

PNEUMONIA IN GRANULOCYTOPENIC PATIENTS

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- 51 year-old woman admitted to hospital because increasing shortness of breath, general malaise and profound asthenia of 2 weeks duration.
- Appendectomy in childhood.
Two children (normal pregnancies and vaginal deliveries)
- FH: Father died at the age of 76 of AMI. Mother alive, type 2 DM

- Physical examination

Afebrile, BP 11/8, RR 14/min, P110/min

Markedly pale, extensive ecchymoses and purpuric lesions in trunk and extremities.

Normal breath sounds, cor rhythmic, SS 2/6

Abdomen soft, no masses.

All pulses present, no edema.

Rectal exam: empty rectal ampulla, no evidence of blood

Neurol: grossly normal

Blood tests and other studies

- Hemoglobin, 6.4 g/dL, Hematocrit, 20%, VCM 114 fl; leucocytes, $8,8 \times 10^9/L$ (C 6, N 26, L 1, blasts 67), 1 erythroblast; platelets, $24,0 \times 10^9/L$. Coagulation, normal
- Biochemistry: Normal, except LDH, 681/UI (VN, 230-460)
- Myelogram: 95% lymphoblasts (LAL₁)
- Immunofenotype blastic population: B
- Cytogenetic analysis: 46, XX
- Lumbar puncture: CSF, crystal clear, acellular.

Initial treatment

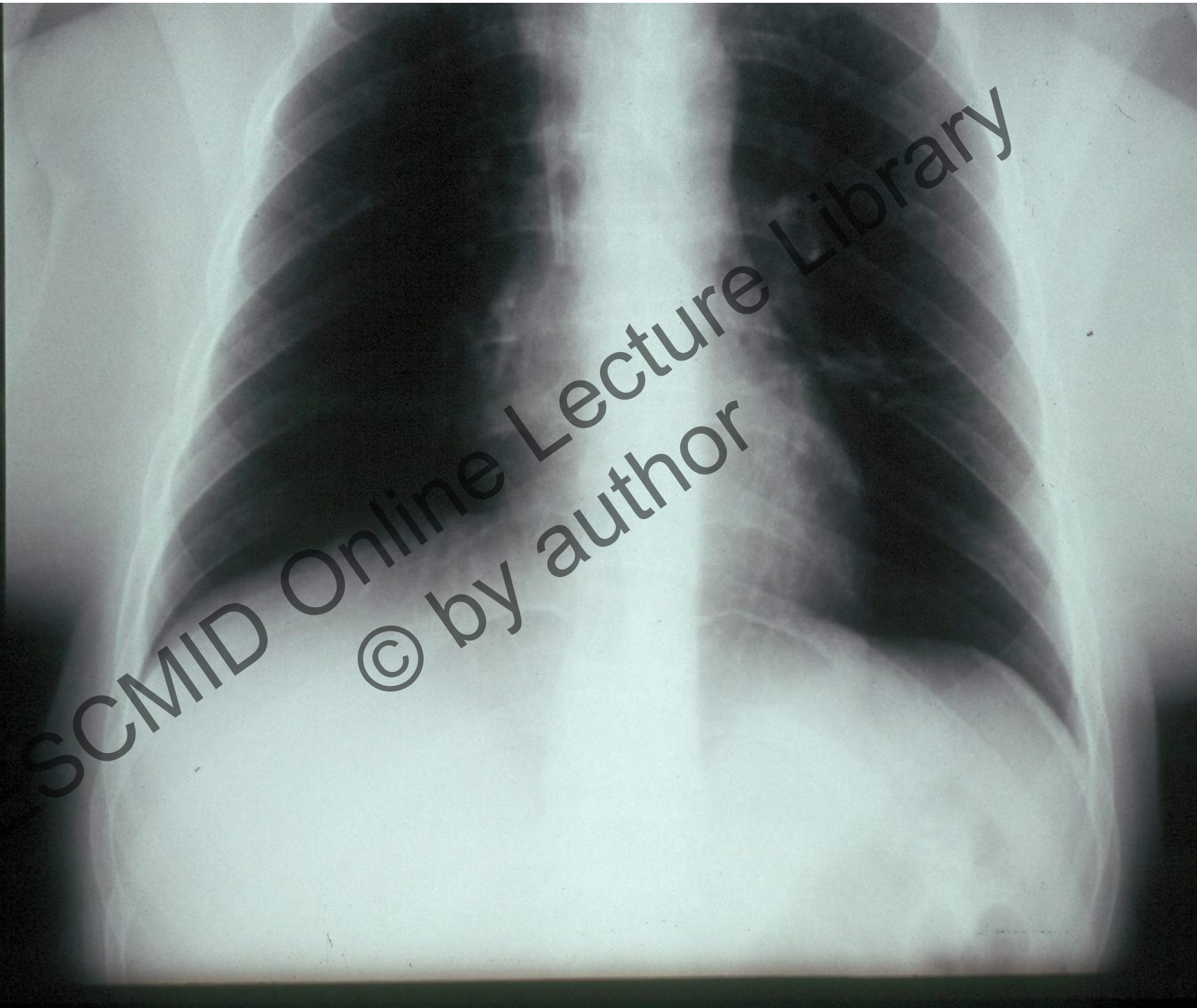
- Induction chemotherapy:
 - Systemic: Vincristin, daunorubicin, cyclophosphamide, L-asparaginase and prednisone (1 mg/Kg/IV/24 h).
 - Intrathecal: Methotrexate
- Antimicrobial prophylaxis: Fluconazol, 50 mg/24 h

Question 1. As far as antibiotic prophylaxis is concerned, select the most appropriate

1. Antibiotic prophylaxis with FQs should be standard practice in the granulocytopenic patient.
2. Only FQs have been shown to be effective in the prophylaxis.
3. The adult with acute myeloblastic leukemia is the only instance where antibiotic prophylaxis has been shown to be effective.
4. Only ciprofloxacin has been found to be effective
5. None of the above

Evolution

- Glucocorticoid-induced hyperglycemia. Insulin given.
- Day 20 post induction, sudden onset of:
 - BP 80/40, signs of poor peripheral perfusion
 - Axillary-rectal temperature dissociation (36°C/40,5°C)
 - Extremities cold and clammy
 - Mild abdominal pain in hypogastrium and aqueous diarrhea (2 bm/day) for 48 hours.
 - Rest of physical examination: no focal findings



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Evolution. II

- Diagnostic work up:
 - CBC: Leucocyte count, $0.120 \times 10^9/L$
 - Urine sediment: 3 RBC/hpf.
 - Chest-rays, no changes
 - Blood, urine and stool cultures taken

Question 2. The most common cause of sepsis in this setting (third week, granulocytopenia, high dose systemic steroids, no clear cut focus of infection) is:

1. GNB sepsis of undetermined origin
2. IV catheter related sepsis. MRSA high in the list
3. Coag negative Staphylococcus IV catheter related sepsis.
4. *Candida spp* sepsis
5. Secondary sepsis to a intraabdoninal focus

Question 3. Choose the most appropriate initial empirical antimicrobial regimen

1. Cefepime + aminoglycoside
2. Ceftazidime + aminoglycoside
3. Carbapenem + aminoglycoside
4. Beta-lactam + aminoglycoside + antifolateric B
5. Beta-lactam + aminoglycoside + voriconazol + Vancomycin

Evolution. III

- New CVC line, Foley catheter, IV fluids.
- Empirical antibiotic treatment:
 - Cefepime, 2g/q12h
 - Amikacin, 15 mg/Kg/24 h
 - Amphotericin B, 5 mg/Kg/day
- G-CSF

Evolution IV

- Hemodynamic stabilization. Progressive clinical improvement.

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Evolución IV

- Hemodynamic stabilization. Progressive clinical improvement
- Blood cultures grew *Escherichia coli* (4/4). Urine culture, negative. Catheter tip culture, negative
- Stool culture: *Campylobacter jejuni*

Antibiotic susceptibility of the *Escherichia coli* isolate

S Amoxi/Clav, Cefuroxime, Ceftriaxone, Cefepime
(MIC, < 0.12 µg/ml), Piper/Tazo,
Imipenem, Meropenem, Ertapenem
Ciprofloxacin, Levofloxacin
Gentamicin, Tobramycin, Amikacina (MIC, 1 µg/ml)

R Ampicillin, Cotrimoxazole

Evolución IV

- Hemodynamic stabilization. Progressive clinical improvement

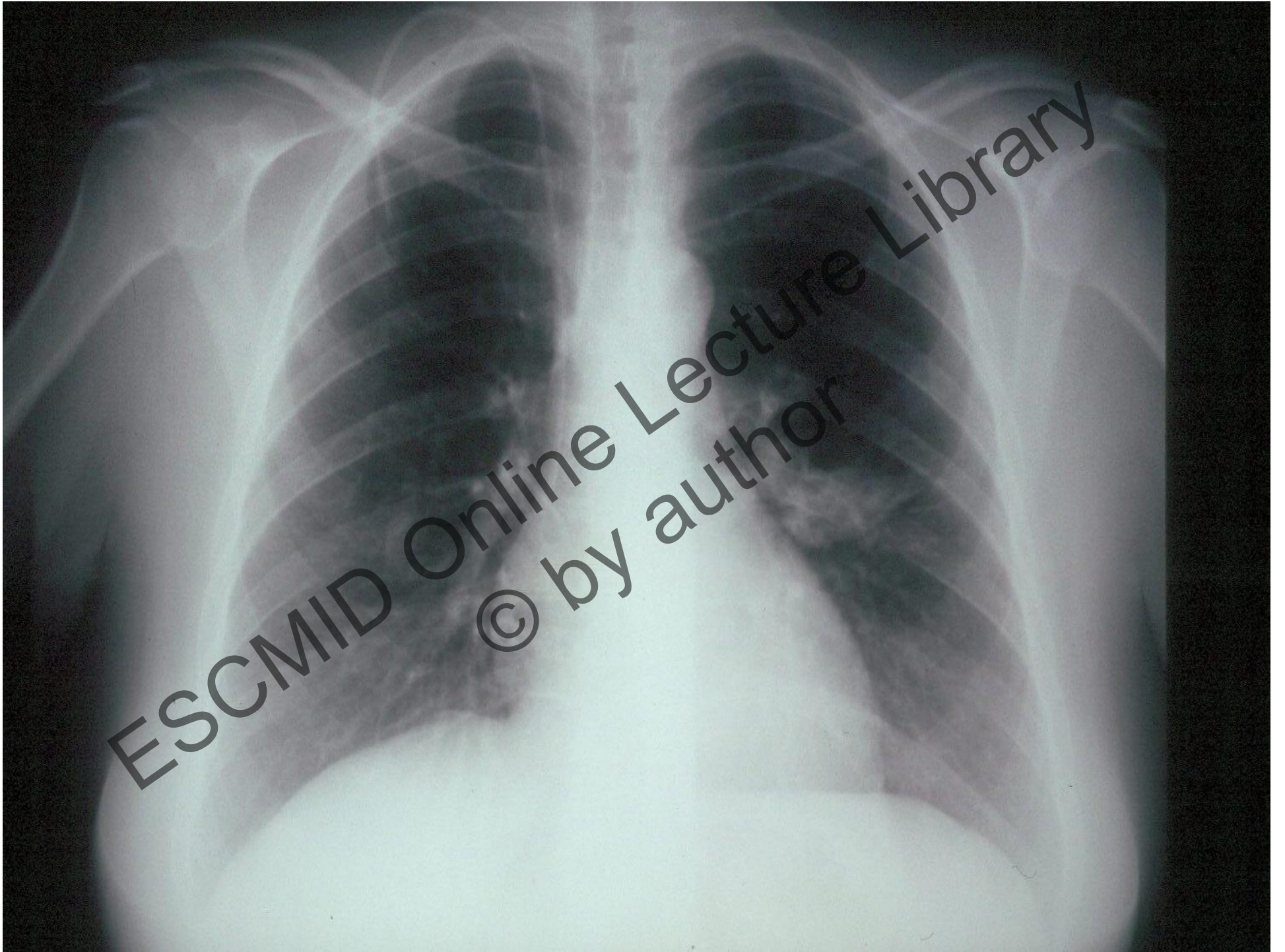
Amphotericin B discontinued,
clarithromycin PO started.

Evolution. V

- Day 7 of antibiotic treatment. Patient persisted febrile (38-38,8°C) and soft stools; vague ill-defined ache in left hemithorax
- Physical examination without changes. Normal breath sounds through both hemithoraces.
- Persistent granulocytopenia

Evolution. V

- Day 7 of antibiotic treatment. Patient persisted febrile (38-40°C) and soft stools; vague ill-defined in left hemithorax
- Physical examination without changes. Normal breath sounds through both hemithoraces.
- Persistent granulocytopenia
- Chest-X rays: image compatible with pulmonary nodule in LLL



Question 4. Please, choose, in your opinion, the best answer

1. Perform bronchoscopy and reinitiate immediately antifungal therapy.
2. Reinitiate antifungal therapy and follow closely the evolution with serial determinations of galactomannan
3. Replace cefepime for meropenem and reinitiate antifungal therapy.
4. Do a Thoracic CT scan, serial galactomannan determinations and reinitiate antifungal therapy.
5. None of the above.

Evolution. VI

- Reinitiation of Anfotericin B
- Thoracic CT scan: Pulmonary nodule in segment 6. Extensive perinodular halo

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MR=Z.1
(316, 331)

R

WL = -600
WW = 1500

6307:43



TORAX

1.0
L/A
SU/HF/VF
FC30/ORG

--- D

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-
- Platelet transfusion.
 - Transthoracic lung puncture

MR=1.4
(239, 266)

L

WL = -600
WW = 1500

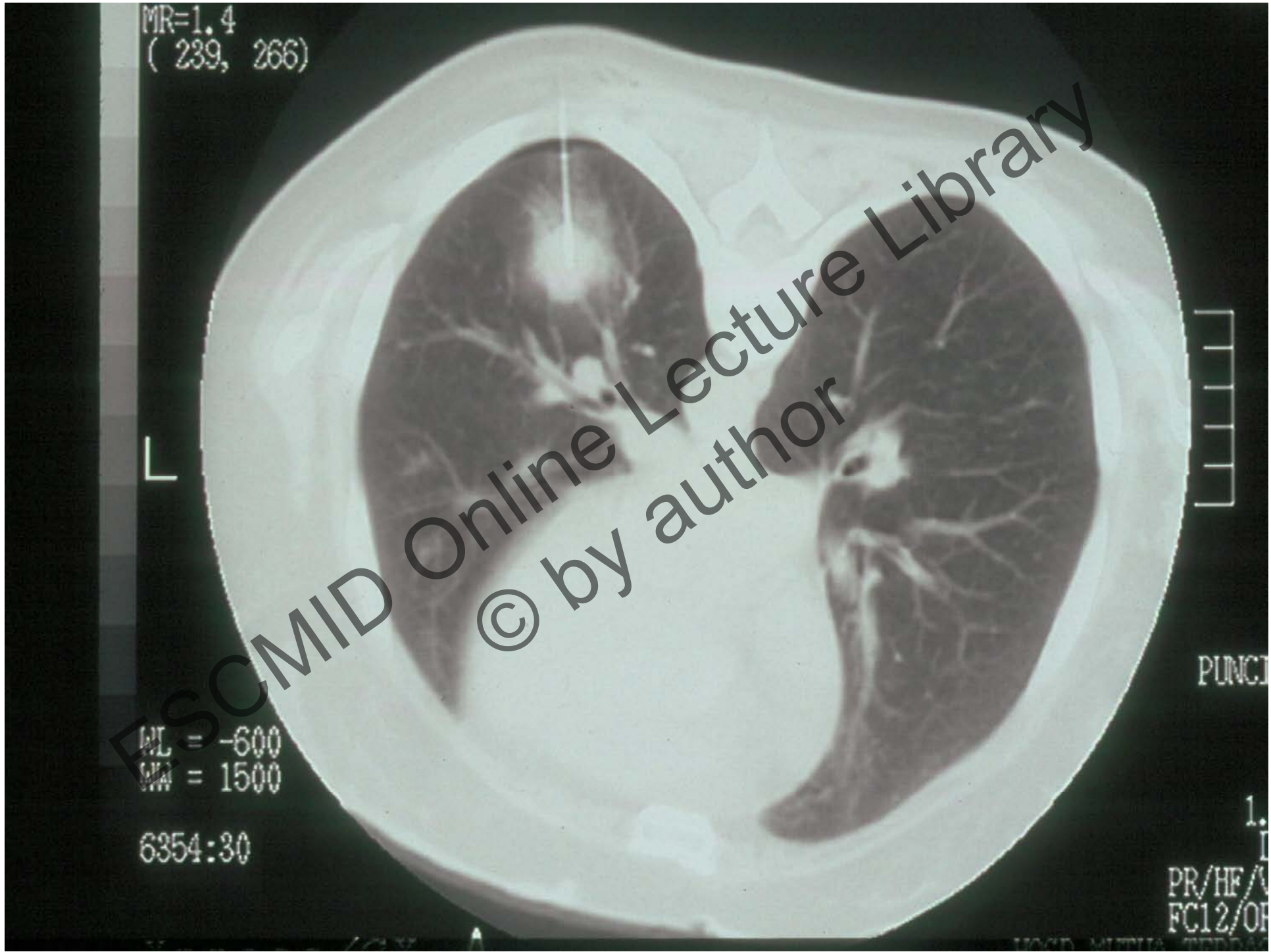
6354:30



PUNCT

1.
PR/HF/A
FC12/OF

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Last opportunity: the offending pathogen is

- *Pseudomonas aeruginosa*
- *Aspergillus fumigatus*
- *Escherichia coli*
- *Campylobacter jejuni*
- *Rhizopus oryzae*
- *Rhodococcus equi*

Results of lung culture

Pure and abundant culture of *Escherichia coli*

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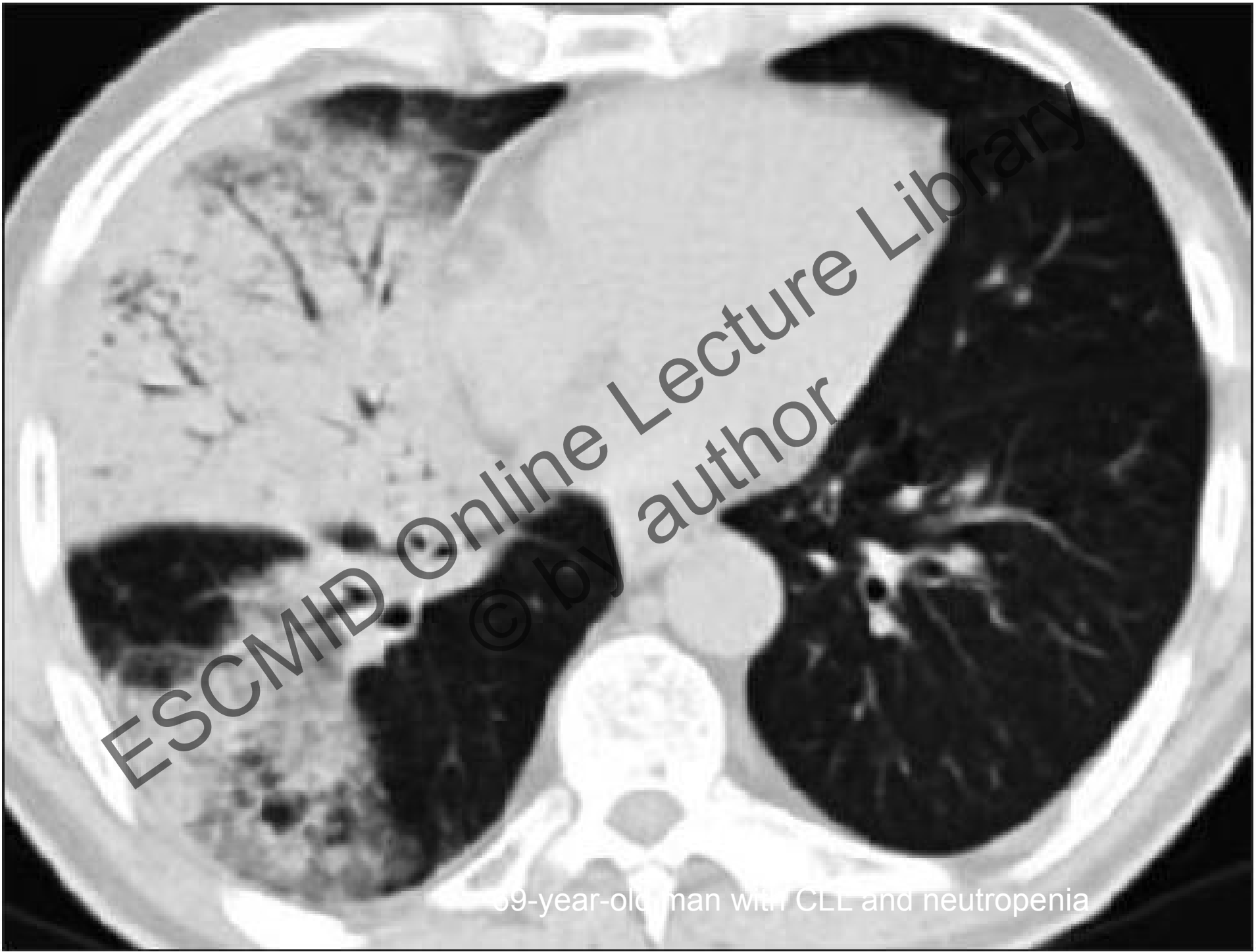
-
- Leukemia in complete remission
 - Persistence of pulmonary lesion until two months post-treatment
 - Administration of three cycles of consolidation followed by autologous peripheral blood stem-cell transplantation.
 - Well into remission for four years. Readmitted with recurrent disease in 2007. She died the same year.

Pathogens cultured from bronchoalveolar lavage (BAL) fluid in 95 immunocompromised patients with pneumonia

<i>Pathogens</i>	<i>Frequency (%)</i>	<i>Classification of pathogens</i>	<i>Frequency (%)</i>
<i>Staphylococcus</i>	23 (25.3%)	Gram positive	40.7%
<i>Enterococcus</i>	9 (9.9%)		
<i>Streptococcus</i>	3 (3.3%)		
<i>S aureus</i>	2 (2.2%)		
<i>Acinetobacter</i>	1 (1.1%)		
<i>Capnocytophaga</i>	4 (4.4%)		
<i>Chlamydia</i>	2 (2.2%)		
<i>Enterobacteriaceae</i>	2 (2.2%)		
<i>Haemophilus</i>	2 (2.2%)		
<i>Legionella</i>	3 (3.3%)		
<i>Pseudomonas</i>	1 (1.1%)	Gram negative	16.5%
<i>Mycobacterium</i>	6 (6.6%)		
<i>Candida</i>	25 (27.5%)	Mycobacteria	6.6%
<i>Aspergillus</i>	7 (7.7%)	Fungi	35.2%
<i>Cytomegalovirus</i>	1 (1.1%)	Viruses	1.1%

BACTERIAL PNEUMONIA

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69-year-old man with CLL and neutropenia

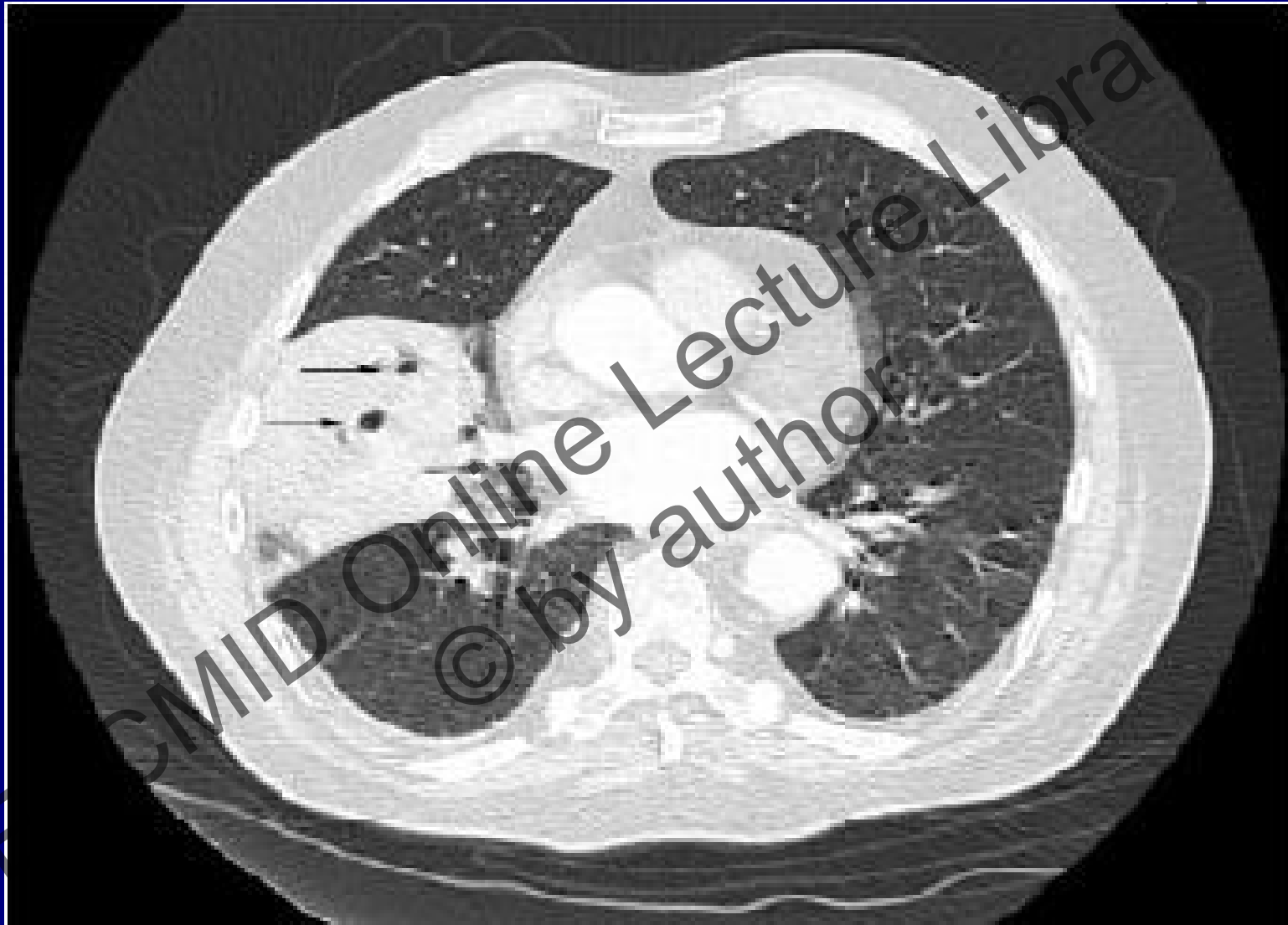
Axial CT image shows consolidation with air bronchograms. Blood culture showed *Streptococcus pneumoniae*.

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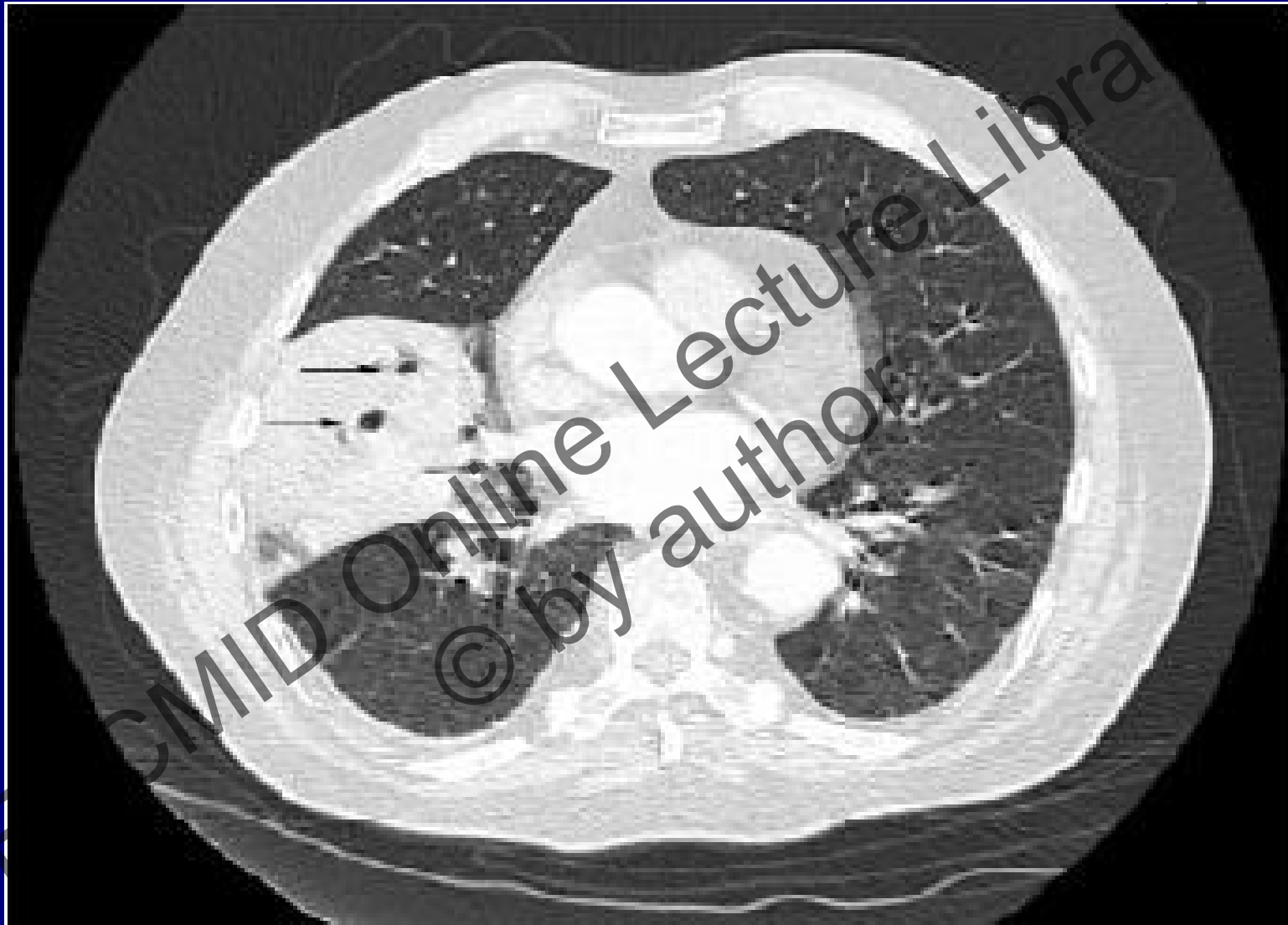
61-year-old bone marrow transplant recipient with myelodysplastic syndrome.

- Axial CT image shows bilateral consolidation and ground-glass densities. *Staphylococcus aureus* was cultured from bronchoalveolar lavage

Chest-CT showing airspace consolidation of the right middle lobe, two small cavitations are present (~1010 mm, black arrows).



Chest-CT showing airspace consolidation of the right middle lobe, two small cavitations are present (~1010 mm, black arrows).



. Tests for Legionella antigen were negative. *L. longbeachae* was immediately detected in BAL fluid by PCR and subsequently confirmed by culture on legionella-selective media

Legionnaires' disease in immunocompromised patients:

- In addition to *Legionella pneumophila*, about 20 *Legionella* species have been documented as human pathogens.
- The majority of infections by non-*pneumophila* *Legionella* species occur in immunocompromised and splenectomized patients.
- Steroid therapy is a recognized risk factor

Kumpers P et al, J Med Microbiol 2008;57:384–387

Diagnostic considerations

- Image studies
- BAL
- Specific microbiological diagnosis

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Table 3. Chest CT findings in immunocompromised patients with pulmonary fungal infection, aspergillus infection, and *Pneumocystis jiroveci* pneumonia (PCP)

CT findings	Fungal infection (n = 20)		Aspergillus infection (n = 10)		PCP (n = 8)	
	n	%	n	%	n	%
Consolidation	7	35	3	30.0	2	25.0
Ground-glass area	0	0.0	0	0.0	8	100.0
Ground-glass nodules	6	30.0	3	30.0	5	62.5
Nodule	18	90.0	9	90.0	0	0.0
Cavitary nodule	8	40.0	4	40.0	0	0.0
Centrilobular nodules	4	20.0	2	20.0	0	0.0
Acinar nodules	1	5.0	0	0.0	1	12.5
Interlobular septal thickening	0	0.0	0	0.0	2	25.0
Thickening of bronchial wall	4	20.0	2	20.0	3	37.5
Pleural effusion	4	20.0	1	10.0	0	0.0

Diagnostic accuracy of BAL samples in immunosuppressed patients with suspected pneumonia

- **BACKGROUND:** Utility of BAL samples has already been established, but studies about them are scarce and limited to few countries. We aimed to evaluate the accuracy of a diagnostic protocol, emphasizing on local epidemiology, rapidity, and yield of different techniques.
- **METHODS:** One year prospective study of 101 consecutive immunosuppressed patients admitted with suspected pneumonia to a university hospital. They all had BAL (n=109) and respiratory sampling.
- Conventional microbiological studies, cytomegalovirus pp65 antigenemia and transbronchial biopsy (TBB), whenever considered pertinent, were done.
- **RESULTS:** HIV/AIDS infection was the most frequent cause of inclusion (n=80). Infections accounted for 79 out of 122 final diagnoses (64.8%).
- Our protocol identified 60 infectious and 3 noninfectious pathologies (general yield: 51.6%). Sensitivity in pulmonary infections was 75.9% (IC95%: 64.8-84.6%), specificity 86.0% (72.6-93.7%), positive predictive value 89.6% (79.1-95.3%), negative predictive value 69.4% (56.2-80.1%), accuracy 79.8% (71.7-86.2%). Mycobacterium spp. (n=27), bacteria (n=19), Pneumocystis jirovecii (n=18) and other fungi (histoplasmosis: 6, aspergillosis: 5, cryptococosis: 3) were the most common infectious pathogens. Direct microscopy allowed an early definite/presumptive diagnosis in 36/49 fungal and mycobacterial infections (73.5%). Up to 30% of mycobacterial infections were missed.
- **CONCLUSIONS:** Systematical study of BAL samples has a high diagnostic yield in our immunocompromised patients with suspected pneumonia. As economical and epidemiological conditions of regions are different, it should be tried everywhere

Velez L et al, Respir Med. 2007;101:2160-7.

VIRAL PNEUMONIA

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CMV Pneumonia

- CMV pneumonia is still an important cause of morbidity and mortality in immunocompromised patients, especially in recipients of allogeneic hematopoietic stem cell transplants.
- Interstitial pneumonia has an incidence in this latter group of 15% and is associated with a mortality rate of 85% if left untreated.
- Patients with nonhematologic disorders who are receiving long-term steroid therapy are also prone to this infectious complication, as well as patients with AIDS.
- The high-resolution CT manifestations of CMV pneumonia are known to be polymorphous and to consist mainly of ground-glass opacities, air-space consolidations, and a nodular or reticulonodular pattern that might be suggestive of this diagnosis in an adequate clinical setting, but not specific.

TABLE 3: Odds Ratios (OR) and 95% CIs of Outcome for Treatment Factors and CT Signs, with the Latter Adjusted by the Former

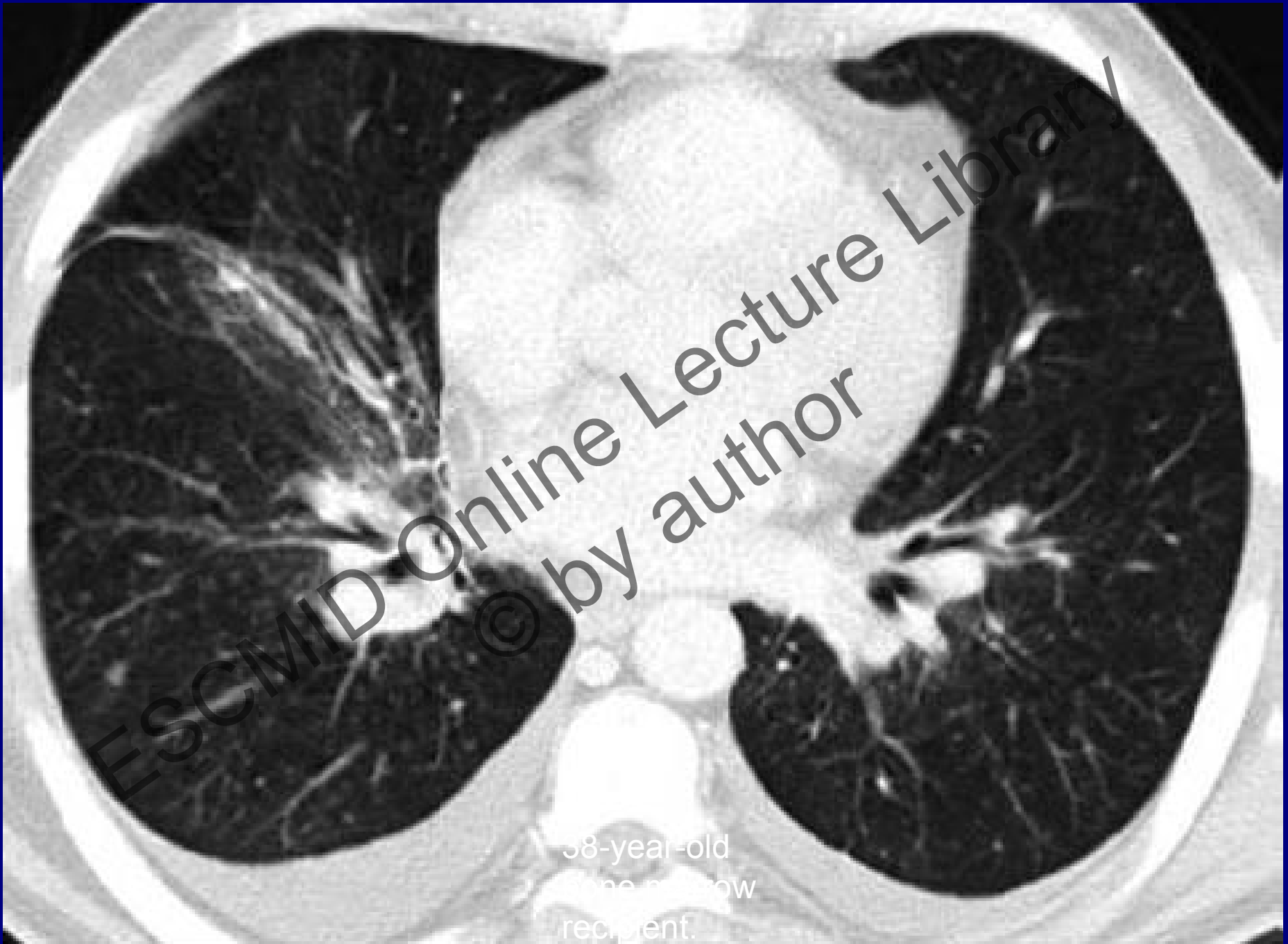
Condition	OR	95% CI	Adjusted ^a	
			OR	95% CI
Treatment factors				
Therapy late vs early	3	0.62–18		
Host CMV-seropositive	0.65	0.024–18		
Donor CMV-seropositive	0.57	0.12–2.5		
GvHD, present vs absent	1.4	0.2252–6.4		
CT signs				
Ground-glass opacity	14	2.1–280	27	2.8–830
Reticulation	1.5	0.057–42	1.4	0.04–47
Consolidation	0.33	0.059–1.6	0.19	0.024–1.1
Centrilobular ill-defined opacities	0.2	0.026–1.04	0.21	0.024–1.2
Diffuse	3.1	0.71–16	2.8	0.55–17
Focal	0.32	0.063–1.4	0.35	0.058–1.8

Note—CMV = cytomegalovirus, GvHD = graft-versus-host disease.

^aAdjusted for all four treatment factors.

Table 2. Chest CT findings in immunocompromised patients with pulmonary bacterial infection and pulmonary cytomegalovirus (CMV) infection

CT findings	Bacterial infection (n = 19)		CMV infection (n = 8)	
	n	%	n	%
Consolidation	13	68.4	2	25.0
Ground-glass area	6	31.6	3	37.5
Ground-glass nodules	6	31.6	3	37.5
Nodule	1	5.3	0	0.0
Cavitary nodule	0	0.0	0	0.0
Centrilobular nodules	6	31.6	6	75.0
Acinar nodules	2	10.5	0	0.0
Interlobular septal thickening	1	5.3	0	0.0
Thickening of bronchial wall	6	31.6	5	62.5
Pleural effusion	4	21.1	0	0.0

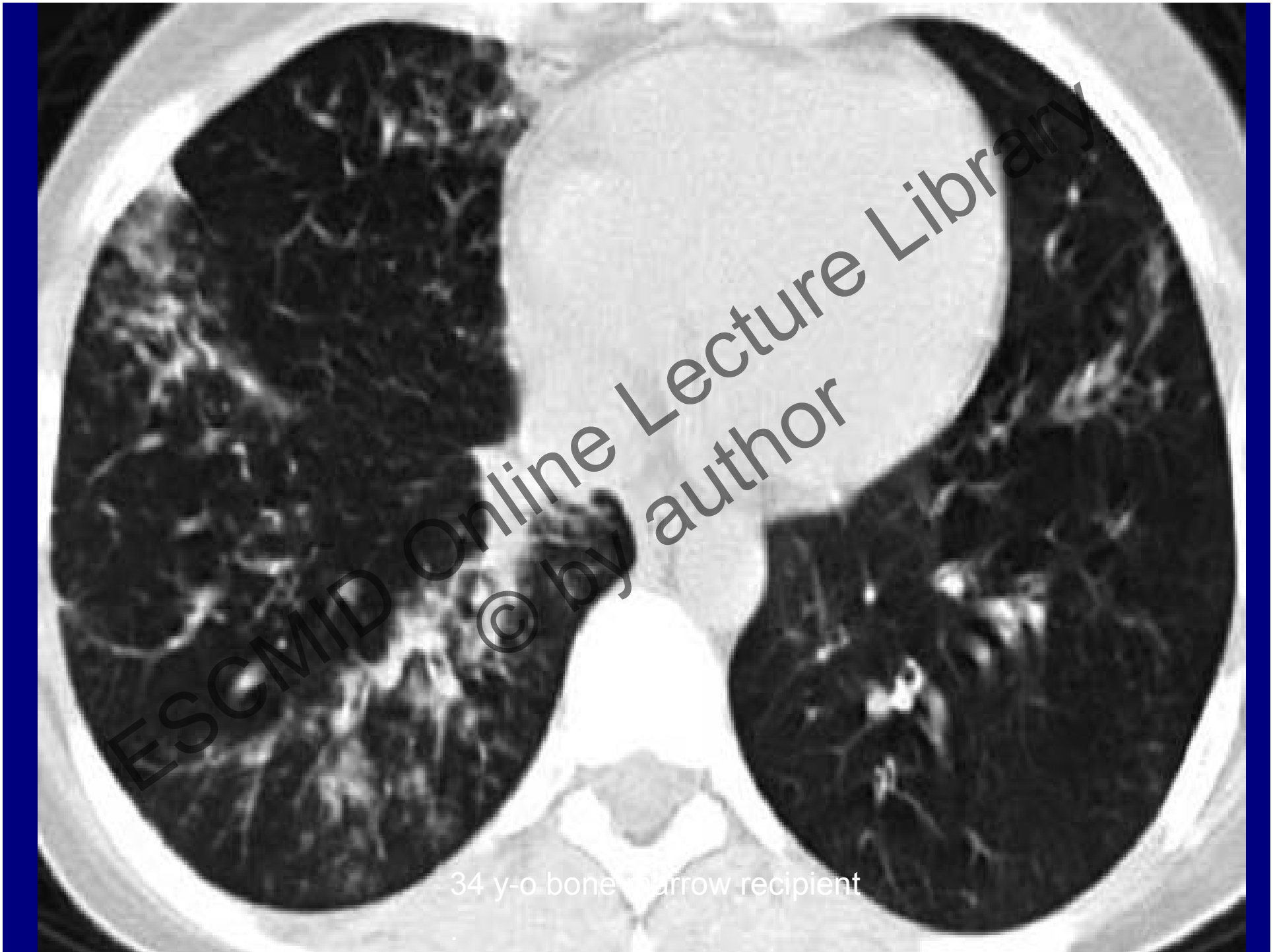


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58-year-old
bone marrow
recipient.

- Axial CT image shows bilateral centrilobular nodules and pleural effusion in *Cytomegalovirus* infection.

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34 y-o bone marrow recipient

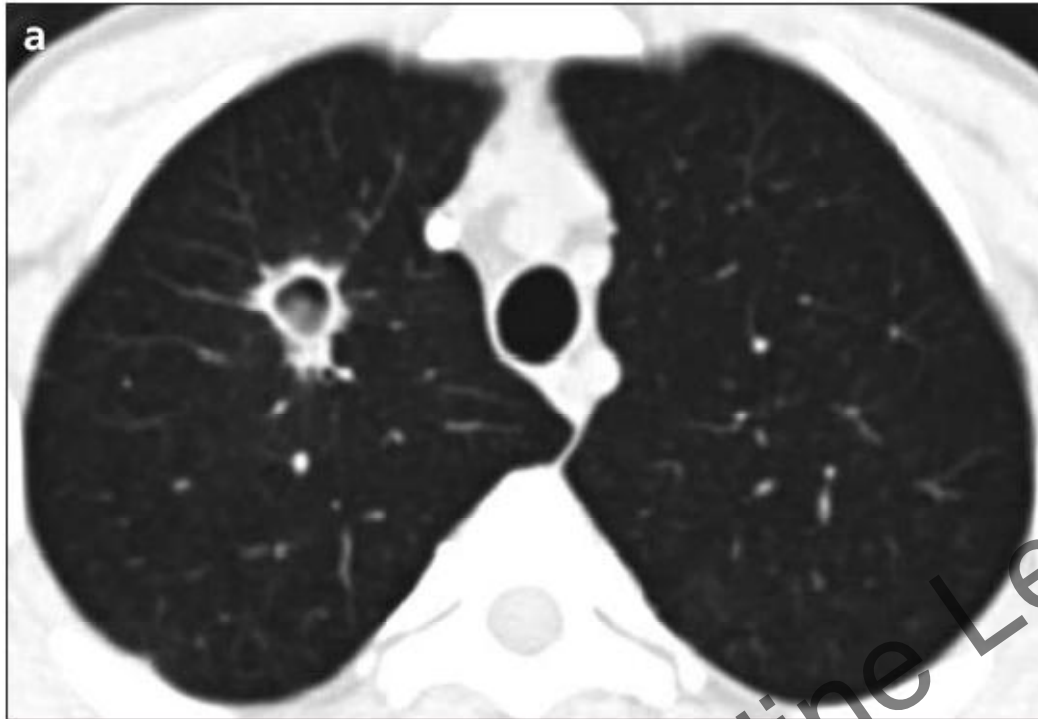
Axial CT image shows bilateral centrilobular nodules, ground-glass densities and thickening of bronchial walls predominantly in the right lower lobe with *Cytomegalovirus* antigenemia

RESPIRATORY VIRUS INFECTION IN THE HEMATOPOIETIC TRANSPLANT RECIPIENT

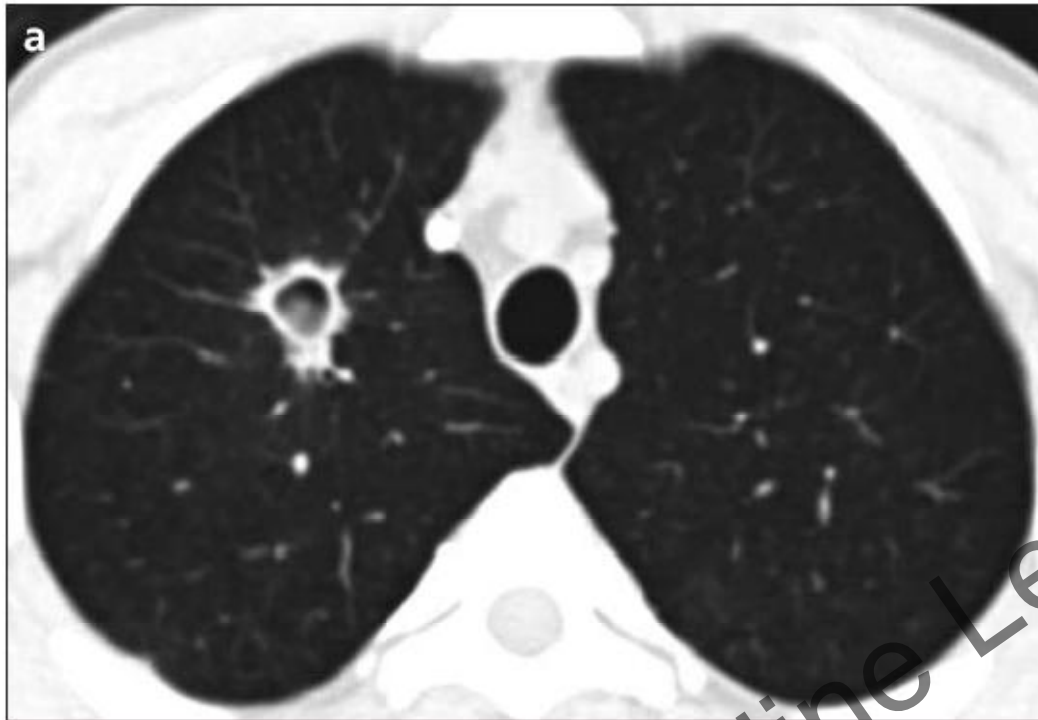
- While respiratory syncytial virus (RSV), human metapneumovirus, parainfluenzaviruses, and influenza viruses are well known for their potential to cause fatal pneumonia, information has only recently emerged regarding the significance of the newly discovered viruses, such as human coronaviruses NL63 and HKU1, and human bocavirus.
- Lymphopenia seems to be the most important risk factor for progression to lower respiratory tract disease.
- Airflow obstruction is another complication of respiratory virus infections after HCT, and data to date indicate this complication may occur following parainfluenza virus and RSV infection.
- Infection control procedures are key for prevention.
- Unfortunately, there are no randomized treatment studies, which make the interpretation of the literature on interventions difficult.

FUNGAL PATHOGENS

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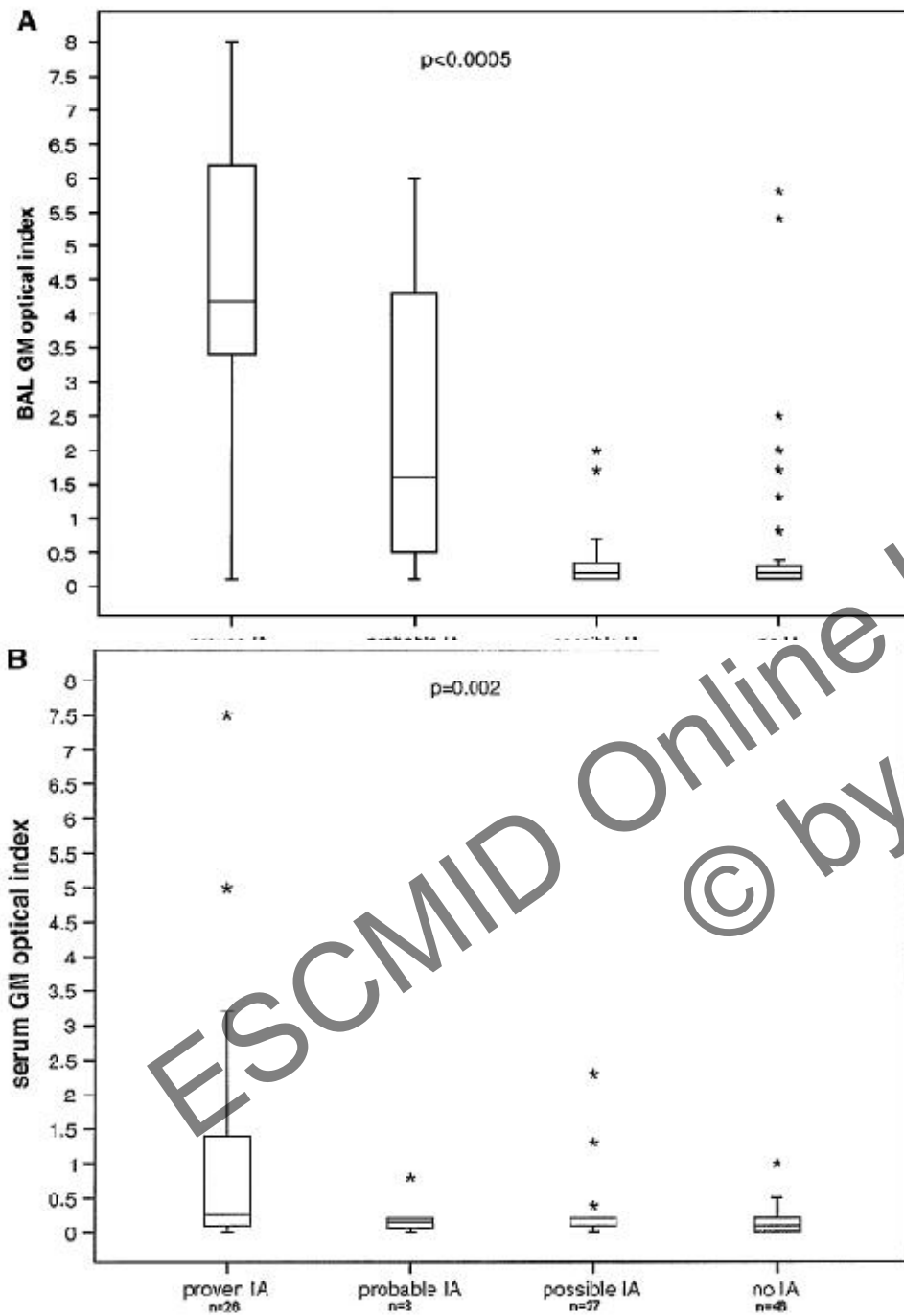


Axial CT images (a, b) showing bilateral cavitary nodules with air crescent sign in a 33-year-old neutropenic patient with acute lymphoblastic leukemia.



Axial CT images (a, b) showing bilateral cavitary nodules with air crescent sign in a 33-year-old neutropenic patient with acute lymphoblastic leukemia.

Invasive aspergillosis was diagnosed on the basis of galactomannan positivity.



(A) Distribution of bronchoalveolar lavage galactomannan (BAL GM) results on Day 1 of inclusion.

(B) Distribution of serum GM results on Day 1 of inclusion.

P values by Kruskal-Wallis test.

Boxes show interquartile range; whiskers show 95% CI intervals.

EORTC criteria include the “classical” host factors proposed by Asciglu and colleagues (12) and three additional ICU-related host factors (cirrhosis, COPD, and steroids).

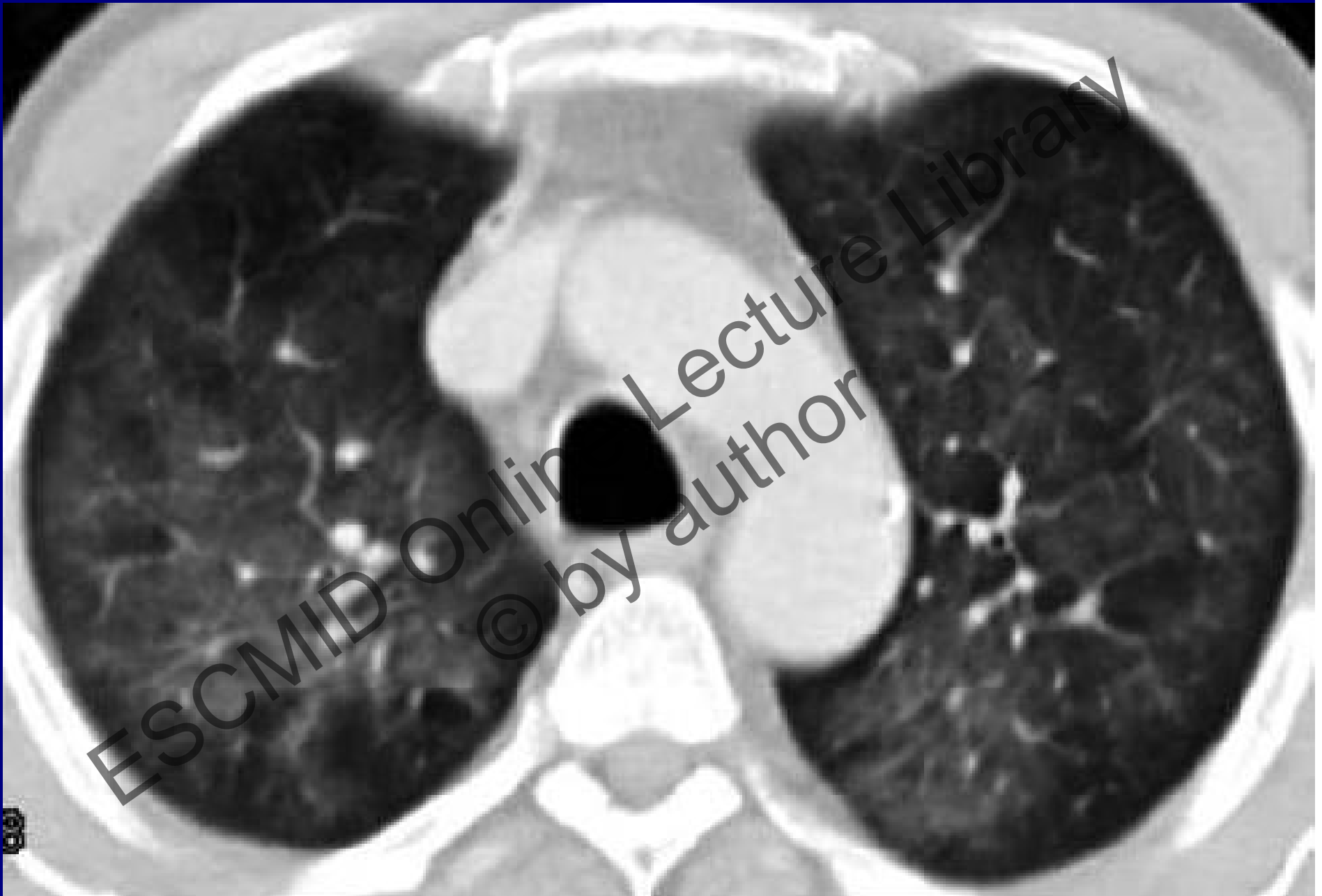
Asterisks represent outliers.

EORTC Classification

Meersseman W et al,
Am J Respir Crit Care Med 2008;177:27–34

CRYPTOCOCCUS

- cryptococcal lung disease is probably underdiagnosed, and knowledge of epidemiology, diagnosis, and treatment is necessary.
- Cryptococcal lung disease ranges from asymptomatic colonization or infection to severe pneumonia with respiratory failure.
- Clinical presentation of pulmonary cryptococcosis is highly variable and often is related to the immune status of the patient.



51-year-old female neutropenic patient

Axial CT image shows bilateral ground glass density in the upper lobes of a 51-year-old female neutropenic patient with *Pneumocystis jiroveci* pneumonia.

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PNEUMOCYSTIS

- *Pneumocystis jiroveci* PCR has higher sensitivity than conventional stains but cannot distinguish colonization from infection.
- **METHODS:** We compared *P jiroveci* PCR and conventional stains in HIV-uninfected immunocompromised patients.
- **RESULTS:** Among the 448 patients, 296 (66%) patients had hematologic malignancies; 72 (16.1%), bone marrow transplants; 44 (9.8%), solid tumors; 21 (4.7%), renal transplants; and 15 (3.4%) were taking immunosuppressants for systemic diseases.
- Diagnostic strategy consisted of BAL in 351 patients and induced sputum (IS) in 97 patients. Conventional pneumocystic pneumonia (PCP) stain was positive in 39 (8.7%) patients,
- **PCR was 87.2% sensitive and 92.2% specific; positive and negative predictive values were 51.5% and 98.7%, respectively. Sensitivity and negative predictive value were 100% on IS.**
- **CONCLUSIONS:** In HIV-uninfected immunocompromised patients with acute pulmonary infiltrates, *P jiroveci* PCR correlates with clinical evidence of PCP. A negative PCR allows withdrawing anti-PCP therapy

Azoulay E et al. Chest. 2009;135:655-61.

Laboratory diagnosis of cytomegalovirus infection and disease in immunocompromised patients.

- **RECENT FINDINGS:** This review summarizes the attempts to use real time PCR for cytomegalovirus deoxyribonucleic acidemia and to compare it to conventional PCR and antigenemia, it also reviews the use of quantitative PCR on bronchoalveolar lavage to assist in the diagnosis of CMV pneumonia. Phenotypic assays of susceptibility in tissue culture are much too slow to assist clinical decisions, taking weeks for completion. Genotypic assays may be performed directly on clinical samples such as blood, and cerebrospinal fluid and can be done by sequencing in a very few days. Finally, assays of lymphocytic functional responsiveness to cytomegalovirus can be used to identify transplant recipients at continuing risk for cytomegalovirus disease. **SUMMARY:** Assays for CMV DNA or antigen in blood are superior to culture for documenting viremia and pneumonia. Genotypic assays have largely replaced phenotypic assays for CMV resistance to antivirals. Lymphocyte responses to CMV antigen(s) may identify patients at risk for CMV disease.

Drew WL. Curr Opin Infect Dis. 2007 Aug;20(4):408-11.