Long Case Presentation

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PGY5 – Alberta Children's Hospital

Cross Canada Rounds

Oct 19th 2017

Outline

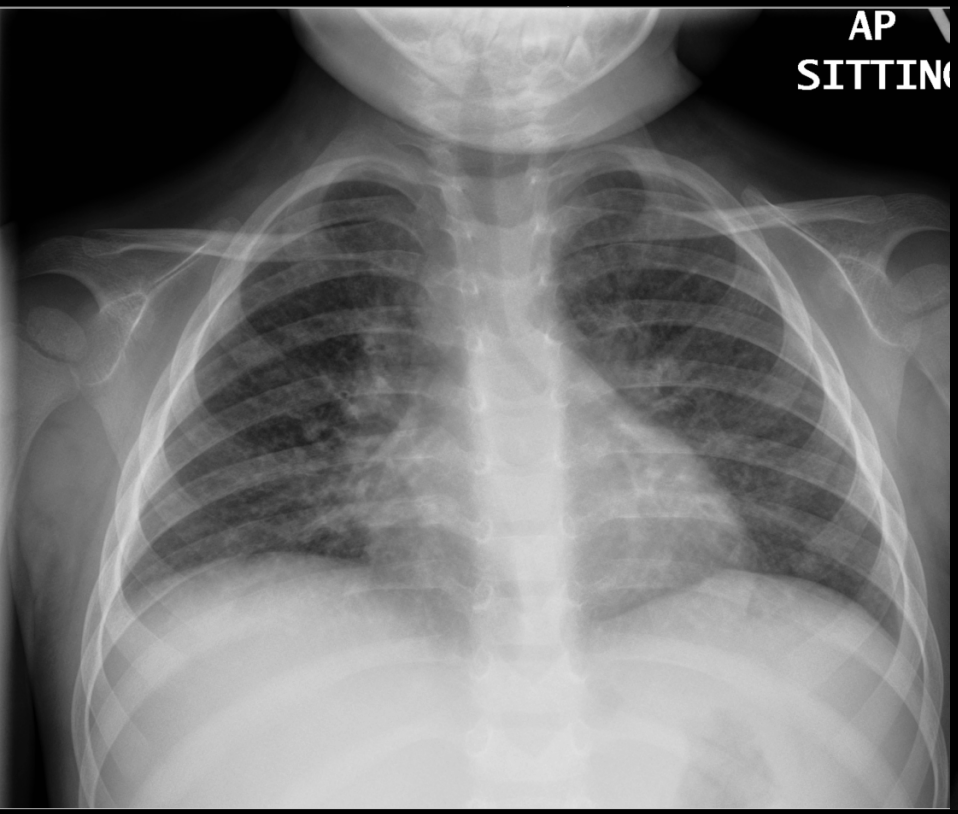
- Case presentation:
  - History
  - Physical exam
  - Initial workup
  - Clinical and lab progress
  - Diagnosis
- Literature review

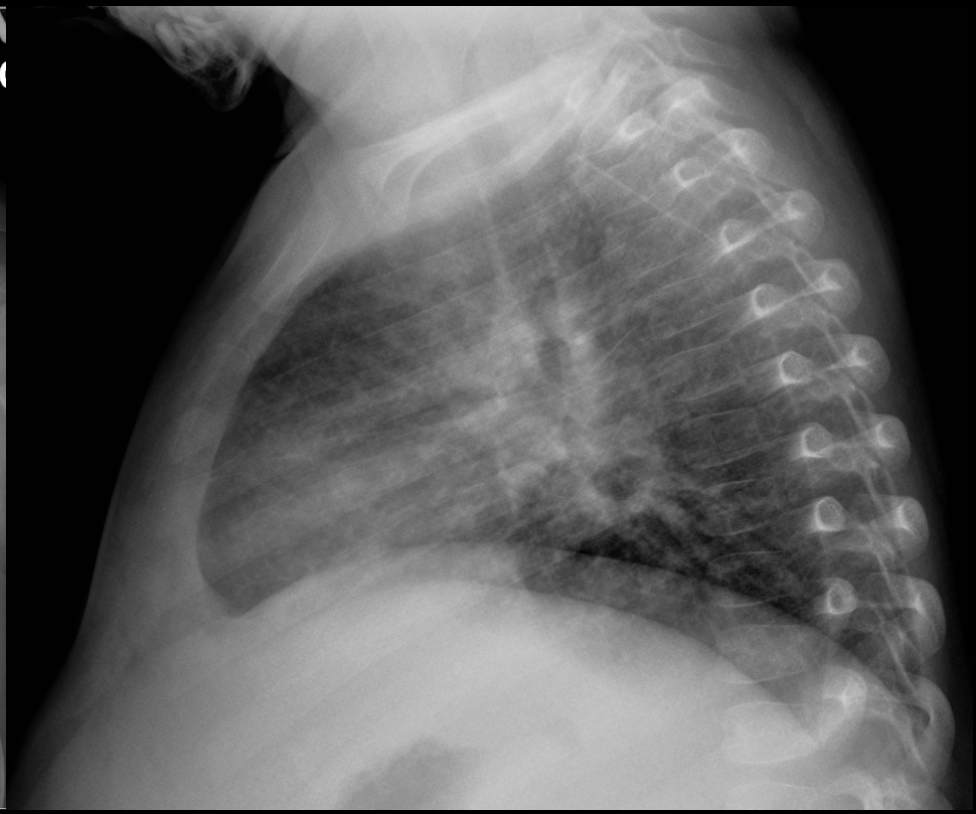
History

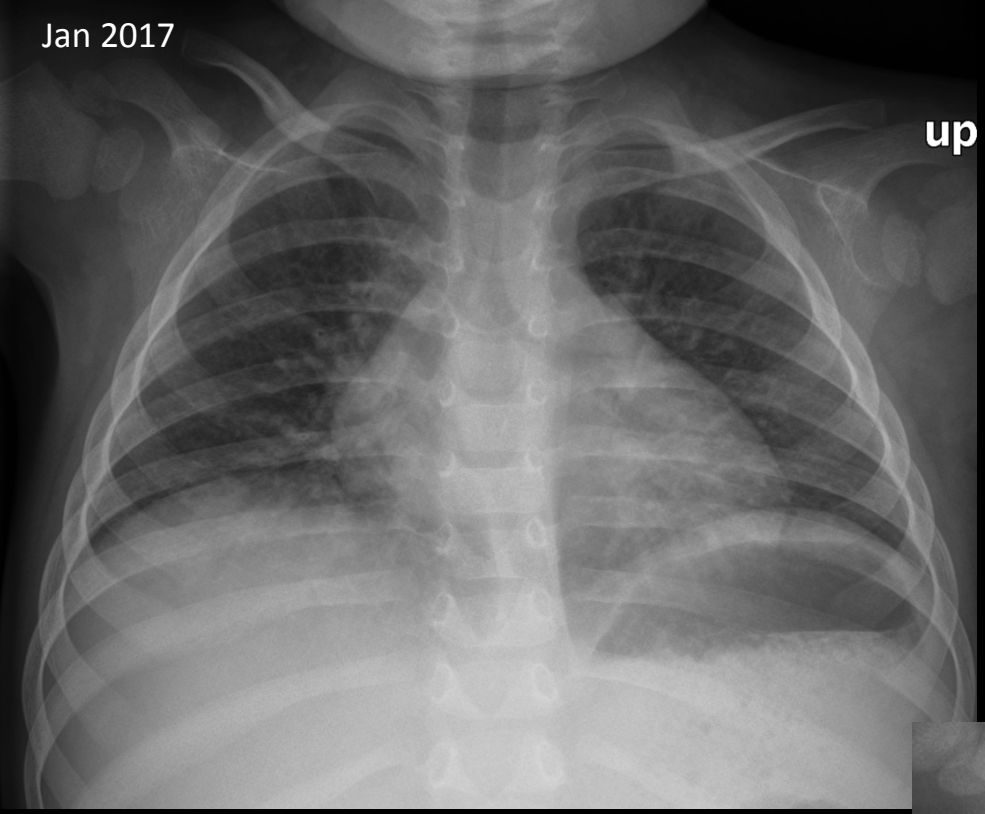
- HPI:
  - 2y 9m old girl, seen in Aug 2017
  - Referred from the community with 7 months h/o microcytic anemia not responding to iron supplementation
  - Daily fever starting June 2017, documented up to 41C, improves with antipyretics
  - Fatigue, decrease appetite and daily night sweats started Dec 2016

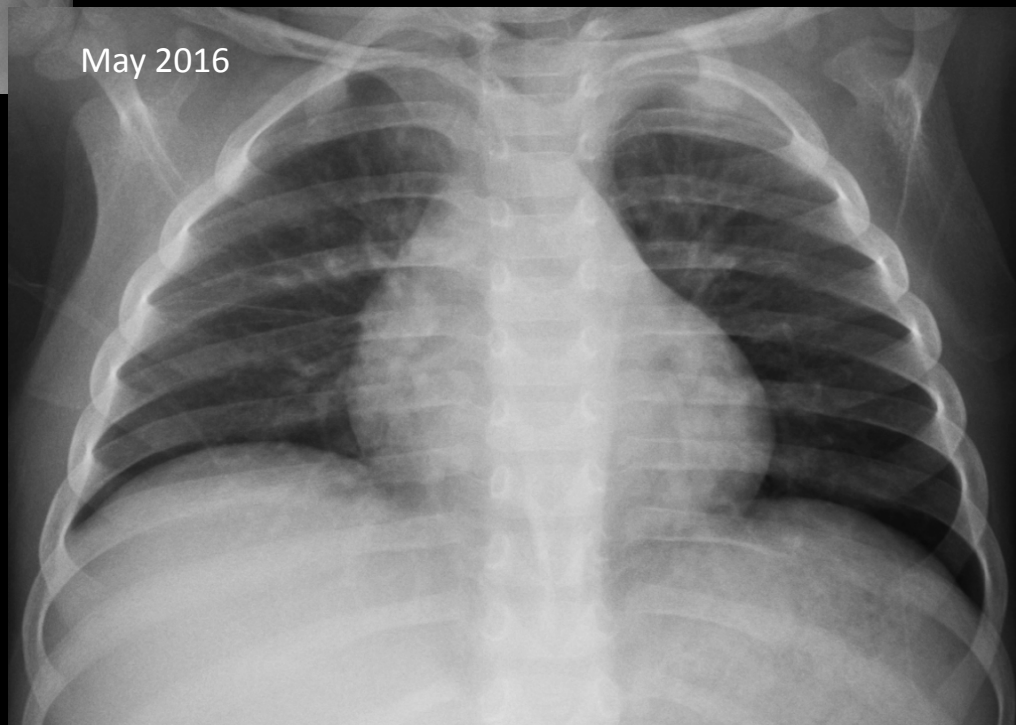
- June: cough and fever, CXR changes, diagnosed with pneumonia, prescribed oral Azithromycin for 5 days, fever and cough improved in few days but restarted once she came off Abx

June 27th 2017






Jan 2017
up

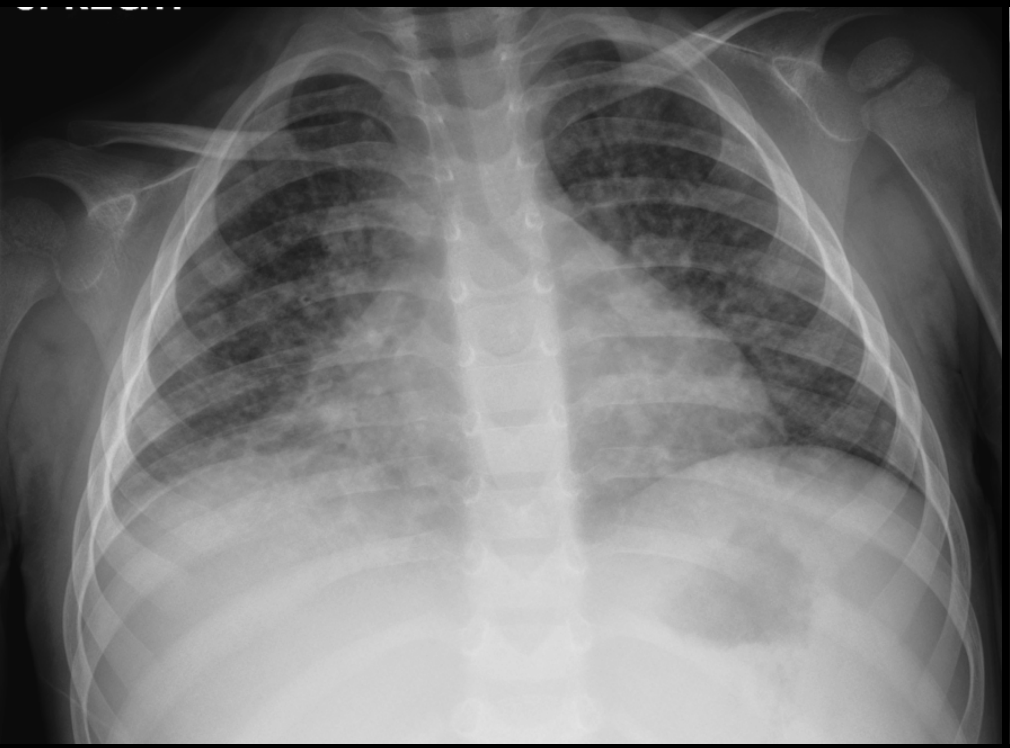

May 2016

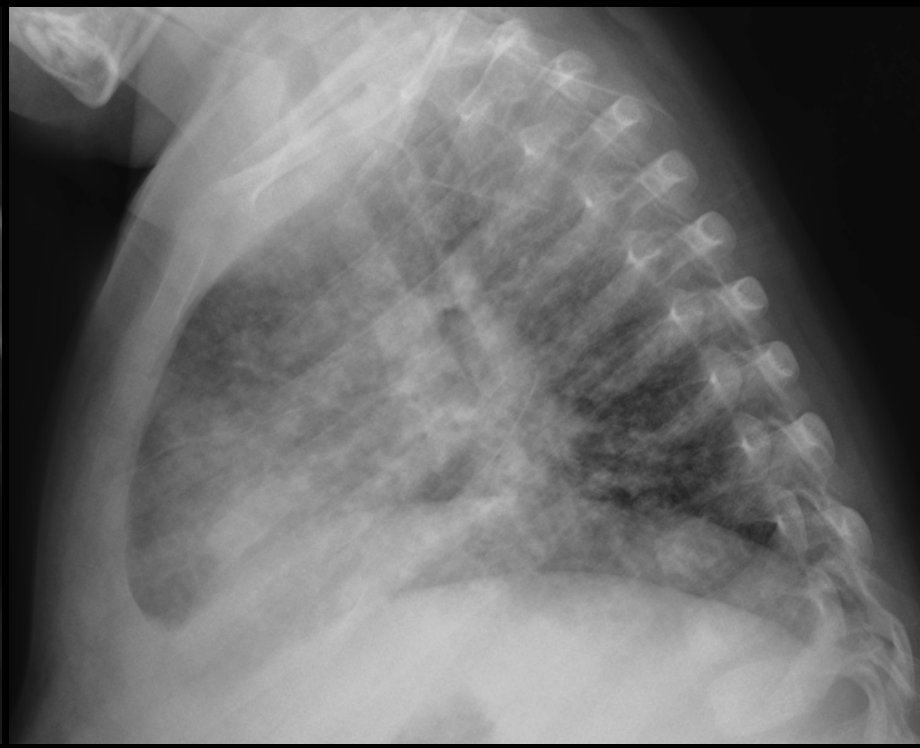
- June: cough and fever, CXR changes, diagnosed with pneumonia, prescribed oral antibiotics for 5 days, fever improved in few days but restarted once came off Abx

- After 2 weeks, seen again in ER and CXR done, prescribed 5 days of Azithromycin for pneumonia.

- Ongoing dry cough, prescribed salbutamol by family MD, not effective

July 17th 2017





- Systemic review:
  - Iron deficiency anemia, on iron
  - Otherwise, unremarkable

- PMHx:
  - Term, unremarkable pregnancy and neonatal history
  - Not vaccinated
  - May 2015: Rt tibia osteomyelitis
  - Aug 2016: 3 small gluteal abscesses, treated with oral antibiotics, no I&D
  - No atopy, no known allergies, no other infections
  - Normal development

- FHx:
  - No consanguinity
  - Mennonite background
  - 4 healthy siblings
  - No known atopy, CF or other chronic respiratory problems. No known immune deficiency
  - Paternal grandmother died with cancer (? organ)

- Social Hx:
  - Lives in a farm (dog, chicken and goats), hay farms around.
  - No recent travel
  - No contact with TB
  - No smoking exposure

Physical examination

- Admission vital signs:
  - Wt 13.3 kg (50th percentile)
  - Ht 101 cm (97th percentile)
  - Temp 39.3C
  - RR 24/min, Sat 95% in RA
  - HR 170 /min, BP 100/57 mmHg

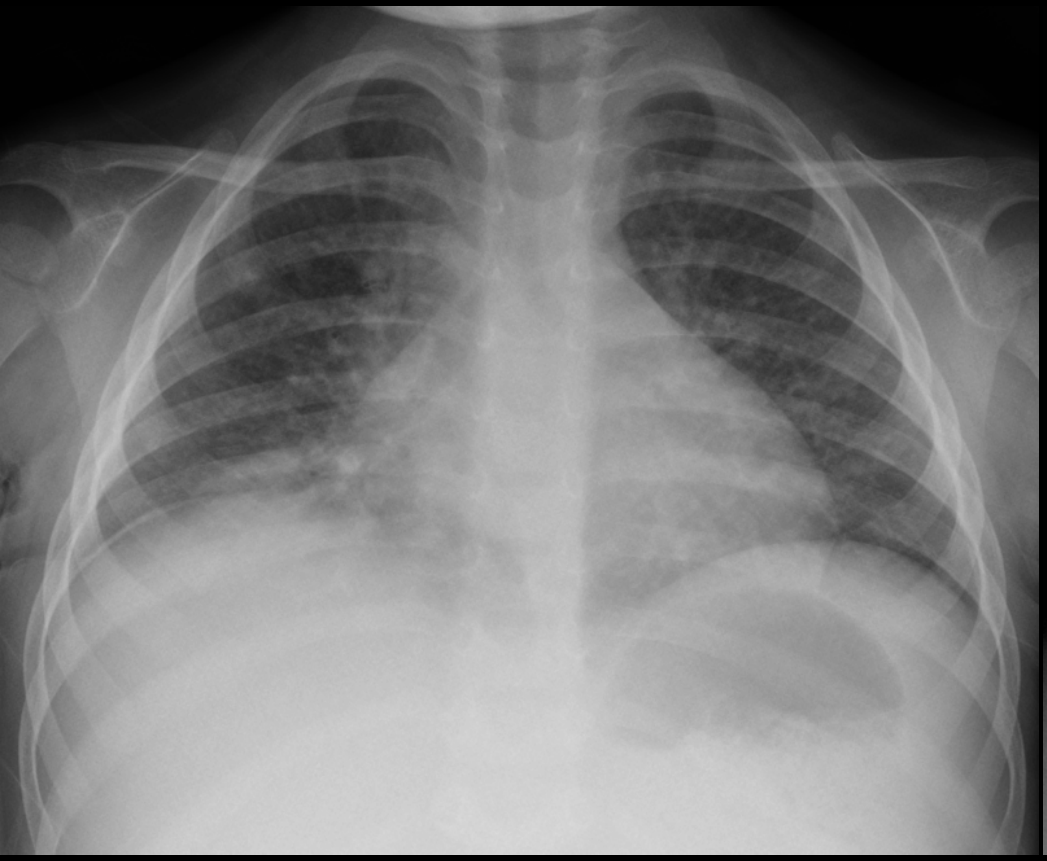
- Systemic examination:
  - Well looking, pale, no lymphadenopathy, no clubbing
  - Abdomen: hepatosplenomegaly
  - Chest: no increased WOB, GAEB, no crackles, no wheeze
  - CVS: normal
  - Skin: normal

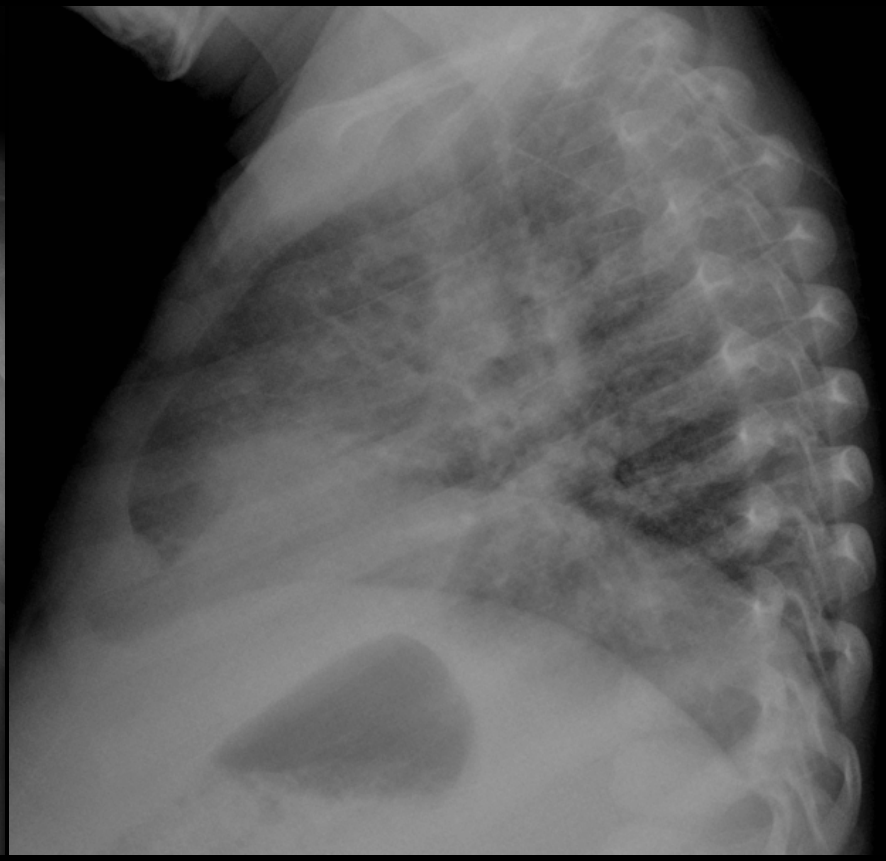
Initial Investigations

- CBC: Hb 75, MCV 68, RDW 21, Plt 486,
  WBC 14.6, ANC 6.8, Lymph 6.8, Eos 0

- CRP 137 (Jan=90, Feb=67, June=119), ESR 44
- Ferritin 264
- Albumin 26, liver enzymes normal
- LDH 215 (N), urate 212 (N)
- Lytes, BUN, creatinine all N
- Urine analysis: moderate blood, large leukocyte, negative nitrite, > 30 WBC, 11-20 RBC

Aug 12th 2017



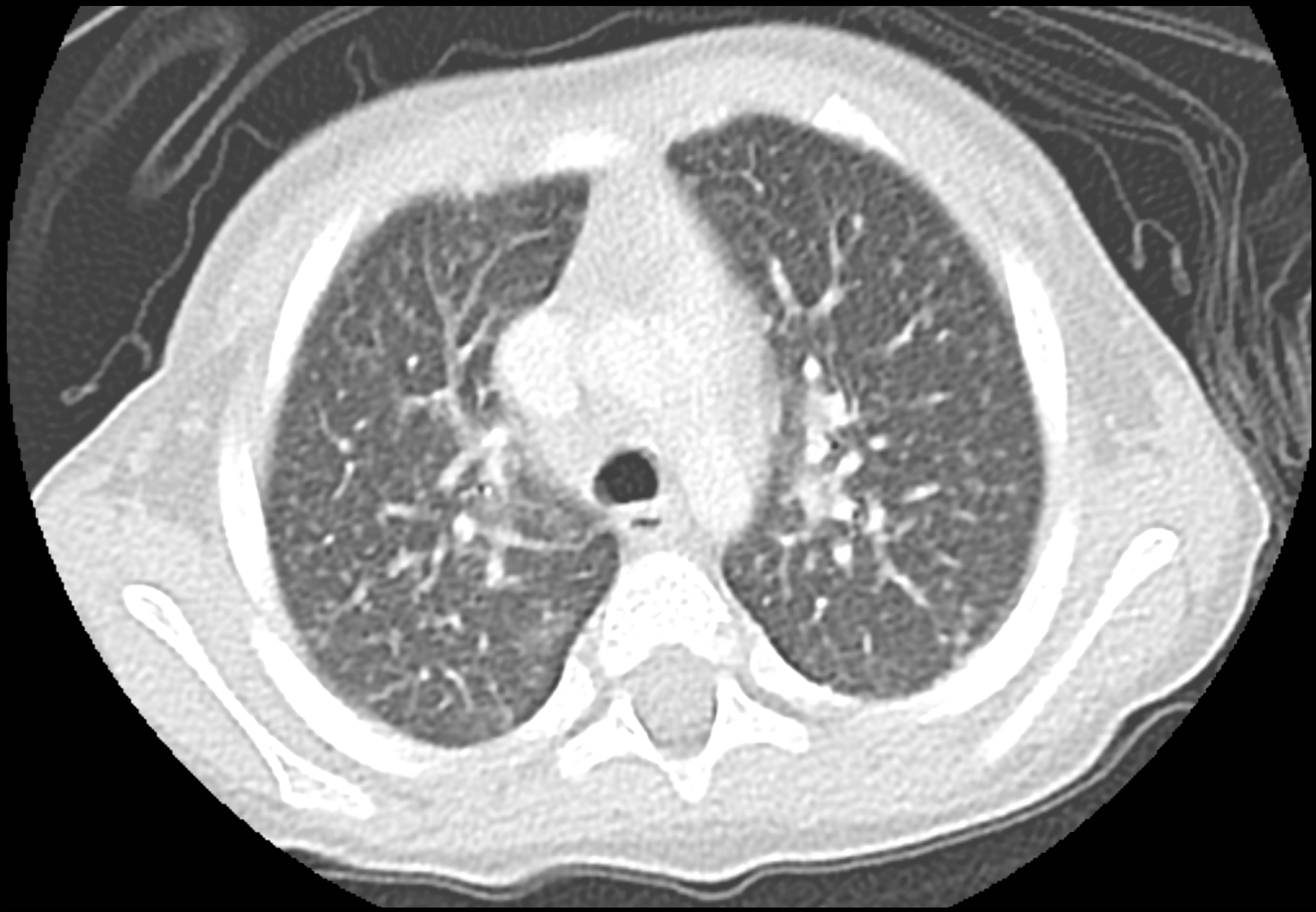


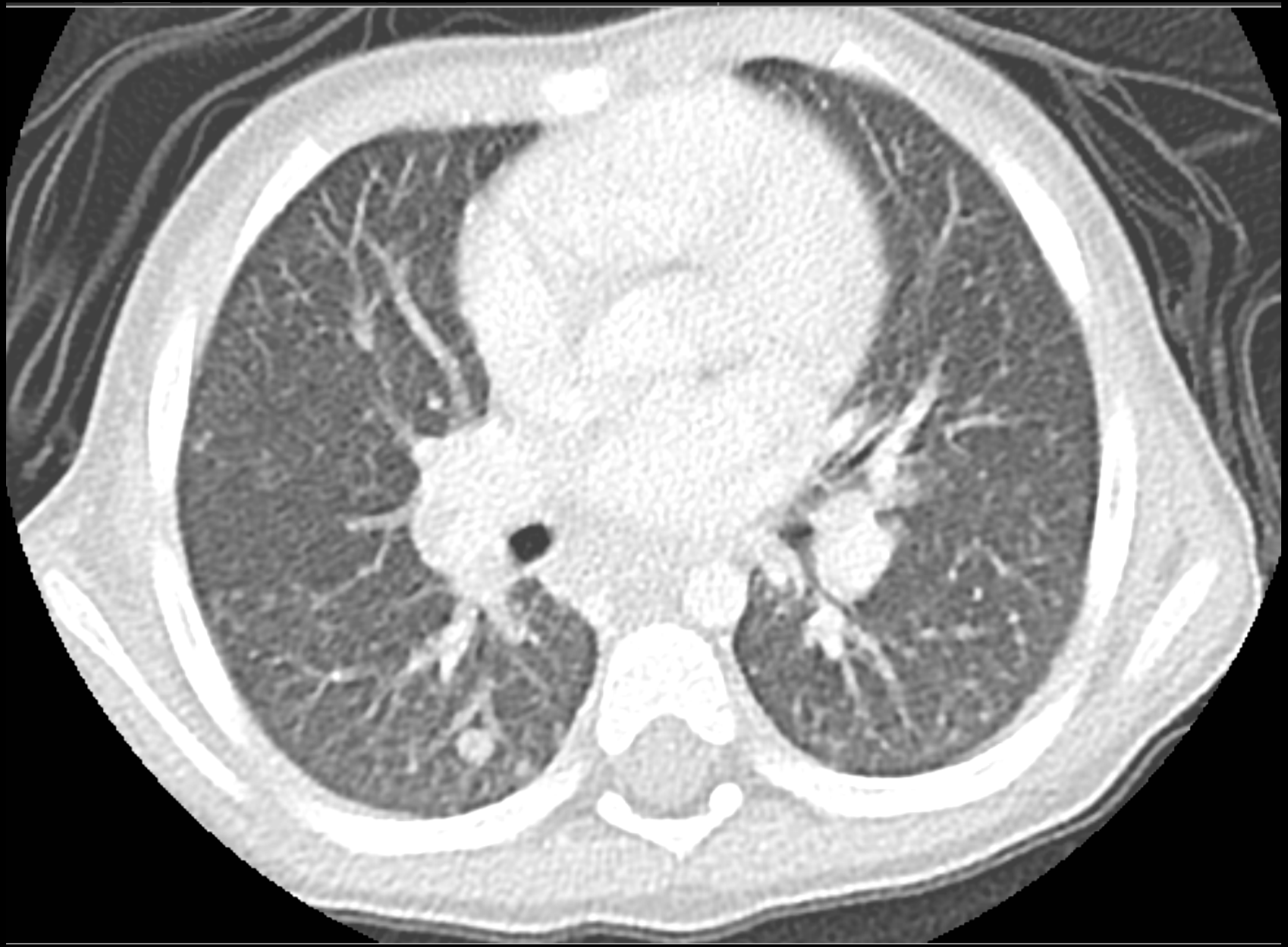
- Differential diagnosis ?

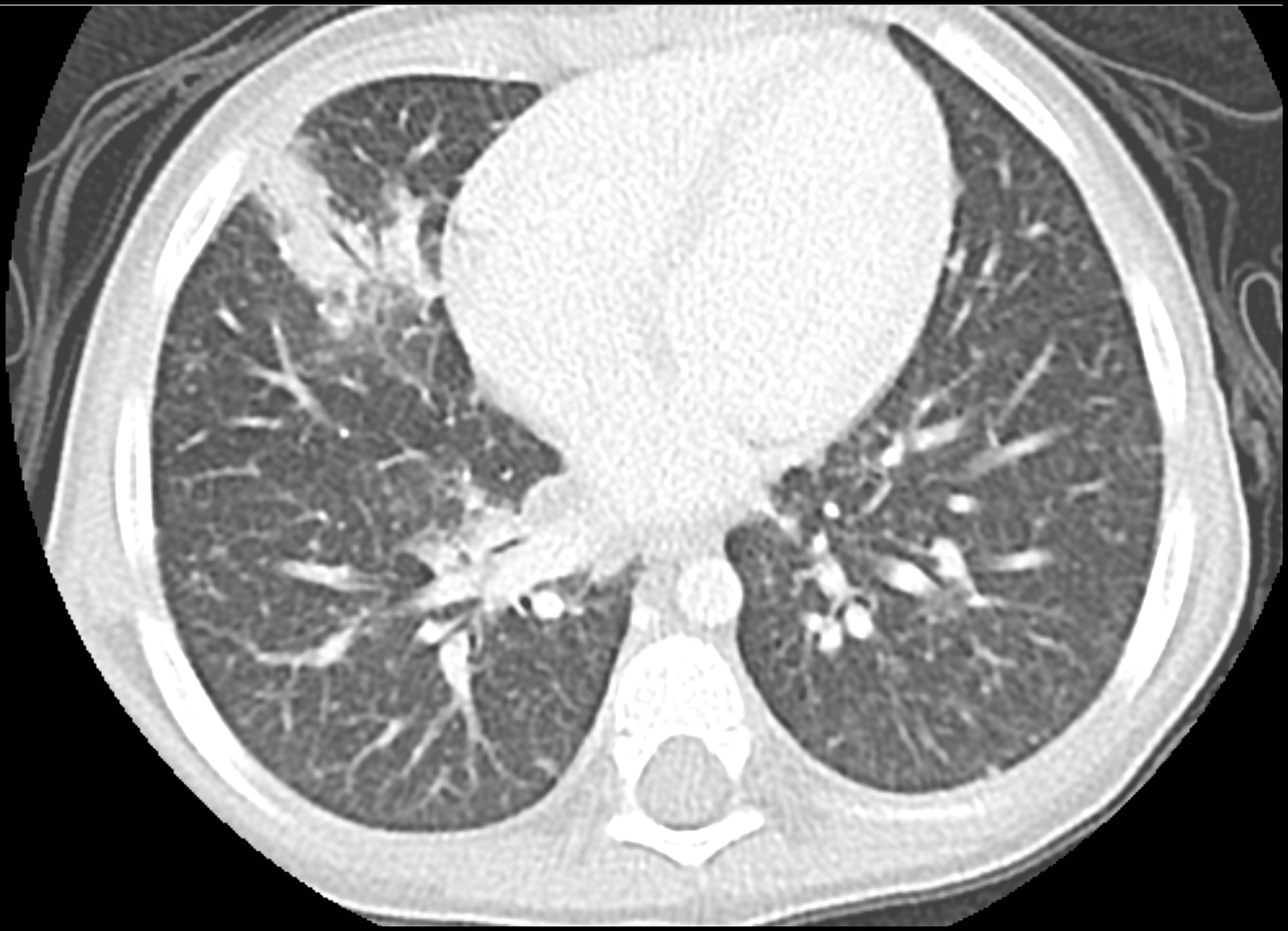
- Further investigations ?

Clinical course:

- Daily high fevers continued
- Resp, ID, Rheum, oncology, hematology and immunology consulted
- Aug 13th: NPA: Entero-Rhinovirus +ve
- Aug 14th:
  - US abdomen: hepatosplenomegaly, no focal lesions. Enlarged lymph node at the porta hepatis (2cm)
  - Echocardiogram: normal
- Aug 15th: CT chest and abdomen

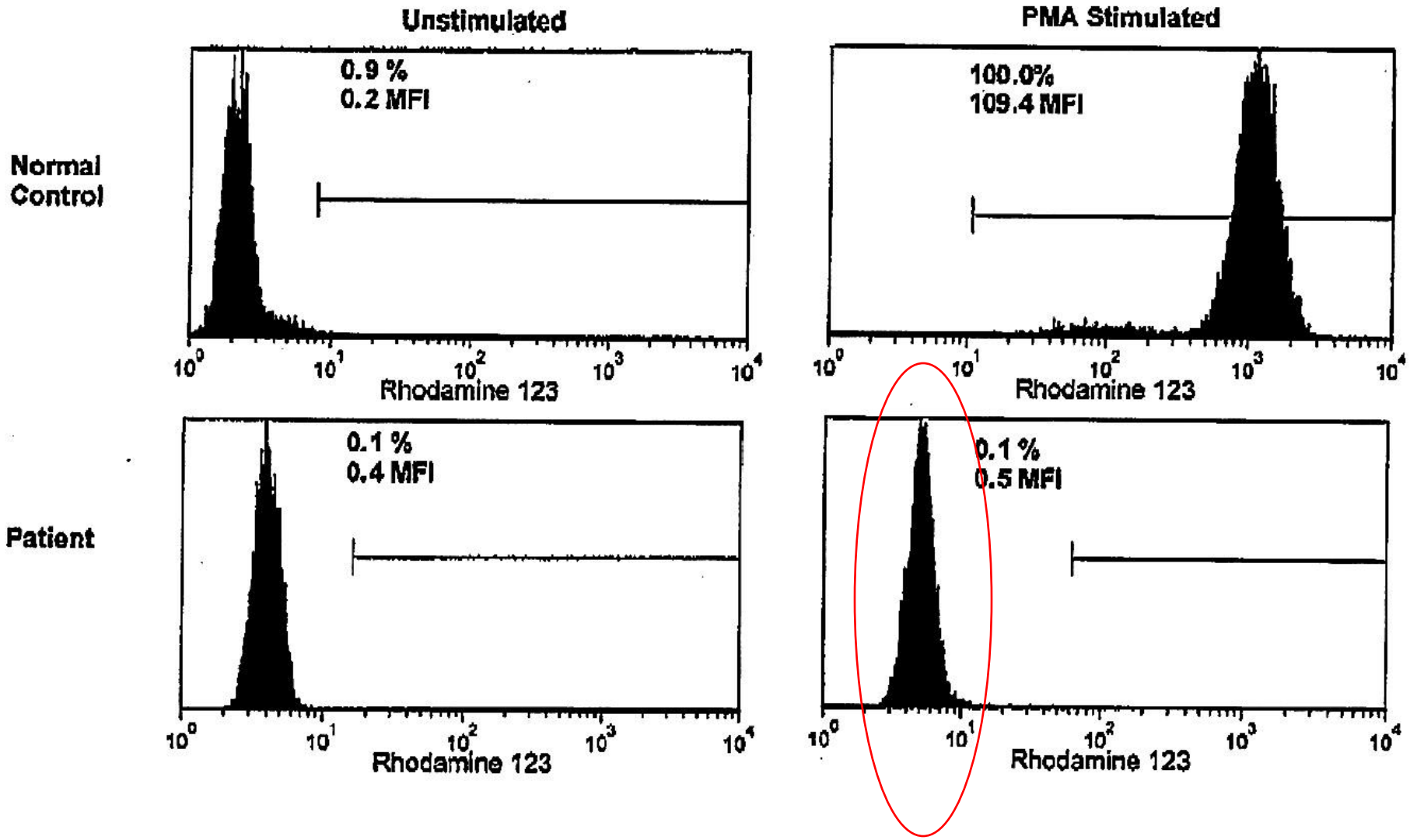






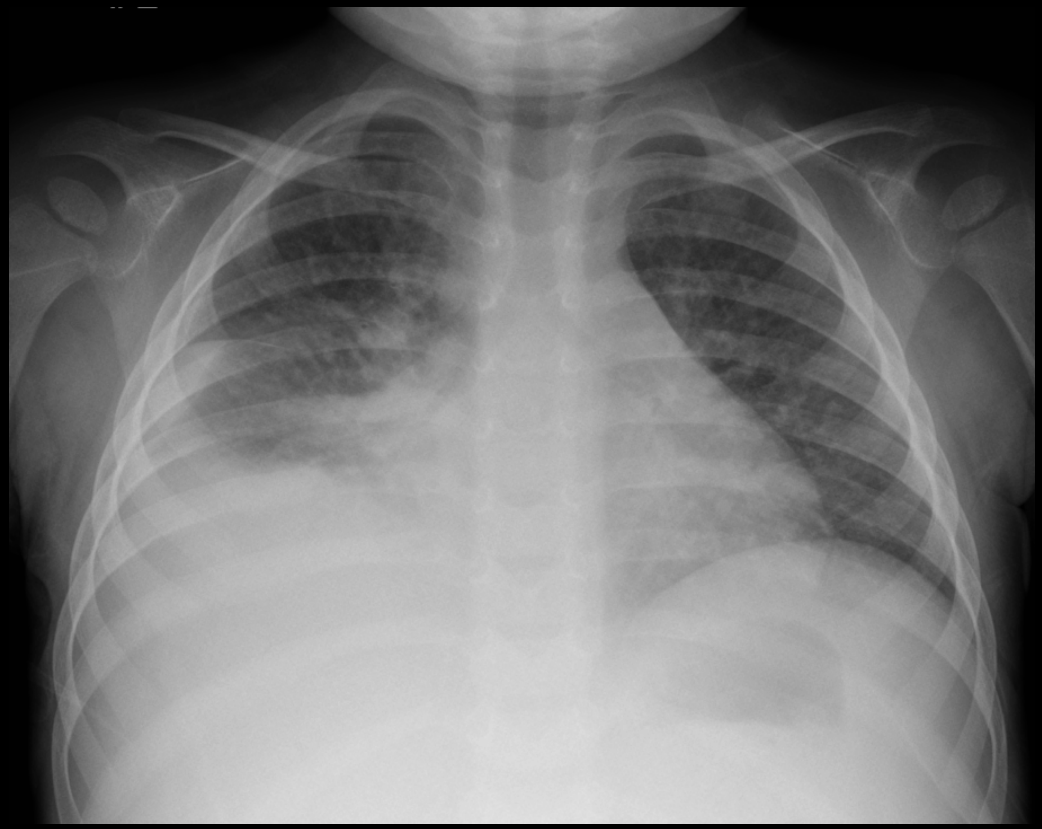
- Radiology report:
  - Multiple scattered lung nodules in both lungs with the largest nodule seen in the superior segment of the right lower lobe measuring 5 x 4 mm.
  - Patchy consolidation noted in the right middle lobe
  - No evidence of interstitial thickening or bronchiectasis.
  - No pleural effusion or pneumothorax.
  - Multiple slightly prominent mediastinal lymph nodes.
  - Hepatosplenomegaly with multiple slightly prominent mesenteric and retroperitoneal lymph nodes.

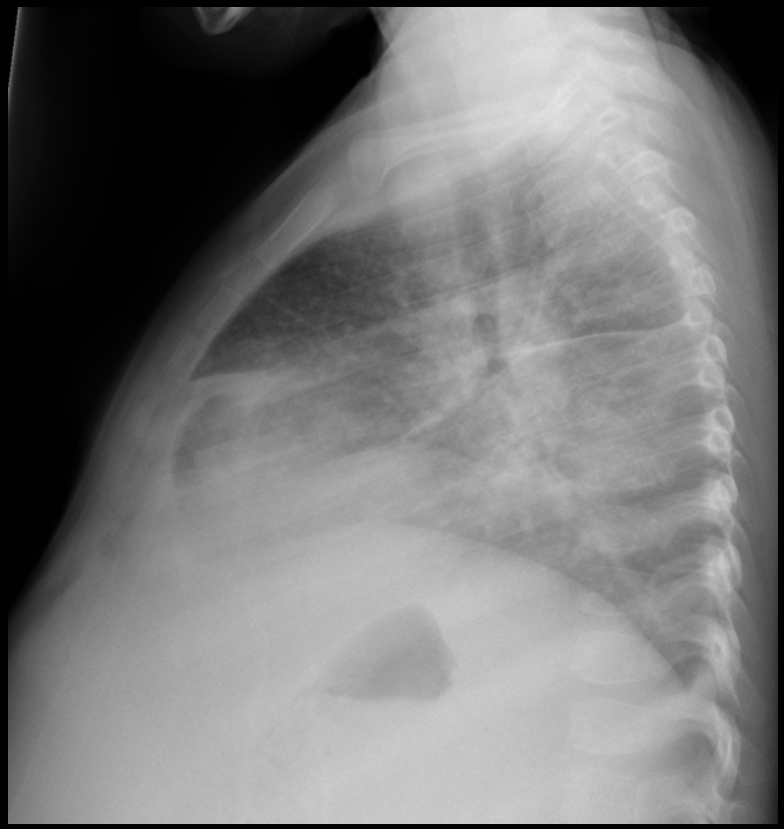
- Further workup:
  - Blood and urine c/s –ve
  - Viral studies –ve
  - Aug 16th: Bone marrow -> not concerning for malignancy, negative bacterial, fungal cultures.
  - MRI skeletal survey + gadolinium: normal
  - Normal C3, C4, ANA, anti-DS DNA, ENA, c-ANCA, p-ANCA and anti-GBM
  - Normal immunoglobulin levels and lymphocytes subset
  - Oxidative burst


Unstimulated
PMA Stimulated
Normal Control
Patient
0.9 %
0.2 MFI
100.0%
109.4 MFI
0.1 %
0.4 MFI
0.1 %
0.5 MFI
Rhodamine 123
Rhodamine 123
Rhodamine 123
Rhodamine 123

- Knowing that, what other investigations your would consider?

- Clinical course continued:
  - Aug 21st: flexible bronch + BAL + LN biopsy by IR
  - BAL cell count: 3% PMNS, 16% lymph, 80% macrophages
  - Aug 23rd: clinical deterioration with increasing O2 requirements, tachypnea (60s), tachycardia. Dropped Hb to 62 g/l. CXR repeated





- Started on Meropenem and Ampho B
- RR improved in 48 hrs, off O2
- No initial growth from BAL
- Ongoing fever
- Aug 25th: CT guided lung biopsy by IR
  - Complicated with hemo/pneumothorax, needed chest tube, admitted to PICU

- **Aug 26th: BAL fungal culture +ve for Aspergillus**
- BAL galactomannan –ve (0.17 units)

- Lung biopsy:
  - Chronic granulomatous inflammation and fibrosis.
  - Negative for fungi and acid fast microorganism
  - Negative for neoplasia

- Plural fluid: -ve fungal culture

- BAL CMV DNA +ve but serum viral load -ve

- Kept on Voriconazole IV, became afebrile starting Aug 31st with clinical improvement.
- Repeat CT day 11 post showed interval worsening, ID decided to keep on IV treatment
- Discharged home

Invasive pulmonary aspergillosis (IA) in CGD

Literature review

- Diagnostic criteria for Invasive fungal infection (IFI)
- Pulmonary IA in CGD
- Challenges with pulmonary IA diagnosis in CGD
  - Imaging
  - Yield of BAL versus tissue biopsy
  - The role of galactomannan in CGD

- The diagnosis of invasive aspergillosis is based upon both:
  - isolating the organism (or markers of the organism)
  - the probability that it is the cause of disease based on host's risk factors for disease (eg, immune status) and the clinical presentation.
- The diagnosis is referred to within a scale of certainty: possible, probable, or proven

Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group

Ben De Pauw,[a] Thomas J. Walsh,[a] J. Peter Donnelly,[a] David A. Stevens, John E. Edwards, Thierry Calandra, Peter G. Pappas, Johan Maertens, Olivier Lortholary, Carol A. Kauffman, David W. Denning, Thomas F. Patterson, Georg Maschmeyer, Jacques Bille, William E. Dismukes, Raoul Herbrecht, William W. Hope, Christopher C. Kibbler, Bart Jan Kullberg, Kieren A. Marr, Patricia Muñoz, Frank C. Odds, John R. Perfect, Angela Restrepo, Markus Ruhnke, Brahm H. Segal, Jack D. Sobel, Tania C. Sorrell, Claudio Viscoli, John R. Wingard, Theoklis Zaoutis, and John E. Bennett[b]

Received 11 September 2007; accepted 20 February 2008; electronically published 5 May 2008.

[a] B.d.P. and T.J.W. served as cochairs and J.P.D. served as secretary for the EORTC/MSG Consensus Group.

[b] Author affiliations are listed at the end of the text.

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Clinical Infectious Diseases 2008; 46:1813–21

1058-4838/2008/4612-0002$15.00
DOI: 10.1086/588660

Table 1. Criteria for proven invasive fungal disease except for endemic mycoses.

Analysis and specimen	Molds[a]
Microscopic analysis: sterile material	Histopathologic, cytopathologic, or direct microscopic examination[b] of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage
Culture	
Sterile material	Recovery of a mold or "black yeast" by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding bronchoalveolar lavage fluid, a cranial sinus cavity specimen, and urine
Blood	Blood culture that yields a mold[d] (e.g., *Fusarium* species) in the context of a compatible infectious disease process
Serological analysis: CSF	Not applicable

Table 2. Criteria for probable invasive fungal disease except for endemic mycoses.

Host factors[a]
Recent history of neutropenia (<0.5 × 10^9 neutrophils/L [<500 neutrophils/mm^3] for >10 days) temporally related to the onset of fungal disease
Receipt of an allogeneic stem cell transplant
Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks
Treatment with other recognized T cell immunosuppressants, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days
Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)

Clinical criteria[b]

Lower respiratory tract fungal disease[c]

The presence of 1 of the following 3 signs on CT:

Dense, well-circumscribed lesions(s) with or without a halo sign

Air-crescent sign

Cavity

Tracheobronchitis

Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis

Sinonasal infection

Imaging showing sinusitis plus at least 1 of the following 3 signs:

Acute localized pain (including pain radiating to the eye)

Nasal ulcer with black eschar

Extension from the paranasal sinus across bony barriers, including into the orbit

CNS infection

1 of the following 2 signs:

Focal lesions on imaging

Meningeal enhancement on MRI or CT

Disseminated candidiasis[d]

At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks:

Small, target-like abscesses (bull's-eye lesions) in liver or spleen

Progressive retinal exudates on ophthalmologic examination

Mycological criteria

- Direct test (cytology, direct microscopy, or culture)
  - Mold in sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate samples, indicated by 1 of the following:
    - Presence of fungal elements indicating a mold
    - Recovery by culture of a mold (e.g., *Aspergillus, Fusarium,* Zygomycetes, or *Scedosporium* species)
- Indirect tests (detection of antigen or cell-wall constituents)[e]
  - Aspergillosis
    - Galactomannan antigen detected in plasma, serum, bronchoalveolar lavage fluid, or CSF
  - Invasive fungal disease other than cryptococcosis and zygomycoses
    - β-D-glucan detected in serum

NOTE. Probable IFD requires the presence of a host factor, a clinical criterion, and a mycological criterion. Cases that meet the criteria for a host factor and a clinical criterion but for which mycological criteria are absent are considered possible IFD.

IFI in CGD

- CGD has the highest prevalence of IFIs among the immunodeficiencies (20 to 40% per patient).
- Aspergillus is most common pathogen
- Generally more indolent than bacterial infections and associated with nonspecific symptoms

E. Liana Falcone and Steven M. Holland. Invasive fungal infection in chronic granulomatous disease: insights into pathogenesis and management. Curr Opin Infect Dis 2012, 25:658–669

- Retrospective review of proven IFIs in a French cohort (159 patient):
  - S & S:
    - FTT: 71% of patients
    - Respiratory symptoms: 55%
    - Fever: 38%
    - Organomegaly: 24%
  - Lungs were involved in 97%, bone in 10%, and central nervous system in 10% of cases

Beauté J, Obenga G, Le Mignot L, et al. Epidemiology and outcome of invasive fungal diseases in patients with chronic granulomatous disease: a multicenter study in France. *Pediatr Infect Dis J*. 2011;30(1):57-62.

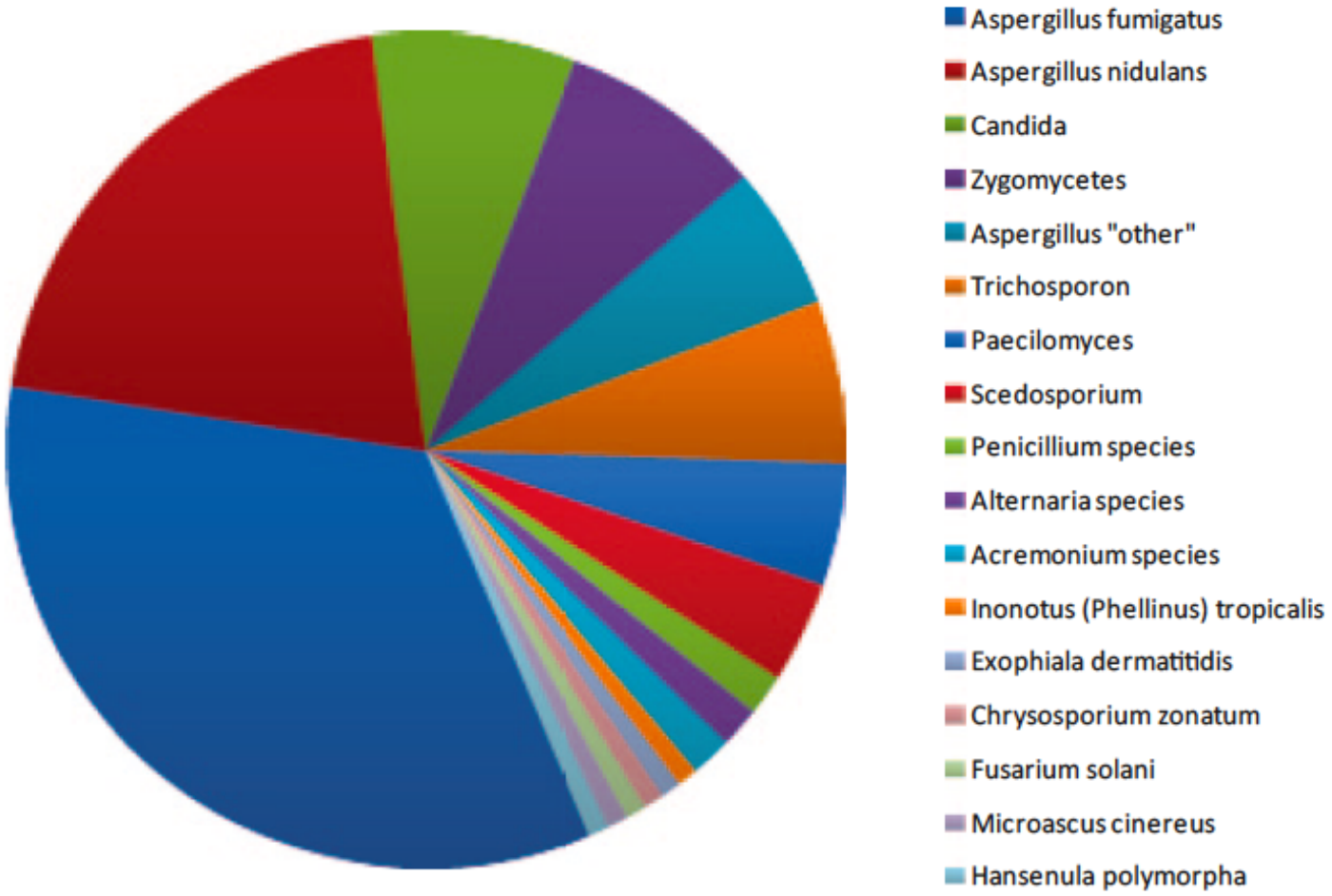
Table 3.1 Epidemiology of invasive fungal infections in CGD: comparison of published registry data

Geographical region [Reference]	Number of patients	*Aspergillus* infections (%)	Organ involvement (%)						AF prophylaxis (%)	Death (*Aspergillus*) (%)
			Lung	Skin	Liver	Brain	Bone	Septicemia		
Europe [18]	409	26	61	5	3	7	16	2	53	28
USA [4]	368	33	78	5	2	4	12	0	NA	35
UK [1]	94	27	85	NA	0	NA	10	0	93	50
Italy [20]	60	34	53	0	0	18	24	0	NA	50
Japan [19]	23	45	NA	NA	NA	NA	NA	NA	48	67
Spain [172]	13	20	NA	NA	NA	NA	NA	NA	77	25
Sweden [3]	21	24	86	NA	NA	NA	NA	NA	NA	0

AF antifungal, *NA* not available

Henriet S, Verweij PE, Holland SM. Invasive Fungal Infections in Patients with Chronic Granulomatous Disease. Hot Topics in Infection and Immunity in Children IX. 2013. doi:10.1007/978-1-4614-4726-9.

Fig. 3.1 Distribution (%) of 127 fungal isolates out of 116 cases of invasive fungal disease in CGD reported between 1970–2010



Henriet S, Verweij PE, Holland SM. Invasive Fungal Infections in Patients with Chronic Granulomatous Disease. Hot Topics in Infection and Immunity in Children IX. 2013. doi:10.1007/978-1-4614-4726-9.

- Invasive pulmonary aspergillosis in CGD may manifest as:
  - a chronic nodular pneumonia or a chronic progressive infection.
  - In contrast to the angioinvasion and infarction that Aspergillus causes in neutropenia, patients with CGD do **not** get hyphal angioinvasion and do not cavitate
  - In contrast to neutropenic patients, haemoptysis is rarely reported in CGD

E. Liana Falcone and Steven M. Holland. Invasive fungal infection in chronic granulomatous disease: insights into pathogenesis and management. Curr Opin Infect Dis 2012, 25:658–669

- A. nidulans almost only found in patients with CGD
- Usually more virulent, more invasive, more likely to disseminate, and more lethal than A. fumigatus
- A. nidulans appears to occur more frequently in patients on antifungal prophylaxis, which may reflect the higher resistance to antifungals

E. Liana Falcone and Steven M. Holland. Invasive fungal infection in chronic granulomatous disease: insights into pathogenesis and management. Curr Opin Infect Dis 2012, 25:658–669

- Mulch pneumonitis:
  - A distinct pulmonary fungal infection syndrome in CGD is acute fulminant fungal pneumonia
  - A medical emergency highly associated with and probably pathognomonic for CGD
  - Due to high-level exposure to aerosolized fungi
  - Can deteriorate rapidly leading to acute hypoxemic respiratory failure, mechanical ventilation, and death

Henriet S, Verweij PE, Holland SM. Invasive Fungal Infections in Patients with Chronic Granulomatous Disease. Hot Topics in Infection and Immunity in Children IX. 2013. doi:10.1007/978-1-4614-4726-9.

- 11 cases have been described since 1986.
- Mean age was 23 years, ranging from 7–64 years
- 4 out of 11 patients were previously well and mulch pneumonitis was the initial presentation leading to the diagnosis of CGD.
- The mortality rate was high (73 %) despite aggressive antifungal treatment, mechanical ventilation and ECMO

Henriet S, Verweij PE, Holland SM. Invasive Fungal Infections in Patients with Chronic Granulomatous Disease. Hot Topics in Infection and Immunity in Children IX. 2013. doi:10.1007/978-1-4614-4726-9.

- Imaging:
  - CXR changes in the CGD host are typically non-specific, with segmental or multi-lobar consolidation, peri-hilar infiltrates, small nodules, or pleural effusions
  - The typical findings of cavitation, pulmonary infarction and the air crescent or halo signs seen in neutropenic patients are **not** found in CGD.
  - Local extension from lung parenchyma to adjacent structures and osteomyelitis of the thoracic cage are findings that are particularly associated with IA in CGD

King J, Henriet S, Warris A. Aspergillosis in Chronic Granulomatous Disease. *J Fungi*. 2016;2(2):15. doi:10.3390/jof2020015.

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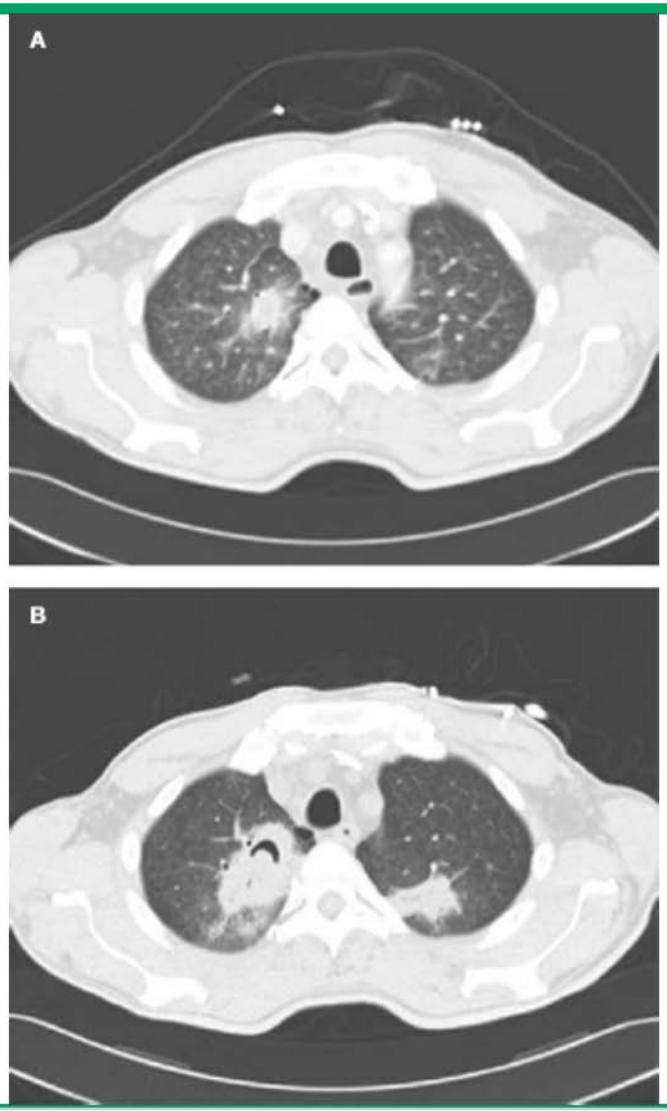
Computed tomography (CT) pulmonary aspergillosis



Halo sign (A) converting to an air-crescent sign (B) after neutrophil recovery.

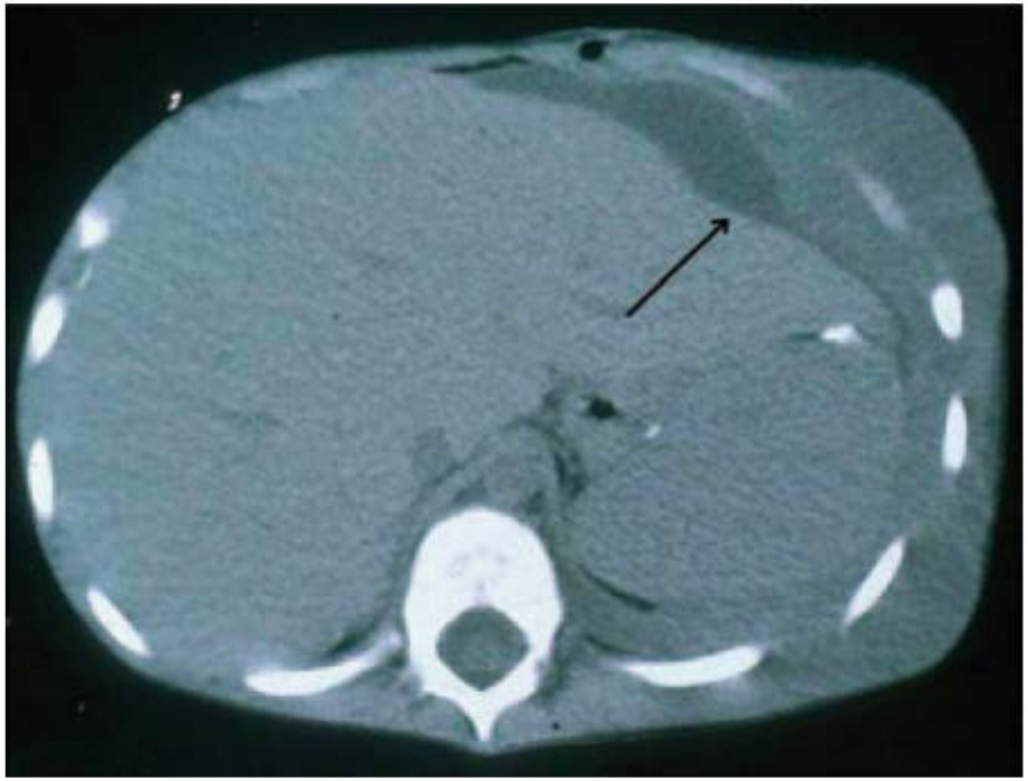


Fig. 3.2 Computed tomography scan of *A. nidulans* infection in a patient with chronic granulomatous disease. (The extensive chest wall invasion and subcutaneous infiltration (*arrow*))

Henriet S, Verweij PE, Holland SM. Invasive Fungal Infections in Patients with Chronic Granulomatous Disease. Hot Topics in Infection and Immunity in Children IX. 2013. doi:10.1007/978-1-4614-4726-9.

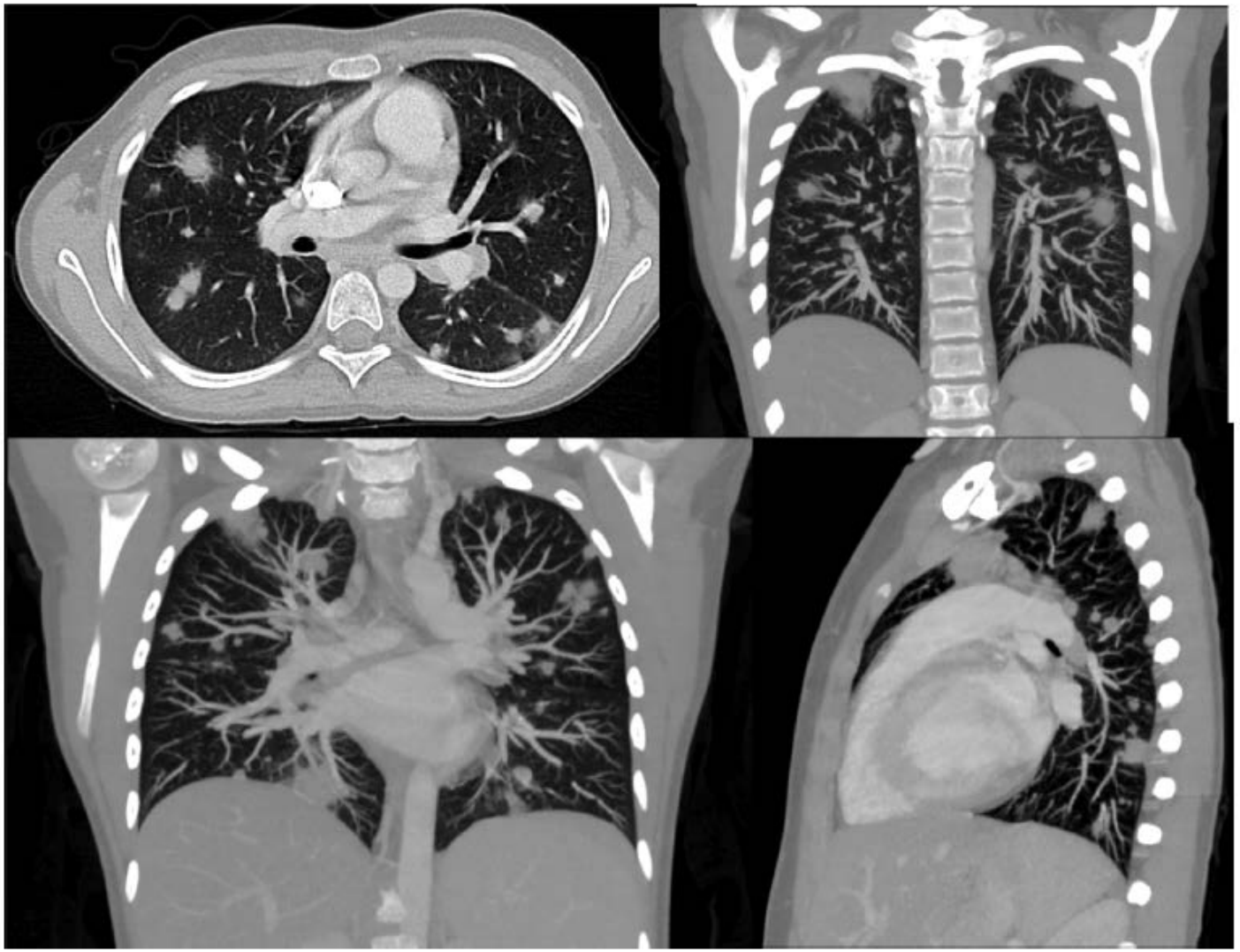


Figure 23: CT scan of the chest of Patient 7, showing numerous bilateral nodular lung opacities scattered through the upper and lower lobes. On the right, the largest measures 3.8 cm × 2.0 cm. On the left, the largest measures 1.7 cm × 1.5 cm. There are multiple enlarged mediastinal lymph nodes with the largest in the prevascular space measuring 1.9 cm × 16 cm.

Murguia-favela L, Manson D. Imaging in patients with chronic granulomatous disease. *LymphoSign J*. 2014;1(2):105-120.

Biopsy and Culture

- In contrast to neutropenic patients, CGD patients with aspergillosis are usually in a reasonable condition and clinically stable, therefore every effort should be made to identify the infecting organism before initiating treatment.

- The importance of identification to species level is highlighted by the inherent reduced susceptibility of A. nidulans to amphotericin B

King J, Henriet S, Warris A. Aspergillosis in Chronic Granulomatous Disease. *J Fungi*. 2016;2(2):15. doi:10.3390/jof2020015.

BAL Vs lung biopsy

- Review of 29 cases of proven IFI in CGD, the invasive procedure that confirmed the diagnosis:
  - Surgical biopsy in 25 (86%) of 29 episodes.
  - 4 out of 19 pulmonary fine-needle aspirations were positive (21%)
  - 5 of 18 BALs led to a positive culture result (sensitivity, 28%).

Blumental S, Mouy R, Mahlaoui N, et al. Invasive mold infections in chronic granulomatous disease: A 25-year retrospective survey. *Clin Infect Dis*. 2011;53(12). doi:10.1093/cid/cir731.

Galactomannan

- GM is a polysaccharide component of the Aspergillus cell wall that is released from growing Aspergillus hyphae

- Results of the test are interpreted based on the optical density (OD) ratio of the sample divided by a threshold control provided in the kit, referred to as the OD index

- Serum GM:
  - Cochrane review 2015:
    - included 54 studies, 5660 patients, 586 proven or probable IA.
    - Included patients with neutropenia or patients whose neutrophils are functionally compromised
    - When using ODI of 0.5 as a cut-off value, the sensitivity of the test was 78% and the specificity was 85%.
    - No difference noted when pediatric data analyzed alone
    - Use of antifungal therapy had a significant effect on sensitivity but not on specificity.

Leeflang MMG, Debets-Ossenkopp YJ, Wang J, et al. Galactomannan detection for invasive aspergillosis in immunocompromised patients. *Cochrane database Syst Rev*. 2015;12(12):CD007394.

- In CGD
  - Galactomannan is quite insensitive, even in the setting of proven infection due to the absence of fungal angioinvasion in CGD.
  - In published case series', serum GM remains negative in the majority of CGD patients despite confirmed IA diagnosis*.
  - In one study: In all 7 patients who were tested before confirmation of invasive aspergillosis was obtained by culture, serum GM was negative**.

* King J, Henriet S, Warris A. Aspergillosis in Chronic Granulomatous Disease. *J Fungi*. 2016;2(2):15. doi:10.3390/jof2020015.
** Blumental S et al. Invasive mold infections in chronic granulomatous disease: A 25-year retrospective survey. *Clin Infect Dis*. 2011;53(12).

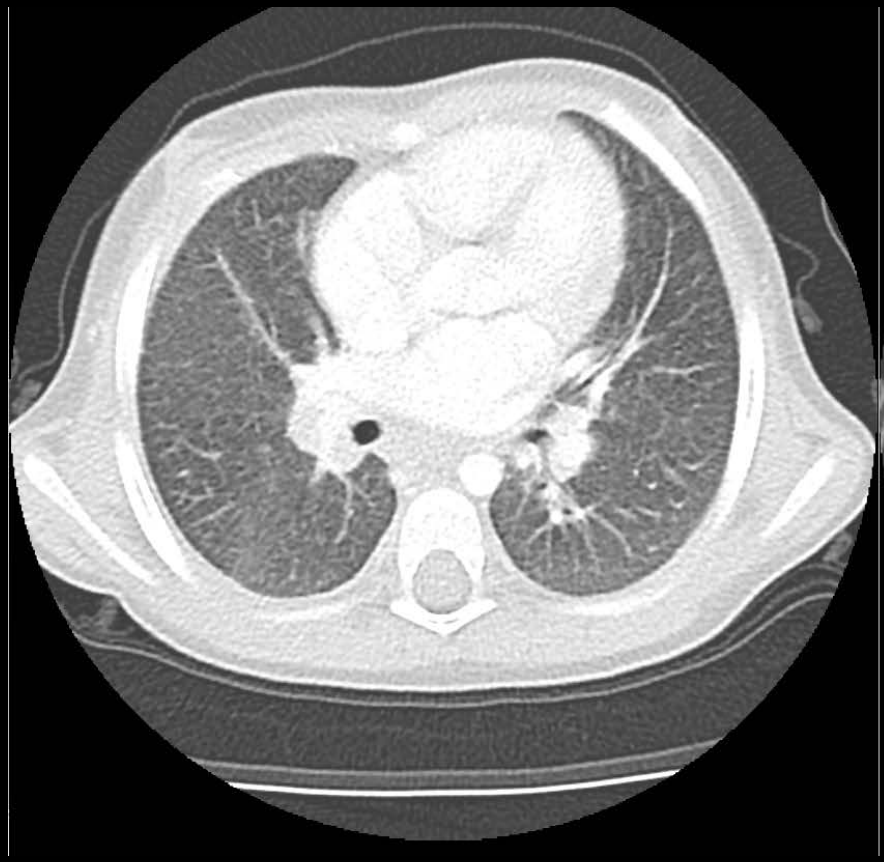
- BAL GM:
  - In general:
    - Variable reported sensitivity and specificity
    - Systematic review of 30 studies reported sensitivity of 87% and specificity of 89% using ODI of 0.5
    - BAL GM is significantly more sensitive for the detection of IPA compared to serum GM**
  - In CGD: there have been no specific reports on the use of BAL galactomannan in CGD patients.^

* Zou M et al. Systematic review and meta-analysis of detecting Galactomannan in bronchoalveolar lavage fluid for diagnosing invasive Aspergillosis. *PLoS One*. 2012;7(8).
** Boch T et al. Direct comparison of galactomannan performance in concurrent serum and bronchoalveolar lavage samples in immunocompromised patients at risk for invasive pulmonary aspergillosis. *Mycoses*. 2016;59(2):80-85.
^ King J, Henriet S, Warris A. Aspergillosis in Chronic Granulomatous Disease. J Fungi. 2016;2(2):15.

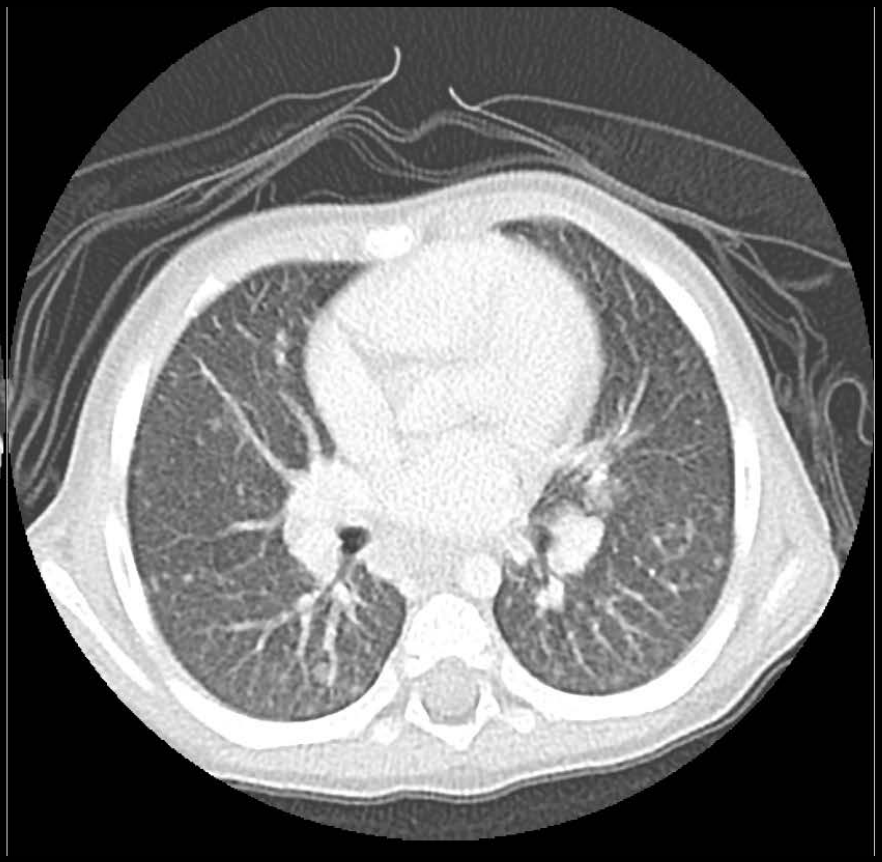
- Others tests:
  - PCR as a biomarker to detect Aspergillus in serum or plasma is of limited use in CGD patients
  - In CGD cases with reported PCR results, serum and CSF samples were negative, however biopsy and sputum specimens have shown positivity

King J, Henriet S, Warris A. Aspergillosis in Chronic Granulomatous Disease. *J Fungi*. 2016;2(2):15. doi:10.3390/jof2020015.

Back to the patient



Oct 6th



Aug 15th

- Repeat CT 6 weeks post treatment:
  - Interval improvement in the number and size of the multiple scattered pulmonary nodules in both lungs.
  - The previously seen largest pulmonary nodule in the superior segment of right upper lobe is stable.
  - Switched to oral Voriconazole for further 3 months with repeat CT

Summary

- CGD has the highest prevalence of IFIs among the immunodeficiencies
- IA is CGD is more indolent than bacterial infections and associated with nonspecific symptoms.
- Clinical presentation and imaging findings of IA is different in CGD compare to other high risk groups.
- Serum GM is insensitive in CGD. No specific reports on the use of BAL GM in CGD patients but it is likely to be useful.

References

- De Pauw B, Walsh TJ, Donnelly JP, et al. Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) C. *Clin Infect Dis*. 2008;46(12):1813-1821.
- E. Liana Falcone and Steven M. Holland. Invasive fungal infection in chronic granulomatous disease: insights into pathogenesis and management. Curr Opin Infect Dis 2012, 25:658–669
- Beauté J, Obenga G, Le Mignot L, et al. Epidemiology and outcome of invasive fungal diseases in patients with chronic granulomatous disease: a multicenter study in France. *Pediatr Infect Dis J*. 2011;30(1):57-62
- Henriet S, Verweij PE, Holland SM. Invasive Fungal Infections in Patients with Chronic Granulomatous Disease. Hot Topics in Infection and Immunity in Children IX. 2013. doi:10.1007/978-1-4614-4726-9.
- King J, Henriet S, Warris A. Aspergillosis in Chronic Granulomatous Disease. *J Fungi*. 2016;2(2):15. doi:10.3390/jof2020015.
- Murguia-favela L, Manson D. Imaging in patients with chronic granulomatous disease. *LymphoSign J*. 2014;1(2):105-120.
- Blumental S, Mouy R, Mahlaoui N, et al. Invasive mold infections in chronic granulomatous disease: A 25-year retrospective survey. *Clin Infect Dis*. 2011;53(12).
- Leeflang MMG, Debets-Ossenkopp YJ, Wang J, et al. Galactomannan detection for invasive aspergillosis in immunocompromised patients. *Cochrane database Syst Rev*. 2015;12(12):CD007394.
- Zou M et al. Systematic review and meta-analysis of detecting Galactomannan in bronchoalveolar lavage fluid for diagnosing invasive Aspergillosis. *PLoS One*. 2012;7(8).
- Boch T et al. Direct comparison of galactomannan performance in concurrent serum and bronchoalveolar lavage samples in immunocompromised patients at risk for invasive pulmonary aspergillosis. *Mycoses*. 2016;59(2):80-85.