacterium tuberculosis	21 (0.8)	5 (0.8)	>.99
NTM	2 (0.1)	5 (0.8)	.002

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Pathogen	Patients, No. (%) Immunocompetent (n = 2626)	Immunocompromised (n = 596)	*P* Value
Fungi			
Aspergillus fumigatus	10 (0.4)	8 (1.3)	.01
Actinomyces	2 (0.1)	0 (0.0)	>.99
Cryptococcus	3 (0.1)	0 (0.0)	.94
Pneumocystis jirovecii	5 (0.2)	13 (2.2)	<.001
Viruses			
Adenovirus	5 (0.2)	0 (0.0)	.62
Coronavirus	3 (0.1)	3 (0.5)	.047
Metapneumovirus	3 (0.1)	2 (0.3)	.51
RSV	7 (0.3)	6 (1.0)	.03
MDR pathogens	231 (8.8)	54 (9.0)	.54

Abbreviations: CAP, community-acquired pneumonia; MDR multidrug-resistant; MRSA methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*; NTM, nontuberculous mycobacteria; RSV, respiratory syncitial virus.

Pathogen and risk factors

Table 3. Multivariable Logistic Regression Analysis

	OR (CI 95%)				
Variable	*Pseudomonas aeruginosa*	Non-CAP Bacteria	Fungi	*Mycobacterium tuberculosis*	Virus Other Than Influenza
Severe COPD	2.89 (1.34–6.22)	…	…	…	…
Tracheostomy	6.95 (2.87–16.85)	2.91 (1.01–8.38)	…	…	…
ICS use	1.76 (1.09–2.82)	…	…	…	…
Indwelling catheter	2.49 (1.02–6.06)	…	…	…	…
Prior *Pseudomonas*	19.20 (11.71–31.50)	…	…	…	…
COPD	…	1.78 (1.07–2.99)	…	…	…
Severe CAP	…	2.36 (1.42–3.93)	…	…	2.56 (1.27–5.19)
AIDS	…	…	15.10 (6.36–35.88)	…	…
Hematological cancer	…	…	4.65 (1.85–11.69)	…	5.49 (2.20–13.70)
Malnutrition	…	…	…	5.14 (2.21–11.93)	…

Blank cells indicate no statistical significancy.

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Empiric antimicrobials After BAL

- IV antibiotics: Piperacillin- tazobactam OR Ceftazidime + Cloxacillin
  - IV Bactrim for PJP (20 mg/kg/day of TMP component divided q6H)
- Antivirals: Oseltamivir for influenza , IV Ganciclovir for CMV
- Antifungals: IV Voriconazole if suspect Aspergillosis

Targeted Antimicrobials: Anti-Bacterials

- Pneumococcus:
- MIC ≤ 2 µg/mL: Ampicillin (200 mg/kg/day, if complicated 300 mg/kg/day).
  - PO amoxicillin (90 mg/kg/day in 2-3 doses)
- MICs ≥4.0 µg/mL : Ceftriaxone 100 mg/kg/day -> PO Levofloxacin
- *S. aureus*:
  - MSSA : IV Cloxacillin 200 mg/kg/day or IV Cefazolin 150 mg/kg/day-> PO cephalexin 75-100 mg/kg/day divided 3-4 doses
  - MRSA : Vancomycin (40–60 mg/kg/day every 6–8 hours or IV Clindamycin (40 mg/kg/day Q 6–8 hours, if sensitive)-> oral clindamycin (30–40 mg/kg/day in 3 or 4 doses)
- *Streptococcus pyogenes*: Ampicillin (200 mg/kg/day)
  - PO Amoxycillin 50-75 mg/kg/day divided in 2-3 doses
- *P. aeruginosa* : Ceftazidime/ piperacillin- tazobactam, (ciprofloxacin)

Targeted Antimicrobials: Anti-Virals

- Cytomegalovirus : IV Ganciclovir 5 mg/kg/dose q 12H or Valganciclovir x 3 wks (16 mg/kg/dose q12h)
- Influenza: Oseltamivir: 5 days (10 days if ICU)
- Adenovirus: IV Cidofovir 5 mg/kg once wkly x 2, then alternate wk x 1-2 doses
  - Need prehydration and probenecid
- RSV: PO Ribavirin 20-25mg/kg/day Q8-12H

Targeted Antimicrobials: Anti-FUNGALs

- Aspergillosis: IV/ PO voriconazole x 6 wk minimum, Check trough levels- target 1-5.5 µg/ml
- IV: < 12 yr old or 12-14yr old and < 50 kg: 9 mg/kg /dose q12H x 2 doses, then 8 mg/kg/dose q 12H

  12-14 yr old and > 50 kg or > 15yr old: load 6 mg/kg/dose q12H x 2 doses, then 4 mg/kg/dose q 12H

  PO: < 12 yr or 12-14 yr old and < 50 kg: 9 mg/kg/dose q 12H

  12-14 yr old and > 50 kg or > 15 yrs old: 400 mg q 12H x 2 doses then 200 mg q12H
  - Alternative: IV liposomal Amphotericin 3 - 5 mg/kg/day
- Candidiasis : IV Micafungin 2 mg/kg OD (max 200 mg) or other echinocandin or fluconazole 10 mg/kg OD (if sensitive)
- *Pneumocystic jiroveci*: IV Bactrim 20 mg/kg/day of TMP component divided q6H
  - Add steroids if moderate/ severe disease

Non- Infectious Causes of Pneumonitis in Stem cell transplant

- Pulmonary damage by Radiation exposure
- Pulmonary damage by chemotherapy e.g. Bleomycin
- Underlying cancer
- Pulmonary oedema
- Alveolar hemorrhage
- Idiopathic Interstitial pneumonia
- Pulmonary vascular disease

Principles of Paediatric Infectious Diseases 2018, Sarah Long, Chapters 96.

CXR and Infectious vs non-infectious causes

Radiographic Manifestation	Infectious Cause	Noninfectious Process
Focal consolidation (lobar or segmental)	Bacteria (routine and nosocomial pathogens) *Legionella* Oral flora (aspiration and postobstructive) *Mycobacterium tuberculosis* Fungi (*Cryptococcus, Histoplasma, Coccidioides*)	Pulmonary hemorrhage Pulmonary infarction Atelectasis Radiation pneumonitis Drug-related pneumonitis Tumor
Diffuse interstitial infiltrate	Viruses *Pneumocystis jirovecii* Mycobacteria, including miliary tuberculosis Disseminated fungi (*Cryptococcus, Histoplasma, Coccidioides*) *Mycoplasma* *Chlamydophila*	Pulmonary edema Adult respiratory distress syndrome Drug-related pneumonitis Radiation pneumonitis Lymphangitic metastasis Lymphocytic interstitial pneumonitis (HIV)
Nodular infiltrate (with or without cavitation)	Molds: *Aspergillus, Mucor, Fusarium* Bacteria (especially *Staphylococcus aureus, Pseudomonas, Klebsiella*, anaerobic bacteria), *Nocardia* Mycobacteria, including *M. tuberculosis* Viruses (e.g., CMV, HSV, VZV, EBV, RSV)	Tumor

Principles of Paediatric Infectious Diseases 2018, Sarah Long, Chapters 98.

Conclusions

- Almost all immunocompromised hosts require a BAL
- Look for multiple pathogens: virus, bacteria, fungus
- Start empiric anti-microbials, then target organisms identified