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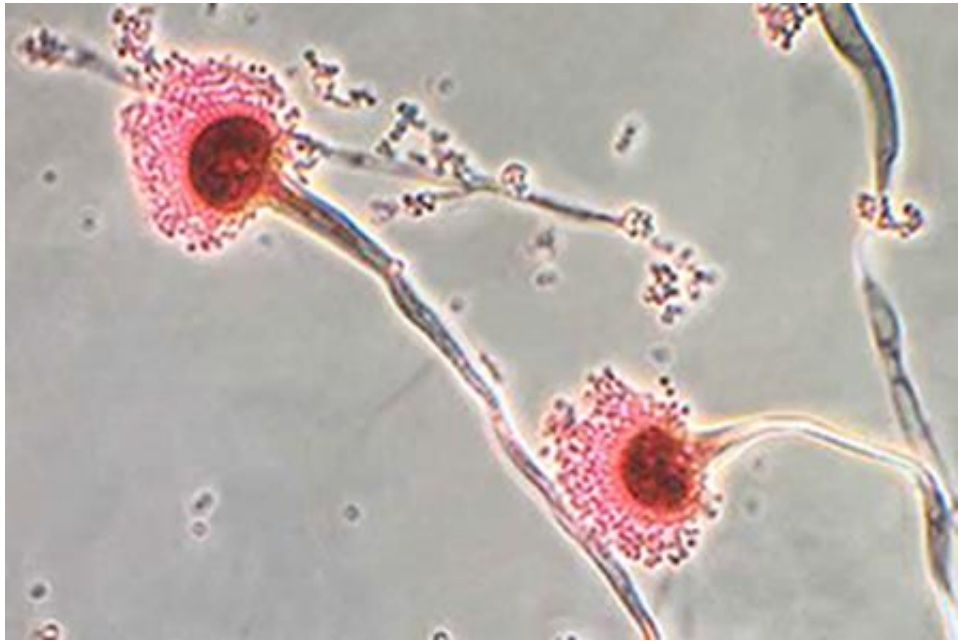
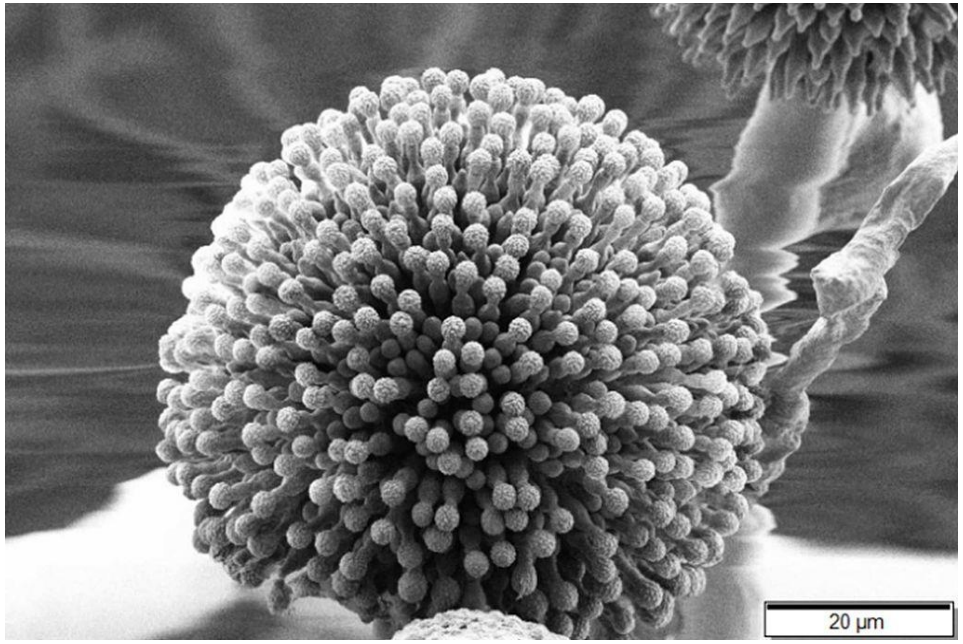
DIAGNOSIS, PREVENTION, AND TREATMENT OF INVASIVE FUNGAL DISEASES IN PAEDIATRIC PATIENTS

DIFFERENT TYPES OF *Aspergillus*

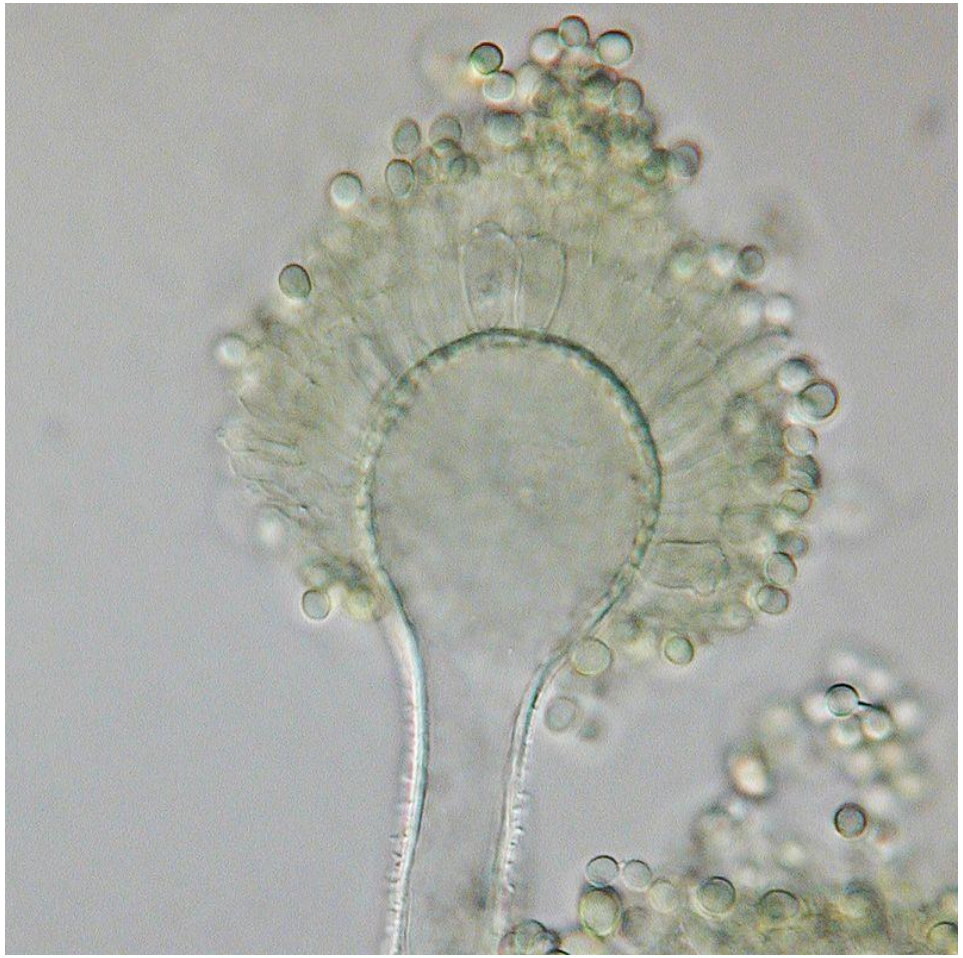
- Aspergillus fumigatus
- Aspergillus niger
- Aspergillus flavus
- Aspergillus terreus



Aspergillus fumigatus



*Aspergillus **niger***

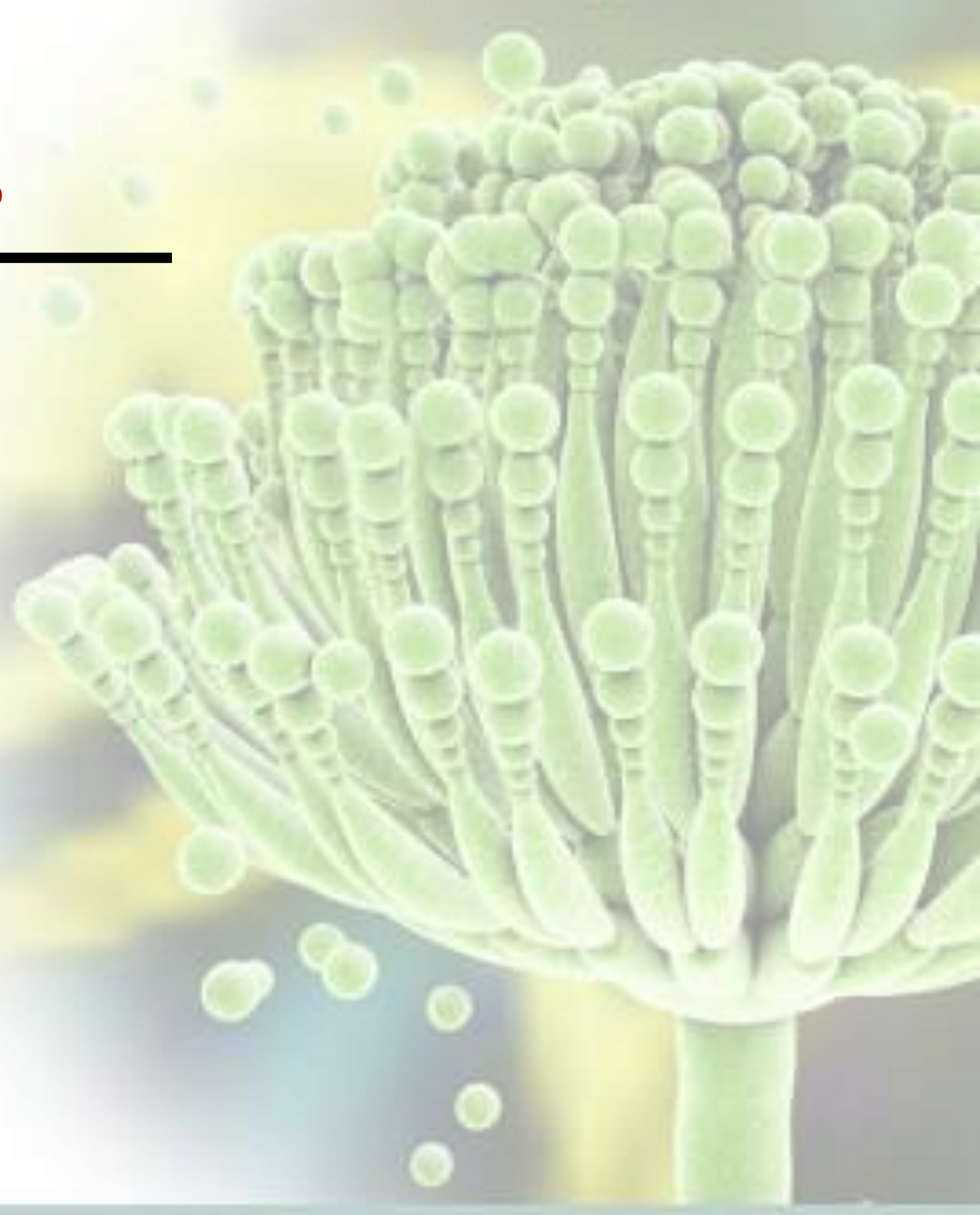


Aspergillus flavus

Aspergillus terreus

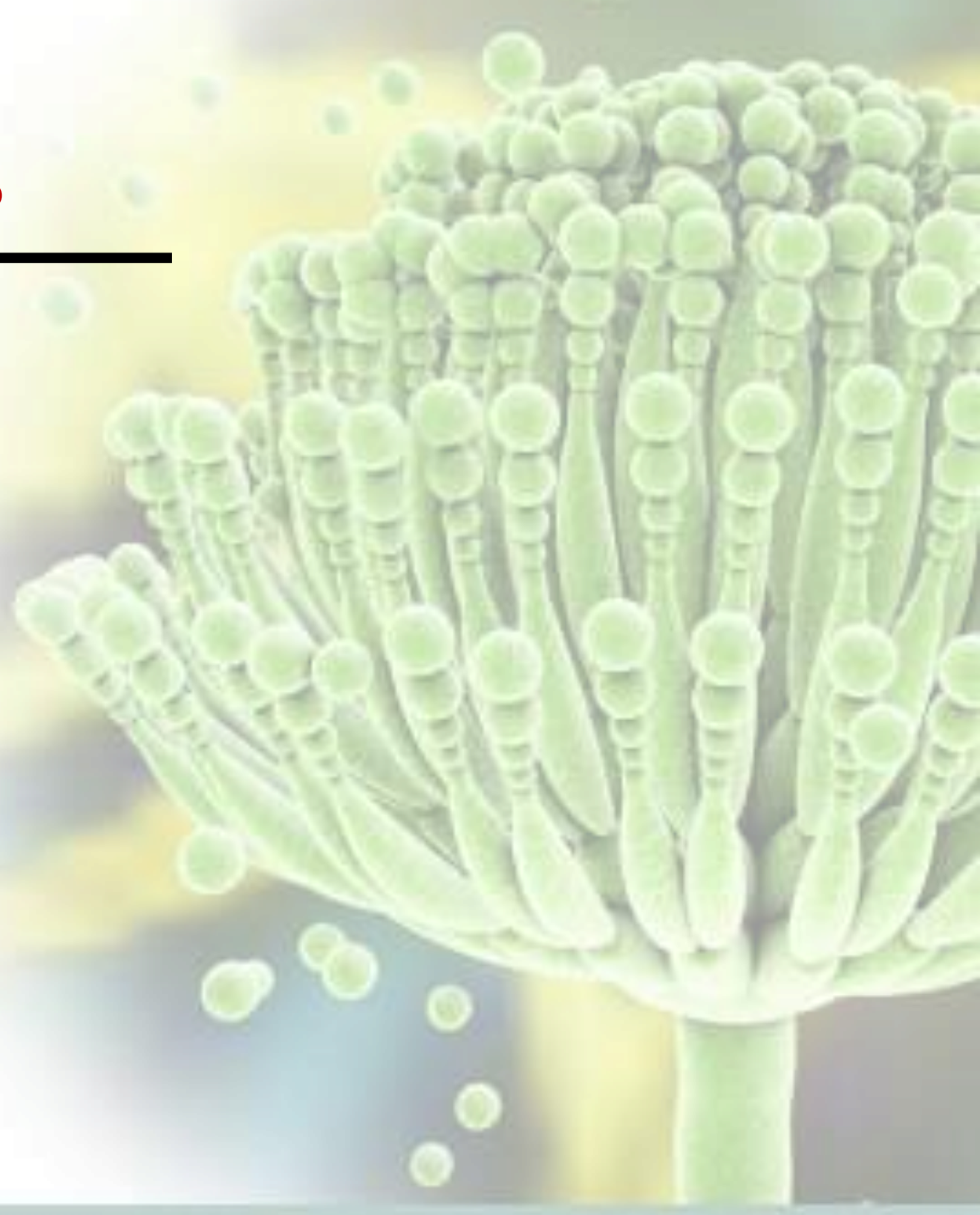
Sources of Aspergillosis

- Aspergillus lives in the environment
- Aspergillus, the mold (a type of fungus) that causes aspergillosis, is very common both indoors and outdoors, so most people breathe in fungal spores every day



Sources of Aspergillosis

- Soil
- Plants and in decaying plant matter
- Household dust
- Building materials
- Spices & some food items



Invasive Aspergillosis

- A disease that usually affects people with immune system problems
- The fungus invades and damages tissues in the body
- Most commonly affects the lungs, but can also cause infection in many other organs & can spread throughout the body

Mode of Transmission

- Inhalation of *Aspergillus* spores (i.e., in a very dusty environment) can lead to infection
- Studies have shown that invasive aspergillosis can occur during building renovation or construction
- Outbreaks of *Aspergillus* skin infections have been traced to contaminated biomedical devices

Protective environment

American Journal of Hematology 66:257–262 (2001)

Invasive Pulmonary Aspergillosis in Neutropenic Patients During Hospital Construction: Before and After Chemoprophylaxis and Institution of HEPA Filters

Period 1 included 4 months, during which adult patients with AL were treated with intensive chemotherapy while housed in a regular ward without any form of Aspergillus prophylaxis

Period 2 covered the 18 months thereafter, during which adult patients with AL were treated with intensive chemotherapy while housed in a regular ward but received chemoprophylaxis with IV continuous low-dose (20 mg/day) AB starting with chemotherapy and until resolution of neutropenia

Period 3 included 36 months,
AL patients were hospitalized and treated in a regular ward (group 3-a)
AL patients were hospitalized and treated in a new ward (group 3-b)

Incidence of Invasive Pulmonary Aspergillosis (IPA) in Different Periods and Groups in Acute Leukemia (AL) Patients According to Length of Neutropic Episodes (NE)

		Patients with IPA		Patients without IPA		
		No. (%) of patients	Median (range) length of NE (days)	No. (%) of patients	Median (range) length of NE (days)	*P*
Period 1	Group 1	6 (50)	20 (12–42)	6 (50)	12 (7–22)	0.0029[a]
Period 2	Group 2	12 (43) $P = 0.95$[e]	22 (15–30)	16 (57)	13 (5–40)	0.0001[b]
Period 3	Group 3-a	13 (29) $P = 0.19$[f]	21 (7–120)	32 (71)	13 (5–40)	0.001[c]
	Group 3-b	0 $P = 0.0003$[g]	–	26 (100)	15 (7–42)	0.65[d]

[a] *P* for comparing median length of NE between patients with IPA and those without in group 1.
[b] *P* for comparing median length of NE between patients with IPA and those without in group 2.
[c] *P* for comparing median length of NE between patients with IPA and those without in group 3-a.
[d] *P* for comparing median length of NE between patients in group 3-a and group 3-b.
[e] *P* for the difference in IPA incidence between group 1 and group 2.
[f] *P* for the difference in IPA incidence between group 1 and group 3-a.
[g] *P* for the difference in IPA incidence between group 1 and group 3-b.

Clinical signs and symptoms

Invasive Pulmonary Aspergillosis (IPA)

- The clinical manifestations early in the course of disease are often muted because of inadequate inflammatory responses. Over time, as IPA progresses, the clinical manifestations evolve and become more pronounced

Clinical signs and symptoms

- Many of the clinical manifestations of IPA are not specific for IPA and may be present in a variety of other infectious syndromes

Clinical signs and symptoms

- Fever (85%)
- Cough
- Shortness of breath
- Chest pain (60%)
- Hemoptysis (40%)

Clinical signs and symptoms

- IPA is rarely the cause of fever early in the course of neutropenia. More commonly, IPA is a cause of persistent or recurrent fever later during neutropenia. Onset of IPA most frequently occurs after 2 weeks of neutropenia, substantially later than most bacterial infections

Clinical signs and symptoms

- Cough is a frequent symptom
- Dyspnea and sputum production are variable accompaniments
- More specific symptoms are hemoptysis and pleuritic pain (compare with bacterial pneumonia)

Clinical signs and symptoms

- Signs of pulmonary consolidation on auscultation, especially rales
- A pleural friction rub is a more specific sign although present only in a minority of cases

HELPFUL CLUES

- The presence of certain individual findings, certain combinations of factors, and the duration of some factors are more likely to be found in patients with IPA than in patients without IPA

- Patients with IPA had a longer duration of neutropenia, more febrile days, more febrile episodes without an etiology established, and more febrile days on antibiotics

Clinical criteria characteristic of *Aspergillus* pneumonia in neutropenic patients with acute leukemia*

Elevated temperature
Neutropenic days > 30
Two or more febrile episodes without a source
Fourteen or more febrile days without a source
Nineteen or more days of fever during antibiotic therapy
Rales in the absence of volume overload
Nasal eschar, ulcer, or discharge plus epistaxis plus sinus tenderness
Pleuritic chest pain
Onset of pulmonary infiltrate after 14th day
Multi-lobed pulmonary infiltrate on radiography
Cavity or nodules on chest radiography

* The presence of four or more of the individual factors was found to be present in patients with IPA

Clinical and radiographic findings likely to be found early and later during invasive pulmonary aspergillosis

	Early IPA	Advanced IPA
Likely clinical findings	Fever	Fever Cough Dyspnoea Sputum Haemoptysis Pleuritic pain Pleural friction rub
Likely radiographic findings	Macronodule(s)	"Non-specific" nodular/localised infiltrates, often multi-lobar
	Halo sign	Air crescent sign

Incubation Period

- Incubation time varies depending on host factors & exposure characteristics

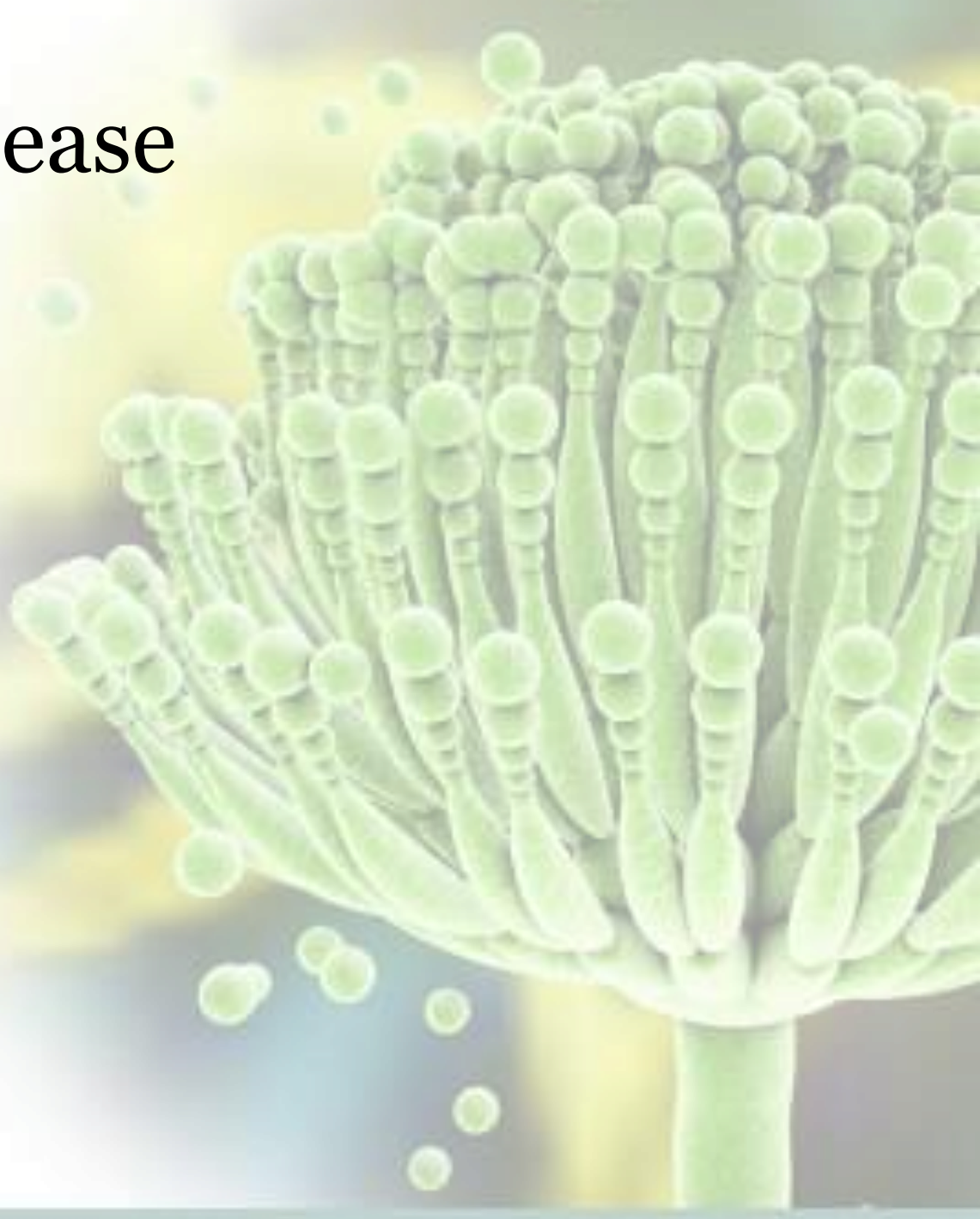
Defining invasive fungal disease

Defining invasive fungal disease

Host factor

- Neutropenia
- Corticosteroids
- Allogeneic HSCT recipient
- T-cell immune suppressants
- Inherited severe immunodeficiency

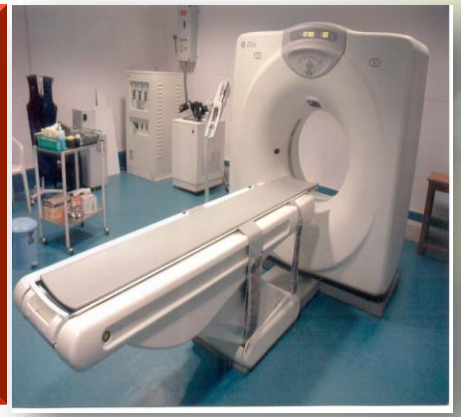
IFD probability



Defining invasive fungal disease

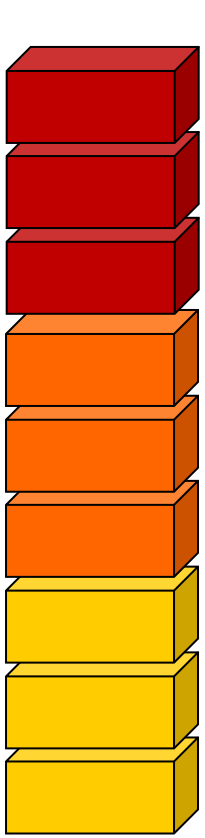
Host factor

Clinical feature



IFD probability

Defining invasive fungal disease



Host factor

Clinical feature

Mycology

IFD probability

Risk factors associated with Aspergillus infection

RISK FACTORS OF IFD

- Underlying diagnosis:
  - AML more than ALL
  - HSCT (severe aplastic anemia, Fanconi anemia)
- Neutropenia:
  - ANC< 100 cells/µL
  - duration > 28 days
  - neutropenia at the start of chemotherapy for leukemia

Journal of the Pediatric Infectious Diseases Society 2018;7(3):191–8

RISK FACTORS OF IFD

- Exposure to corticosteroid (high-dose, prolonged)
- Chemotherapy regimen:
  - intensive-induction timing vs standard-timing in AML
  - relapse vs front-line chemotherapy in AML
  - reduced-intensity conditioning regimen in allogenic HSCT
- GVHD: severe acute GVHD, chronic GVHD
- Age: > 7.5-10 years

Journal of the Pediatric Infectious Diseases Society 2018;7(3):191–8

Diagnosis of Aspergillus infection

Recommendations for Fungal infections diagnosis

- Direct microscopy, preferably using optical brighteners
- Histopathology
- Culture are strongly recommended
- Non- culture
  - Serum/BAL galactomannan
  - β-D-Glucan
  - LFD
  - PCR should be considered in conjunction with other diagnostic tests
- Pathogen identification to species complex level is strongly recommended for all clinically relevant isolates
- Antifungal susceptibility testing should be performed in patients with invasive disease in regions with resistance found in contemporary surveillance programs

Aspergillus Galactomannan EIA clinical utility

- Used in conjunction with other diagnostic procedures to aid in the diagnosis of Invasive Aspergillosis:
  - microbiological culture
  - histological examination of biopsy specimens
  - radiographic evidence

KEY BENEFITS

- Screening high-risk patients with Aspergillus EIA, twice-weekly, provides early diagnosis of IA
- GM Ag was positive 6-10 days before onset of clinical signs
- GM positivity preceded positivity of CT-Scan or culture by >1 week
- Aspergillus EIA was most sensitive (compared to RT-PCR and β-D-glucan) at predicting the diagnosis of IA in patients with hematologic disorder

Comparison to other diagnostic methods

Diagnostic Method	Sensitivity	Specificity
Chest Radiograph	94%	60%
CT-Scan (any abnormality)	78%	7%
CT-Scan (halo sign)	28%	93%
Culture (BAL)	50%	92%
GM EIA :		
Single sample ≥ 1.5	94%	85%
2 consecutive samples ≥ 1.5	94%	99%

J. Maertens JID 2002

Screen & Diagnose of IA in High-Risk patients

- **For maximum sensitivity,** the test should be performed at **least twice-weekly during hospitalization. For all positive patients,** it is recommended that **a new aliquot of the same sample** be repeated as well as **collection of a new sample** from the patient

- According to the **EORTC/MSG criteria, two consecutive positive results** are required for classification as **true positive.** In daily practice, it is important that physicians submit a **follow-up specimen** upon receipt of the initial positive result, ideally **before initiating antifungal therapy** to achieve **the highest specificity** using the test

Specimen type & specimen handling

- **Serum**:
- Collect 3 to 5 ml blood specimen in a serum separator tube (SST) without anti-coagulants
- Allow specimen to clot, then centrifuge specimen within 2 hours of the draw to pellet cells below the gel
- Minimum volume of 1.0 ml serum following centrifugation is required
- Specimen should be stored at 2 to 8° C or frozen in a non-self-defrosting freezer & shipped with frozen gel packs or dry ice for overnight delivery

Specimen type & specimen handling

- **BAL**:
- 1 to 3 ml collected in a sterile, screw-cap tube
- specimen should be stored at 2 to 8° C or frozen in a non-self-defrosting freezer
- shipped with frozen gel packs or dry ice for overnight delivery

Causes for rejection of specimen

- **Lipemic, icteric, or hemolyzed specimens**
- **Specimens that have been stored at ambient temperature**
- **Specimens that have been stored at 2 to 8° C for >5 days**
- **If storage longer than 5 days is needed, samples should be frozen at -70° C**

Assay ranges

- The reference range is an index of <0.5
- Numerical index values will be reported
- Patients with an index of >0.5 are considered to be positive for galactomannan antigen
- Patients with an index of <0.5 are considered to be negative for galactomannan antigen

False-positive galactomannan test results

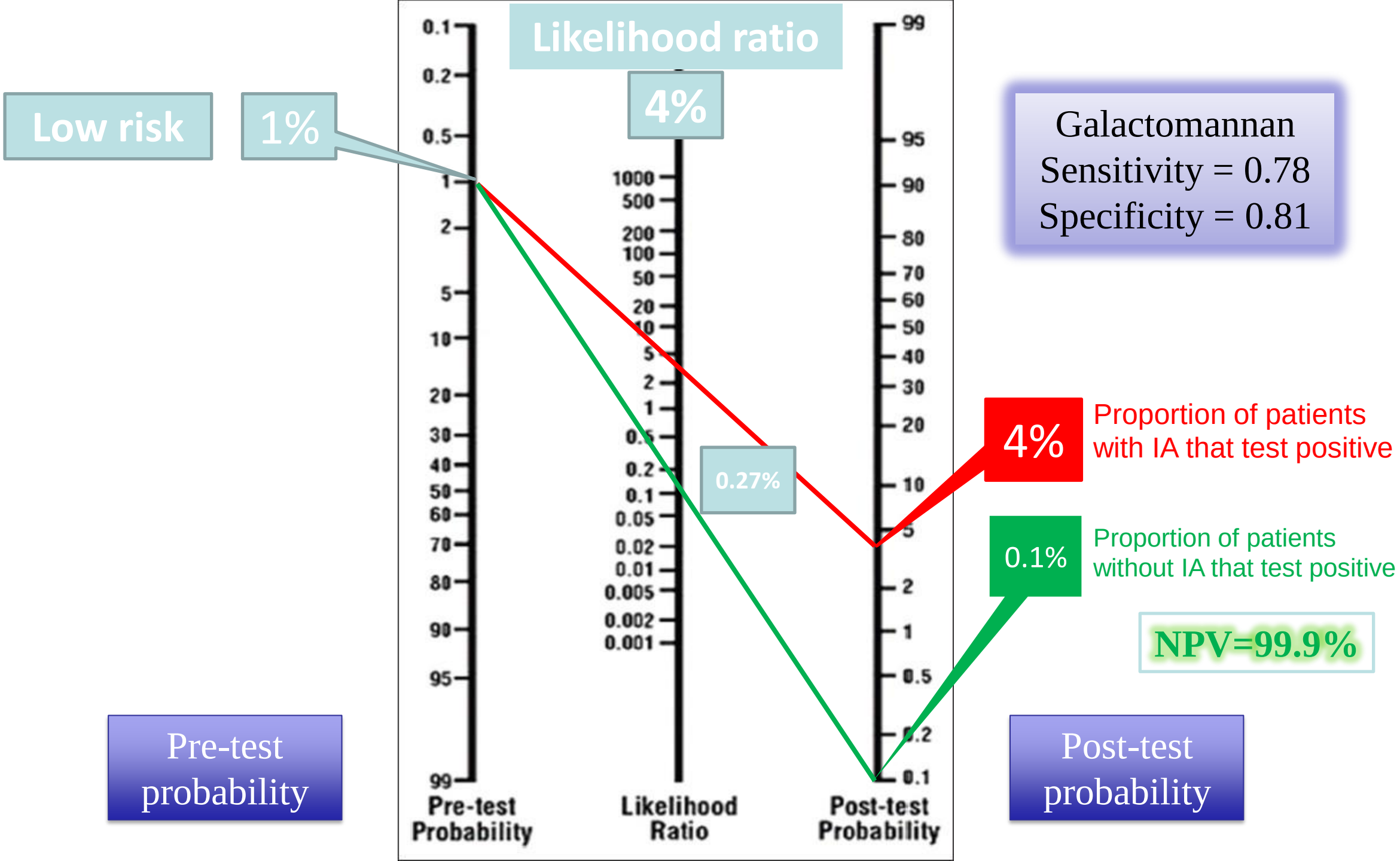
- patients receiving **piperacillin/tazobactam**; interpret results in these patients with caution & confirm with other diagnostic methods
- Patients with intestinal mucositis caused by chemotherapy, irradiation, which allows for extra absorption of dietary galactomannan

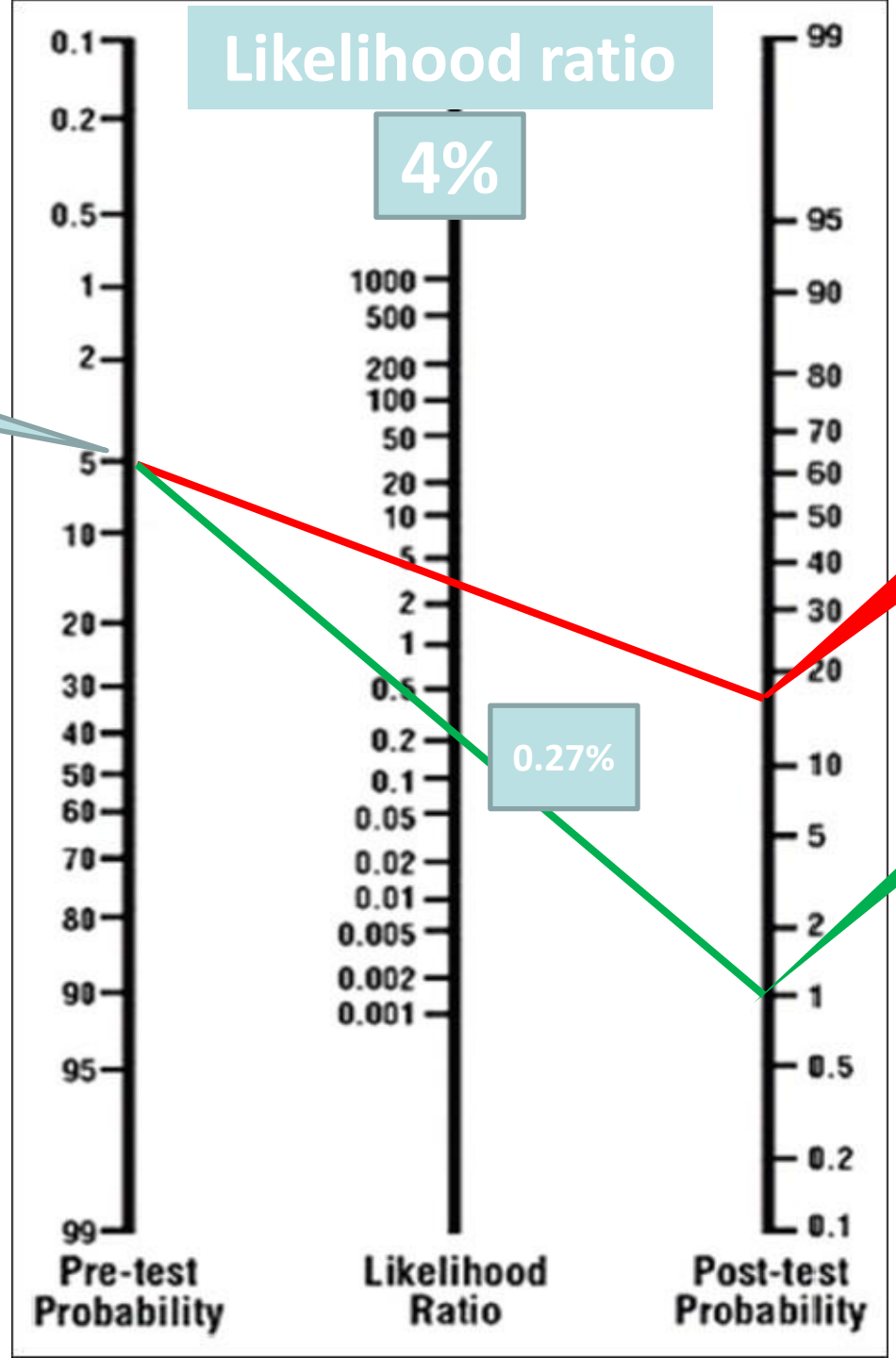
Fungal pathogen	1, 3 β-D-glucan	Galactomannan
Aspergillosis	✓	✓
Candida spp.	✓	✗
Pneumocystis jirovecii	✓	✗
Mucormycosis	✗	✗
Cryptococcosis	✗	✗

GM TEST INTERPRETATION

Optimal use of GM

1. Exclude IA when the prevalence is low (<5%) (NPP ✚ ✚ ✚); **Screening role**
2. Confirm IA when the prevalence is high (>20%) (PPV ✚ ✚ ✚); **Diagnostic role**
3. Monitoring response (repeated detection indicates failure)


Low risk
1%
Likelihood ratio
4%
0.27%
Galactomannan
Sensitivity = 0.78
Specificity = 0.81
4%
Proportion of patients with IA that test positive
0.1%
Proportion of patients without IA that test positive
NPV=99.9%
Pre-test probability
Post-test probability
Pre-test Probability
Likelihood Ratio
Post-test Probability



Intermediate risk

5%

Galactomannan
Sensitivity = 0.78
Specificity = 0.81

18%

Proportion of patients with IA that test positive

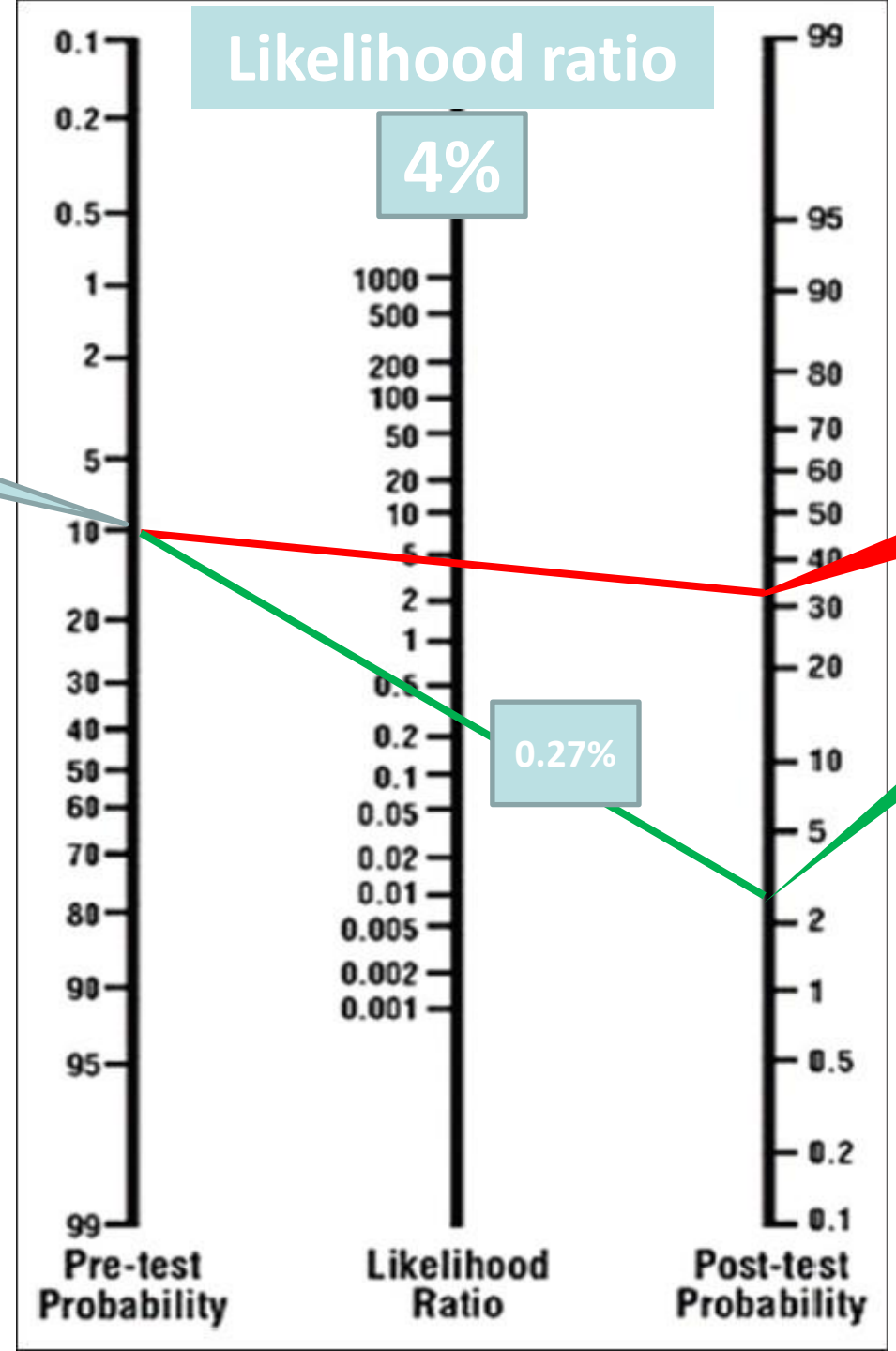
1%

Proportion of patients without IA that test positive

NPV=99%

Pre-test probability

Post-test probability



High risk

10%

Galactomannan
Sensitivity = 0.78
Specificity = 0.81

31%

Proportion of patients with IA that test positive

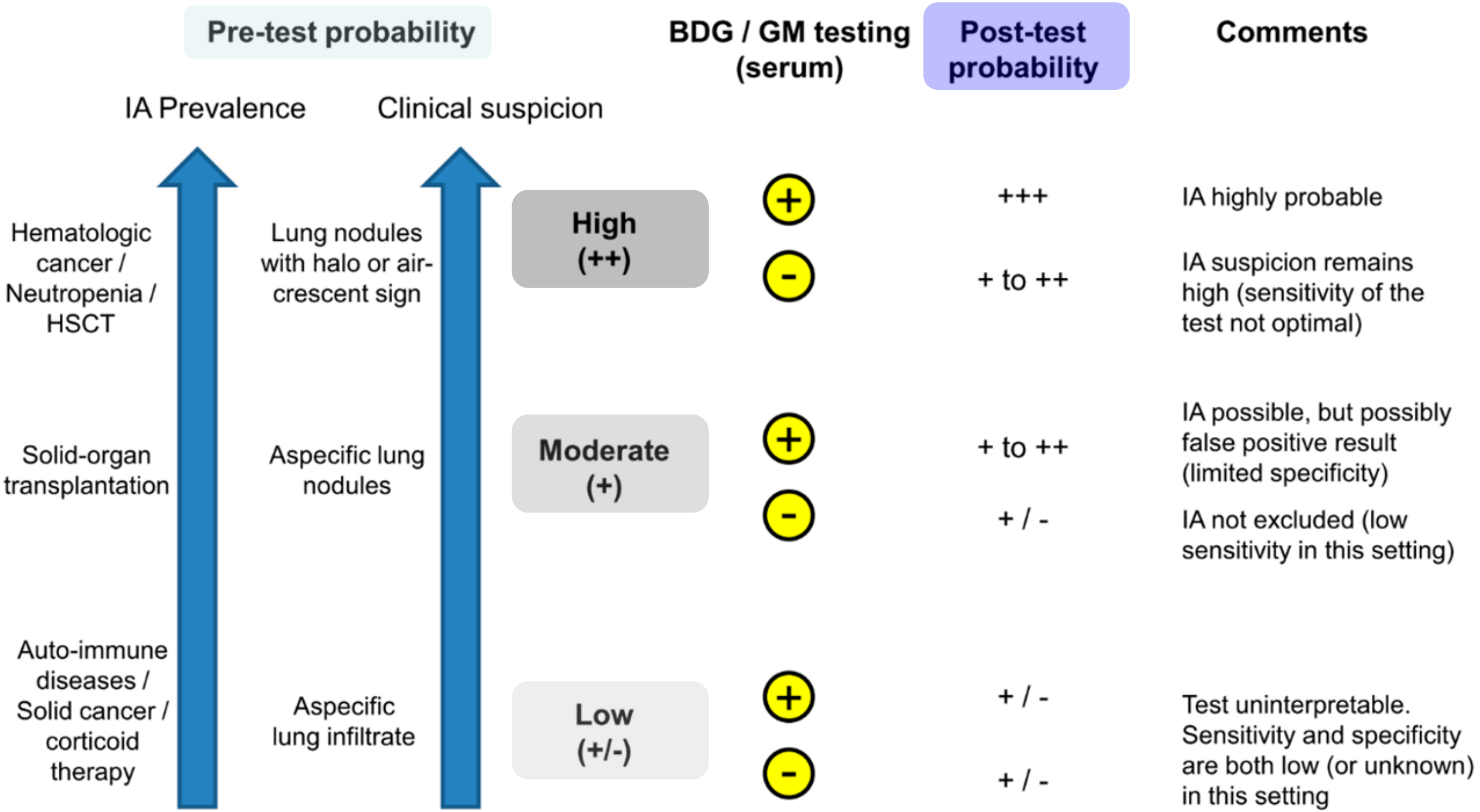
3%

Proportion of patients without IA that test positive

NPV=97%

Pre-test probability

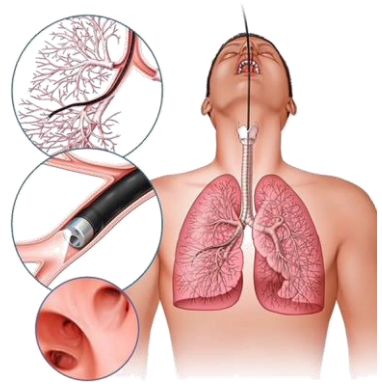
Post-test probability


Pre-test probability
BDG / GM testing (serum)
Post-test probability
Comments
IA Prevalence
Clinical suspicion
Hematologic cancer / Neutropenia / HSCT
Lung nodules with halo or air-crescent sign
High (++)
+
+++
IA highly probable
-
+ to ++
IA suspicion remains high (sensitivity of the test not optimal)
Solid-organ transplantation
Aspecific lung nodules
Moderate (+)
+
+ to ++
IA possible, but possibly false positive result (limited specificity)
-
+ / -
IA not excluded (low sensitivity in this setting)
Auto-immune diseases / Solid cancer / corticoid therapy
Aspecific lung infiltrate
Low (+/-)
+
+ / -
Test uninterpretable. Sensitivity and specificity are both low (or unknown) in this setting
-
+ / -

DETECTION OF FUNGAL NUCLEIC ACIDS

Acceptable specimens

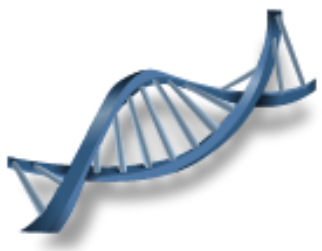
- To confirm the microbiological diagnosis
  - Blood
  - Bronchoalveolar lavage fluid



- For species identification in frozen tissue
  - when molds or yeasts are seen in formalin-fixed paraffin-embedded tissue

UTILITY OF PCR-BASED METHODS

Monitoring versus diagnosis

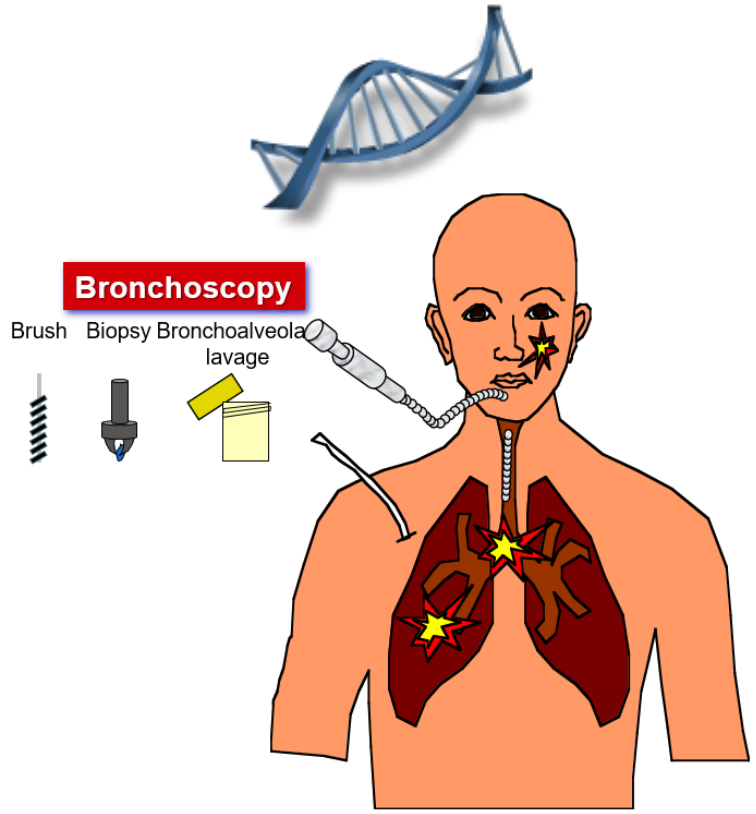


- Pooled sensitivity of 76% (95% CI 62–86%)
- Pooled specificity of 58% (95% CI 42–72%)
- Positive LR: 1.81
- Negative LR: 0.41

PCR-based assays in plasma, serum, or whole blood can be recommended for diagnostic use only, with moderate support (grade B recommendation, level of evidence IIt)

Diagnosis ✓ Monitoring ⊖

- Mold-active antifungal prophylaxis
- Interinstitutional variations in test performance
- Suboptimal specificity



- The use of PCR on bronchoalveolar lavage fluid, diagnostic aspirates, or tissue specimen is strongly recommended whenever the respective specimens are obtained (grade A recommendation, level of evidence IIt)

DIAGNOSTIC IMAGING

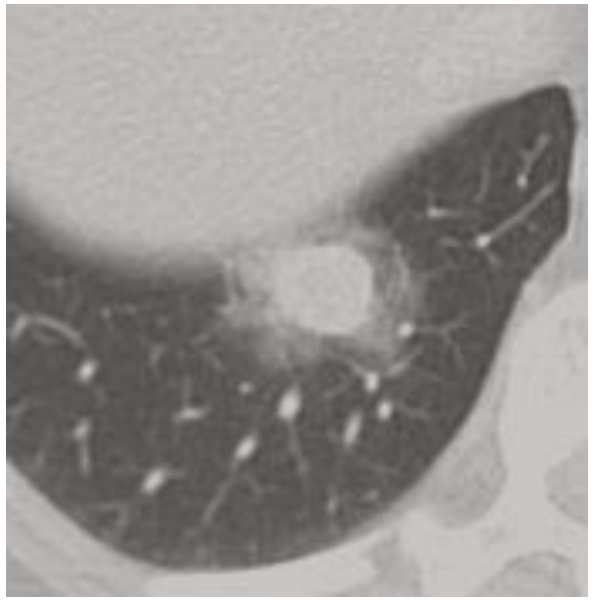
Radiographic manifestations of invasive pulmonary aspergillosis at diagnosis

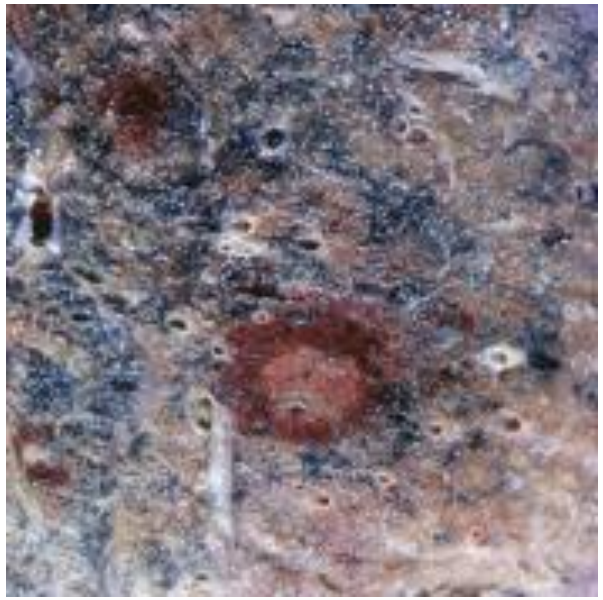
Imaging finding	Percentage of patients with finding
One or more macronodule (>1.0 cm in diameter)	94
Two or more macronodules	79
Halo sign	61
Consolidation	30
Infarct shaped macronodule	27
Cavitary lesion	20
Air bronchograms	16
Clusters of small nodules (<1.0 cm in diameter)	11
Pleural effusion	11
Air crescent sign	10
Non-specific ground-glass opacification	9
Infarct shaped consolidation	8
Small-airway lesions	7
Atelectasis	3
Hilar/mediastinal lesion	2
Pericardial effusion	1

The halo sign

It is typically seen in angioinvasive aspergillosis

- A dense nodule surrounded by a perimeter of ground-glass opacity (due to oedema or hemorrhage)





It was noted in 61% of cases

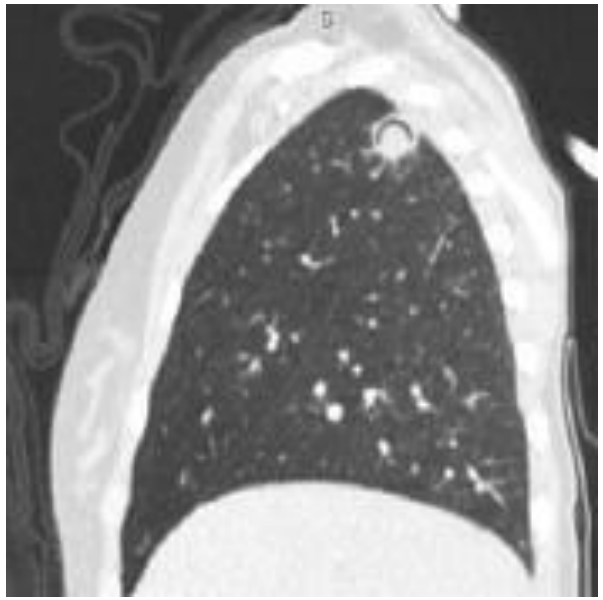
DIFFERENTIAL DIAGNOSIS

- Fungi
  - pulmonary aspergillosis
  - pulmonary mucormycosis
  - pulmonary coccidioidomycosis
  - pulmonary cryptococcosis
  - pulmonary candidiasis
- Mycobacterial
  - pulmonary tuberculosis
  - pulmonary non-tuberculous mycobacterial infection
    - pulmonary *Mycobacterium avium* complex infection

The air crescent sign

It is typically seen in semi-invasive aspergillosis and angioinvasive aspergillosis

- A sequestrum resided in a crescentic pocket of gas surrounded by a rim of viable lung



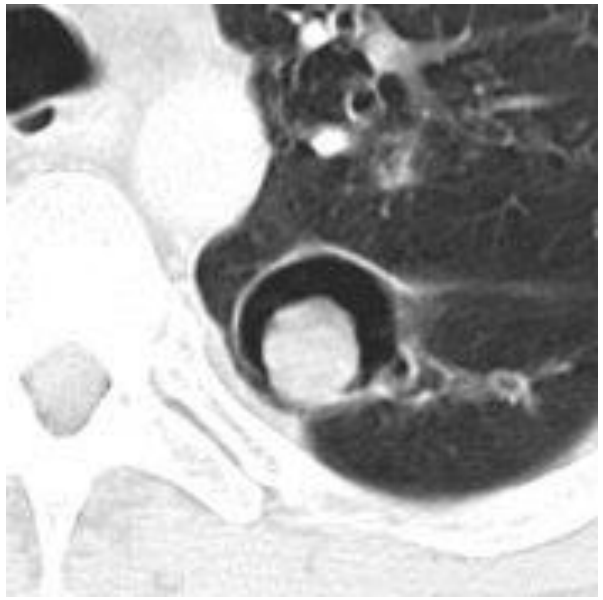
It was noted in 10% of cases
It usually heralds recovery and is the result of increased granulocyte activity

DIFFERENTIAL DIAGNOSIS

- aspergilloma: often described as the Monod sign
- angioinvasive aspergillosis
- hydatid cyst
- other rare causes
  - pulmonary tuberculosis
  - Rasmussen aneurysm in a tuberculous cavity
  - pulmonary abscess
  - lung cancer
  - pulmonary hematoma
  - *Pneumocystis jirovecii* pneumonia (PJP)

The “Monod” (Monad) sign

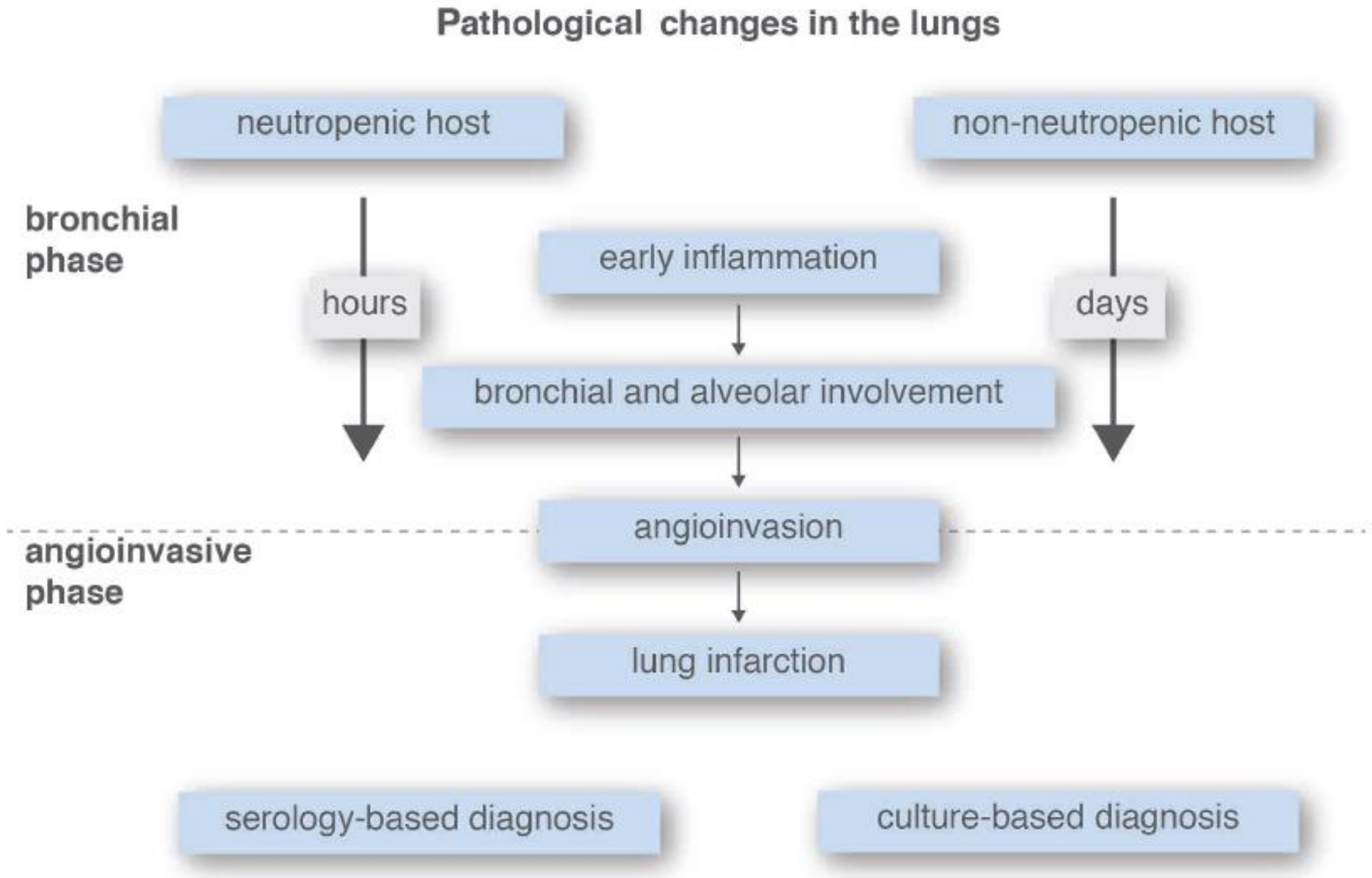
- Gas that surrounds a mycetoma (most commonly an aspergilloma) in a pre-existing pulmonary cavity



The sign implies a freely mobile mass, which moves on mobilizing the patient. This is best demonstrated by acquiring images in a prone position, causing the mass to fall, to a gravity-dependent location and favoring a Monod sign; as compared to an air crescent sign

ADVANTAGES

- Earlier diagnosis of invasive pulmonary aspergillosis
- Improve prognosis
- Useful tool for early response prediction


Pathological changes in the lungs
neutropenic host
non-neutropenic host
bronchial phase
hours
early inflammation
days
bronchial and alveolar involvement
angioinvasion
angioinvasive phase
lung infarction
serology-based diagnosis
culture-based diagnosis

Fact 1

- Positive cultures from respiratory secretions occurred in 83% of patients with radiological signs of bronchoalveolar IPA and in 17% of patients with the angioinvasive form of IPA

Haematologica 1658 | 2013; 98(11)

Fact 2

- Since the angioinvasive phase occurs earlier the more severely neutropenic the patient is, serum galactomannan is more likely to be positive

Haematologica 1658 | 2013; 98(11)

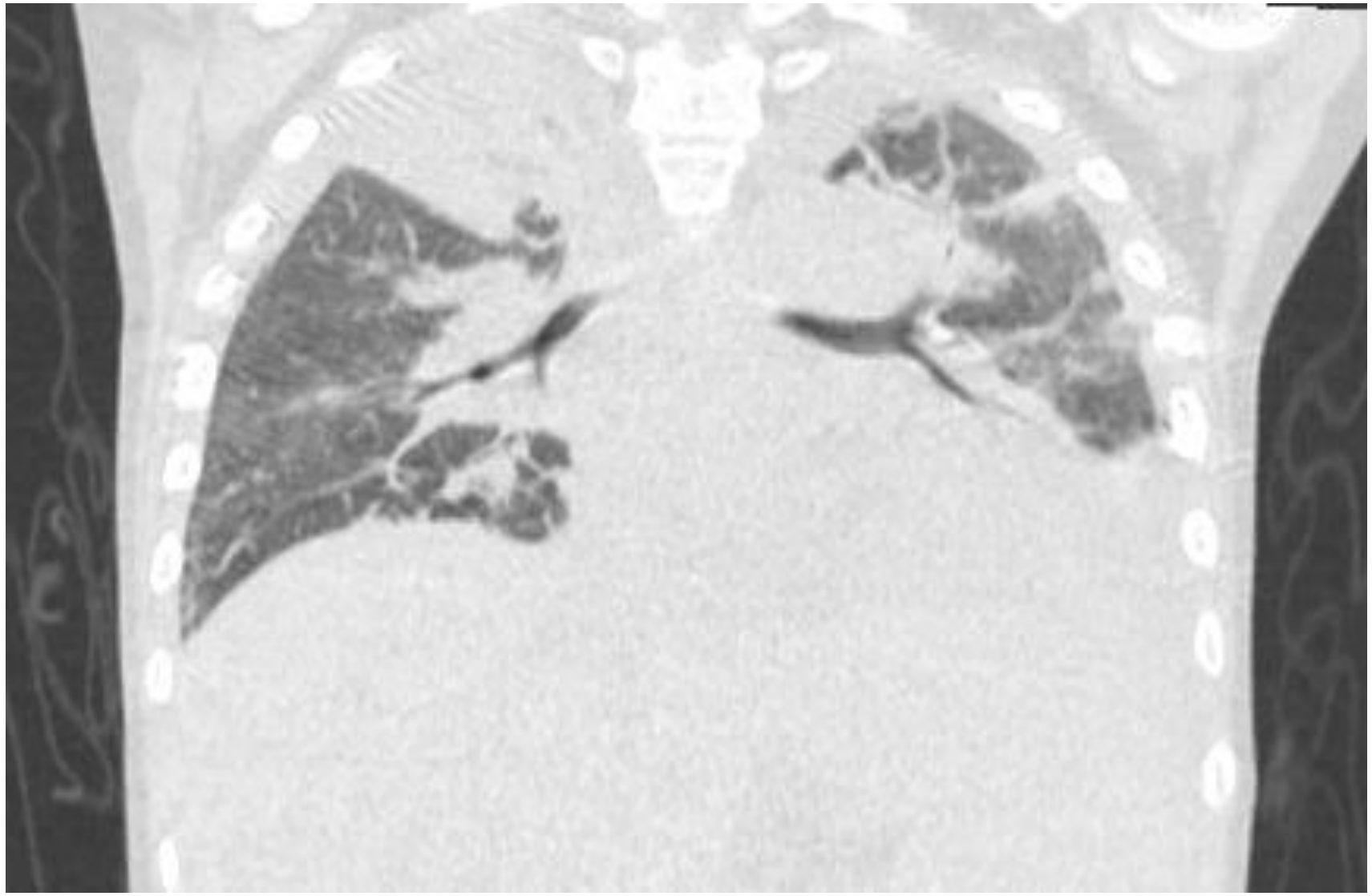
- By contrast, in patients with higher neutrophil counts the angioinvasive phase is delayed (or even does not occur at all) and serum galactomannan is less likely to be positive

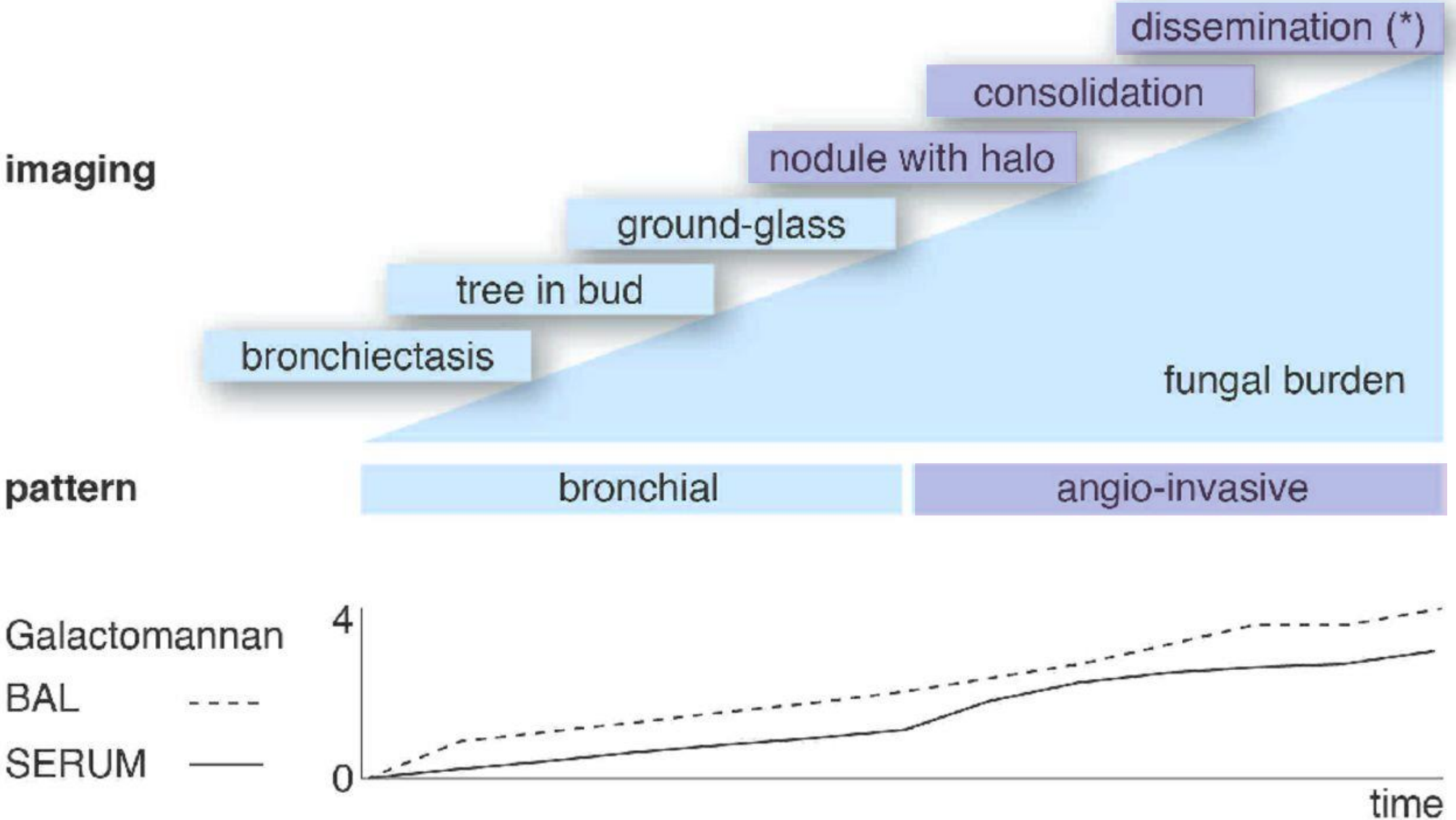
A DIFFERENT CATEGORY OF INVASIVE ASPERGILLOSIS

- Probable invasive aspergillosis without pre-specified radiological findings

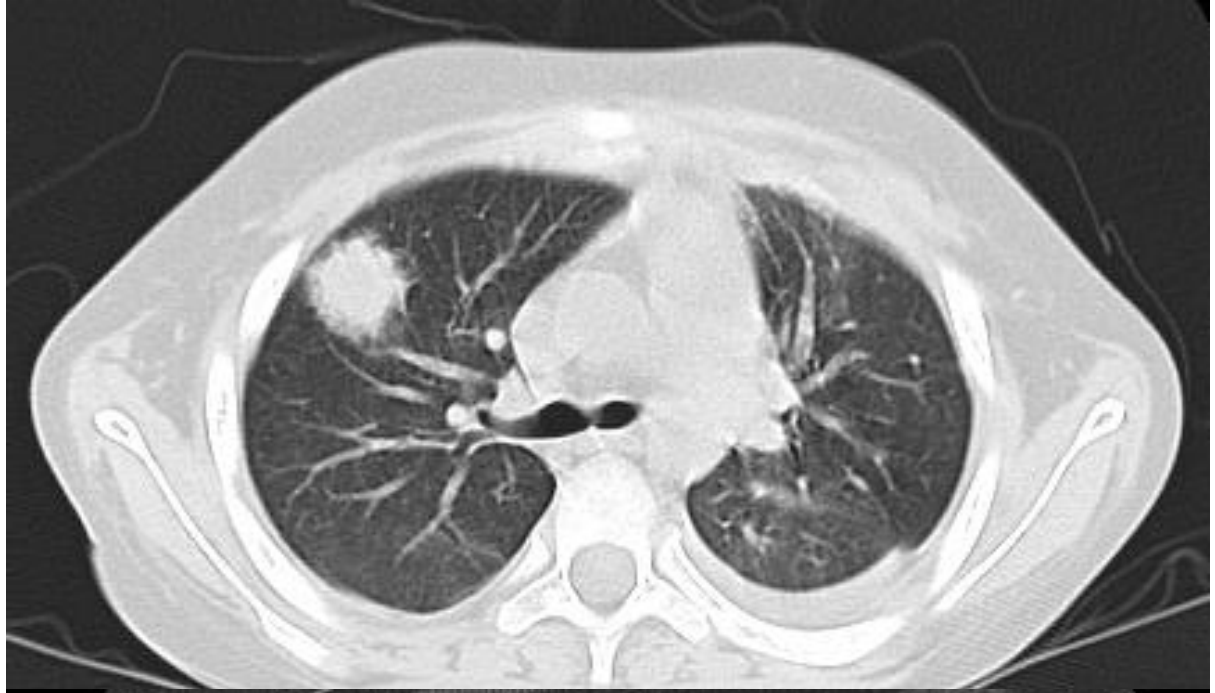
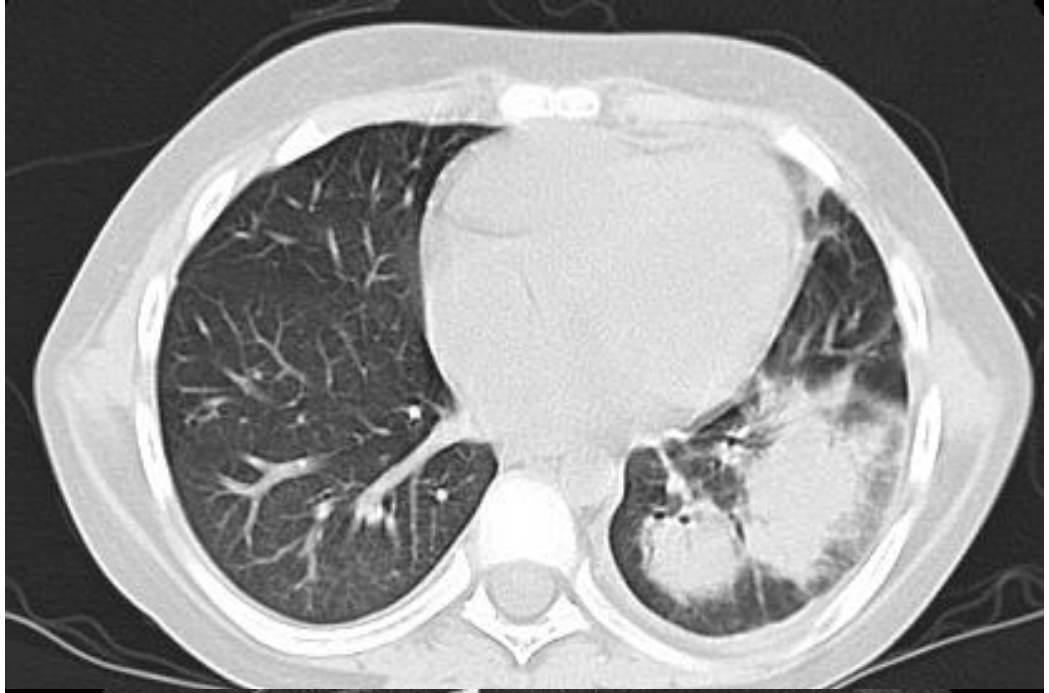
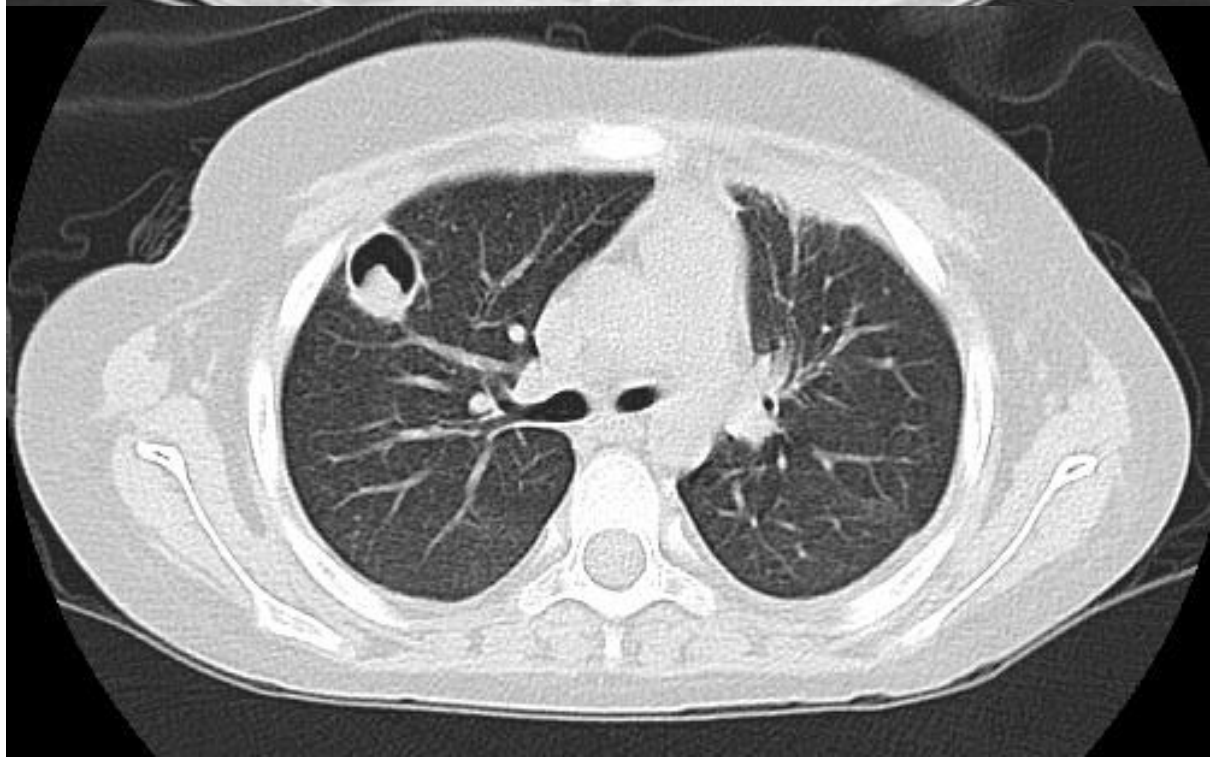
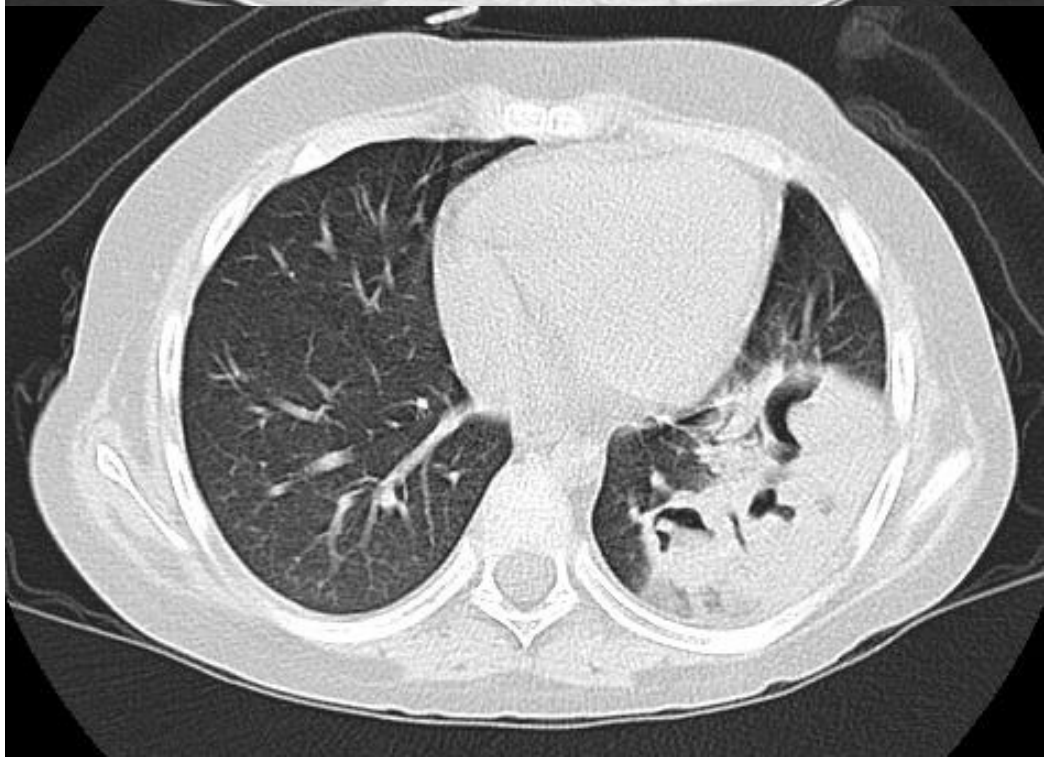
- Radiological findings consisted mostly of ill-defined consolidations and ground-glass infiltrates

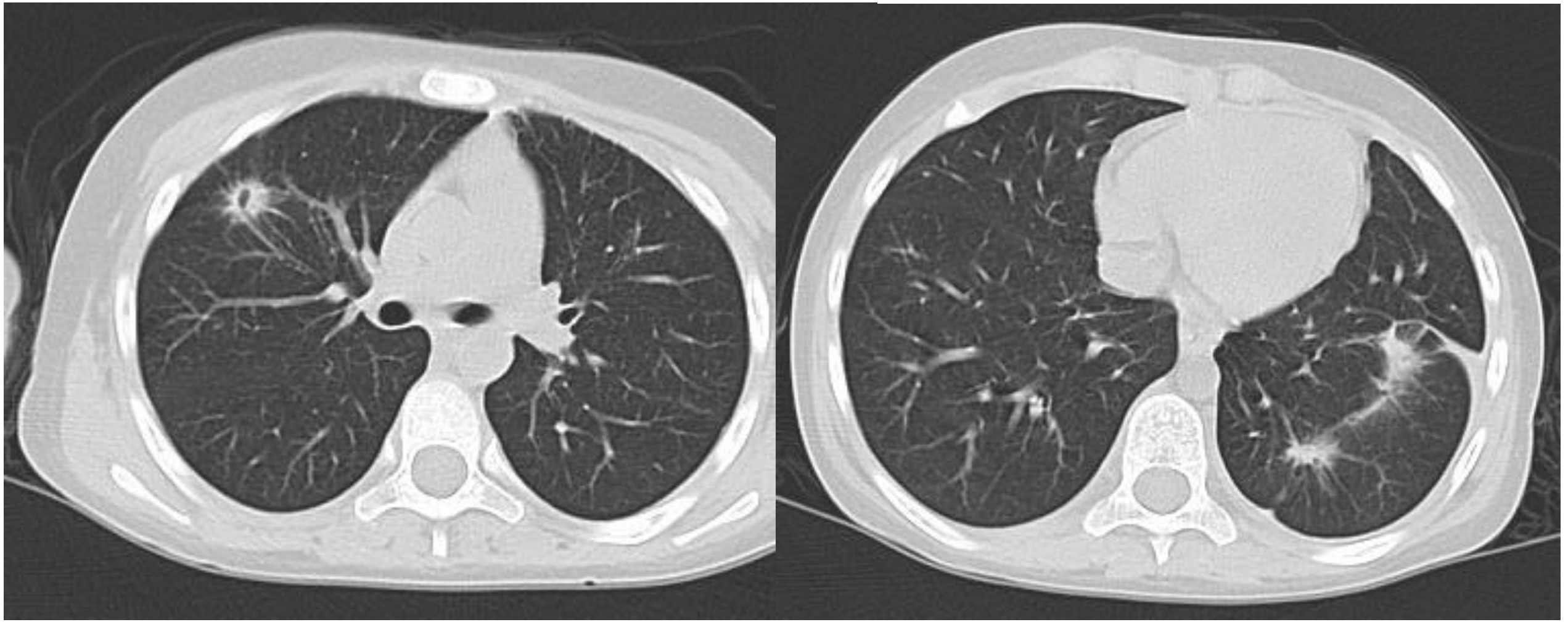
- All clinical and mycological criteria may be similar in non-neutropenic patients, with the exception of the radiological findings
- Marconodules with halo sign were more likely to be present in neutropenic patients
- Repeat imaging usually showed an evolution from the early images to the EORTC/MSG-defined images

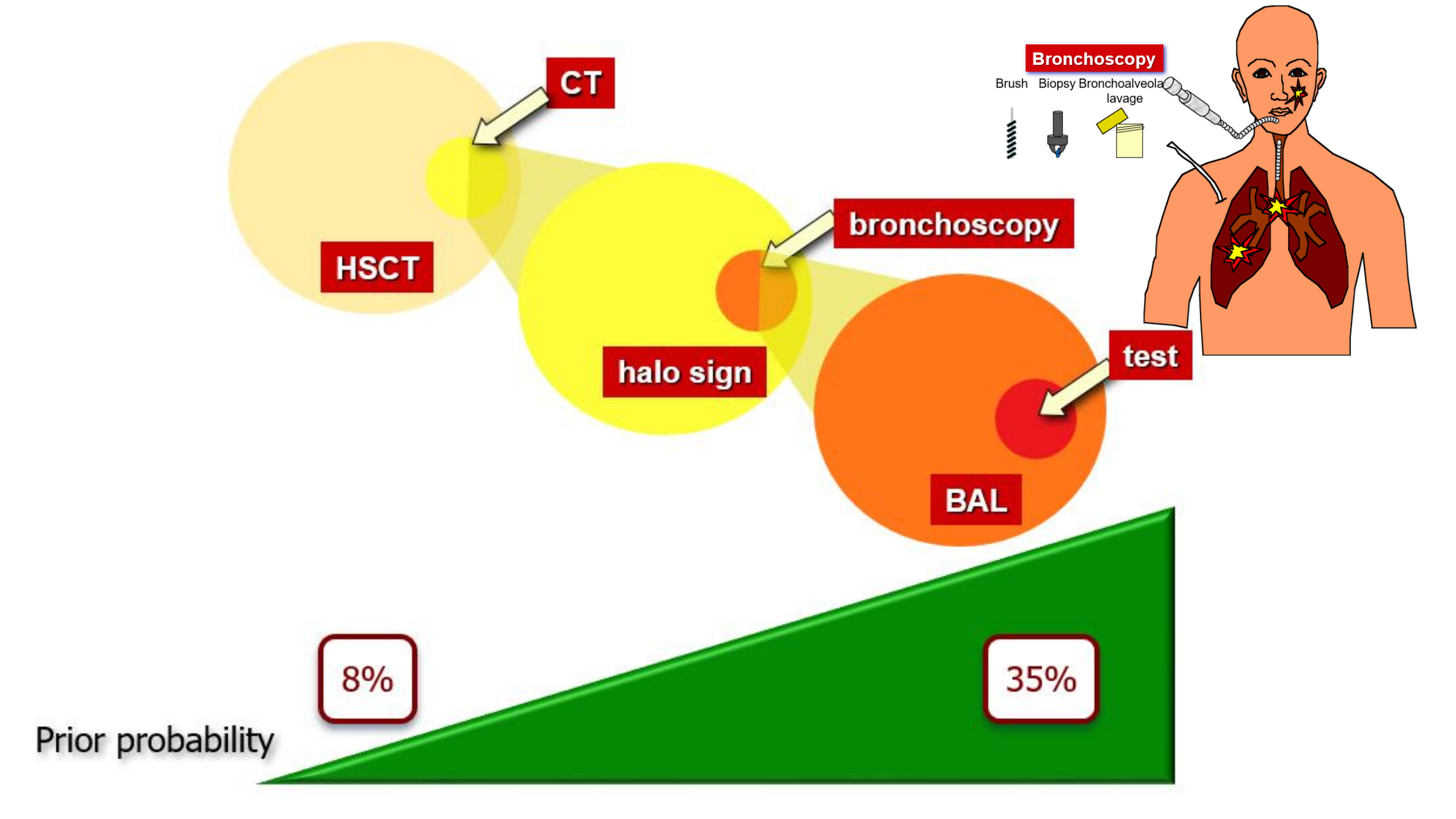


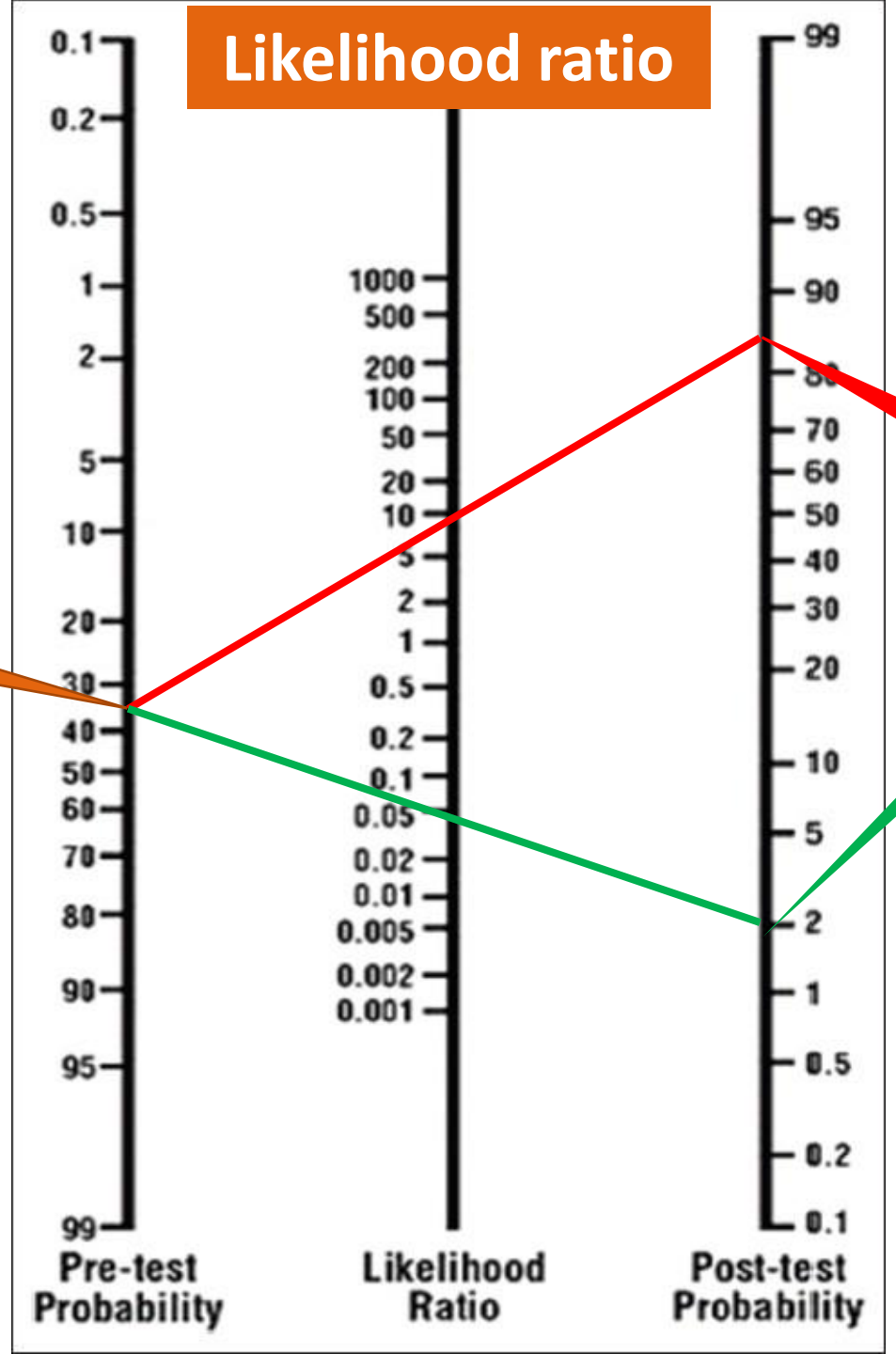


* lesions evolve to air crescent and cavity when neutrophils recover
BAL: bronchoalveolar lavage.




CT
HSCT
bronchoscopy
halo sign
test
BAL
Bronchoscopy
Brush
Biopsy
Bronchoalveolar lavage
8%
35%
Prior probability



BAL

35%

Galactomannan
Sensitivity = 0.97
Specificity = 0.90

80%

Proportion of patients with IA that test positive

2%

Proportion of patients without IA that test positive

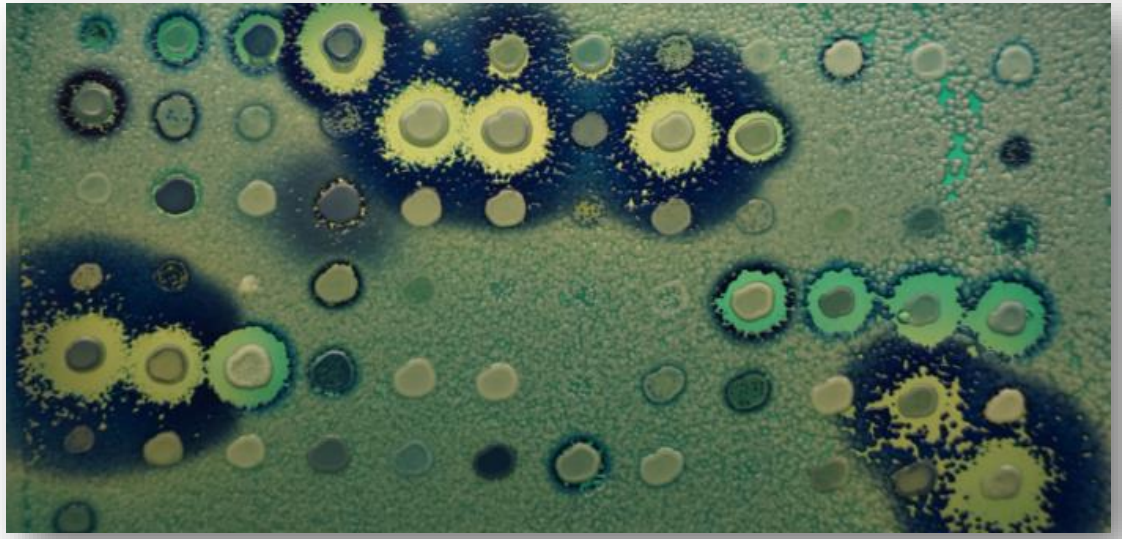
NPV=98%

Pre-test probability

Post-test probability

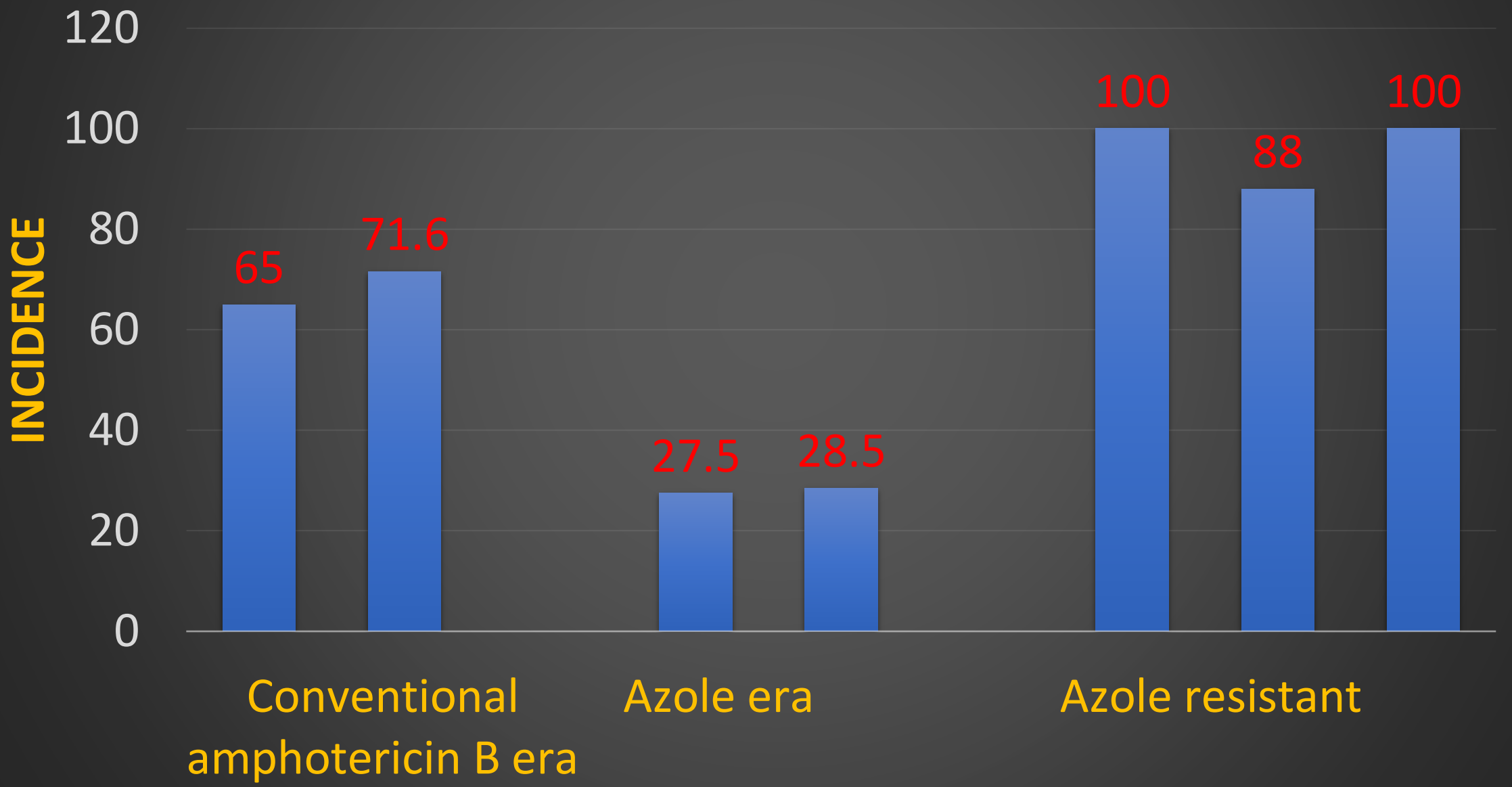
Treatment of Invasive Aspergillosis

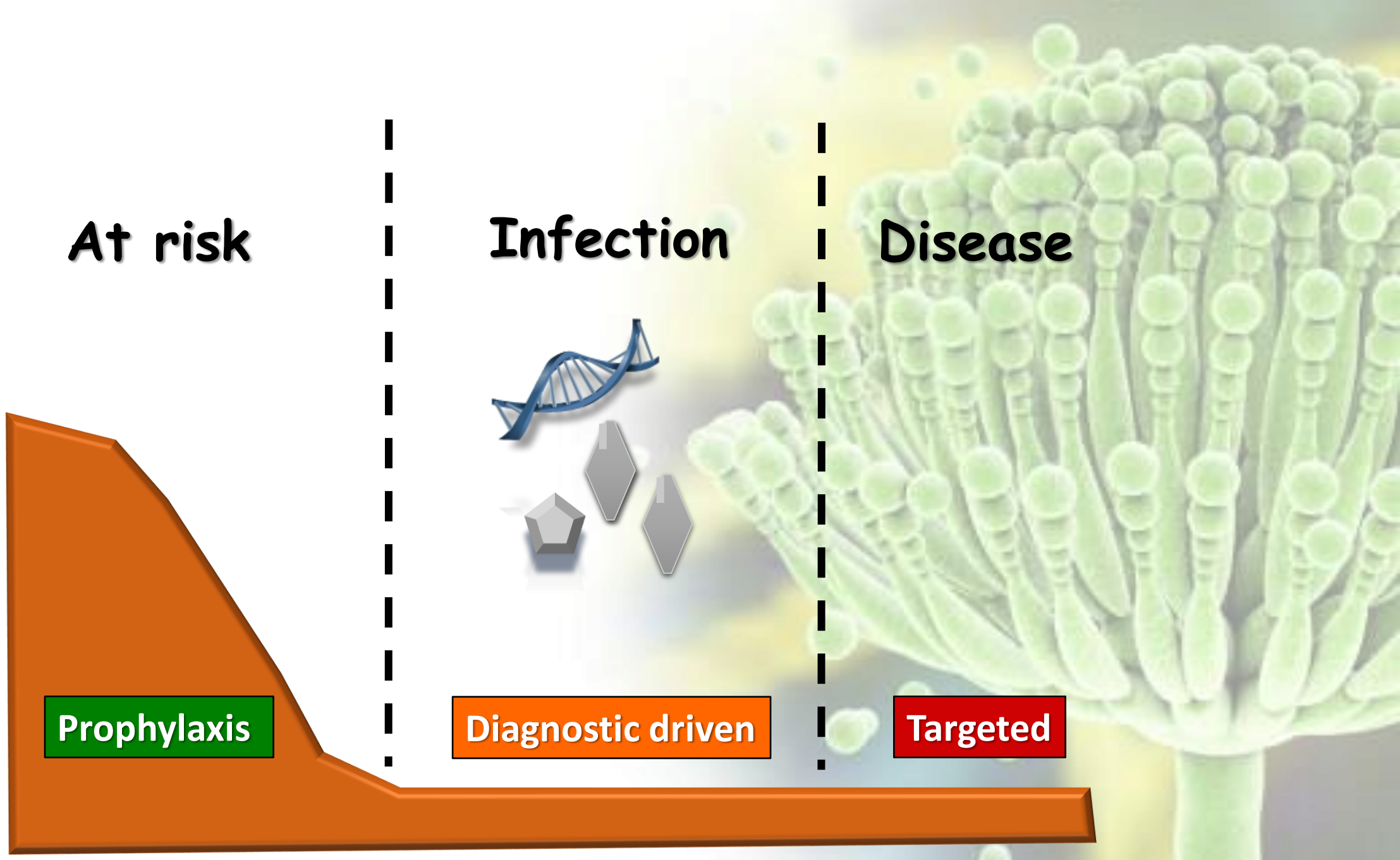
- Several classes of antifungal agents can be used to treat IFDs, but some fungi have developed resistance and no longer respond to standard antifungals intended to eradicate them



Difficult-to-Treat IFDs

Reported Mortality Rates in Patients With Invasive Aspergillosis in Different Time Periods



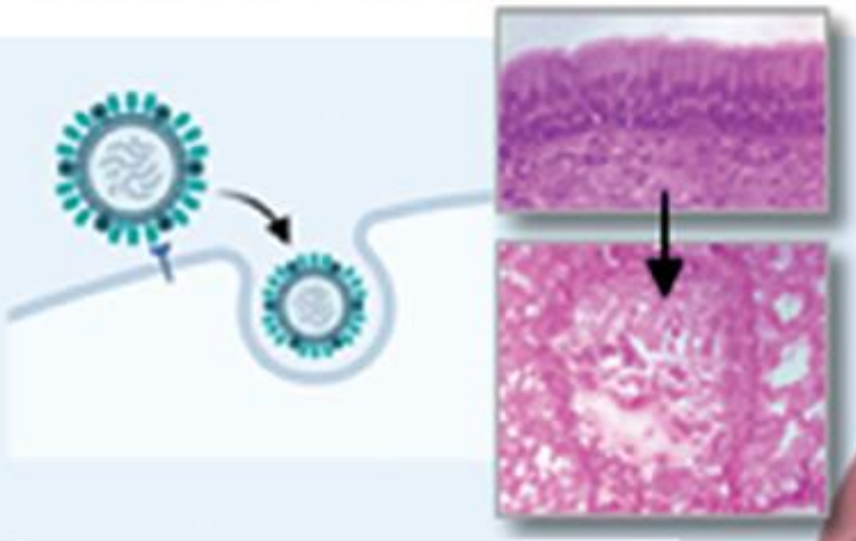

At risk
Infection
Disease
Prophylaxis
Diagnostic driven
Targeted

Invasive aspergillosis					
Voriconazole	Patients aged 2–12 years, or aged 12–14 years and weighing less than 50 kg: 8 mg/kg (9 mg/kg on day 1) twice a day intravenously or 9 mg/kg twice a day orally; patients aged 12–14 years and weighing 50 kg or more, or aged 15 years and older: 4 mg/kg (6 mg/kg on day 1) twice a day intravenously or 200 mg twice a day orally	A	IIt	Approved for patients older than 2 years; TDM suggested (target:trough concentration of between 1·0 and 5·0 mg/L); current treatment of choice for infections involving the CNS; a switch in class is to be considered in patients with breakthrough aspergillosis on mould-active azole prophylaxis	Clinical trials in adults; TDM dosing target; pharmacokinetic and safety and efficacy studies in paediatric patients
Liposomal amphotericin B	Single dose 3 mg/kg per day intravenously	B	IIt	Pivotal phase 3 trial compared two different doses but no head-to-head comparison to the reference agent at the time of its conduct (ie, voriconazole); first option if azole resistance is suspected or confirmed	Clinical trials in adults; pharmacokinetic and safety and efficacy studies in paediatric patients
Amphotericin B lipid complex	Single dose 5 mg/kg per day intravenously	C	II	No controlled first-line data available, but there are solid second-line data from treatment-naive patients receiving the compound on the basis of its improved safety profile relative to amphotericin B deoxycholate	Clinical trials in adults; pharmacokinetic and safety and efficacy studies in paediatric patients
Combination therapy (voriconazole or liposomal amphotericin B plus echinocandin)		C	IIt	Randomised clinical trial of voriconazole plus anidulafungin versus voriconazole in adults showed no differences in the primary endpoint; randomized clinical trial of liposomal amphotericin B plus caspofungin was underpowered	
Isavuconazole	10 mg/kg (maximum 372 mg) isavuconazonium sulfate intravenously once daily (every 8 h on days 1–2)	A	IIt	Equivalent to voriconazole in randomised phase 3 clinical trial in adults; paediatric development ongoing in phase 2 trials	Clinical trials in adults; pharmacokinetic studies in paediatric patients

COVID-19-ASSOCIATED ASPERGILLOSIS AND INFLUENZA-ASSOCIATED ASPERGILLOSIS

Influenza-associated pulmonary aspergillosis (IAPA)

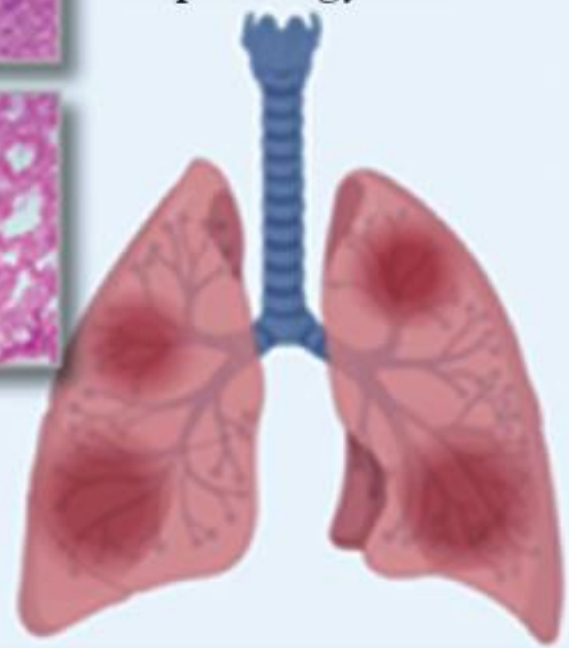
Baseline immunocompromising condition in 20%-30% of patients



Influenza targets sialic-acid expression in tracheobronchial epithelium

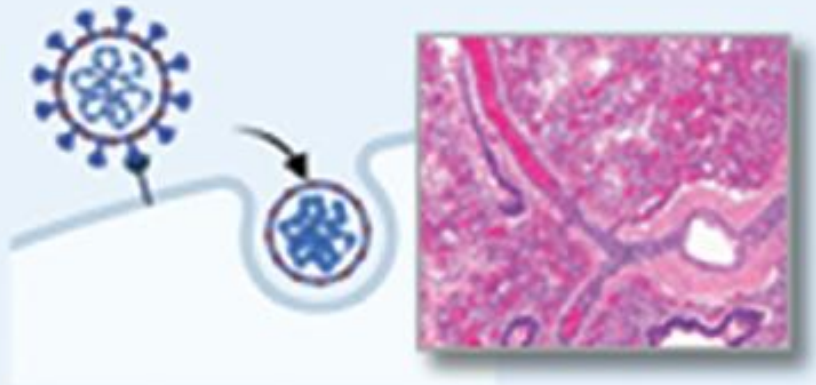
Panbronchiolitis → microthrombosis (< 25%) → diffuse alveolar damage

Underlying viral pathology



COVID-19-associated pulmonary aspergillosis (CAPA)

Baseline immunocompromising condition in <10% of patients



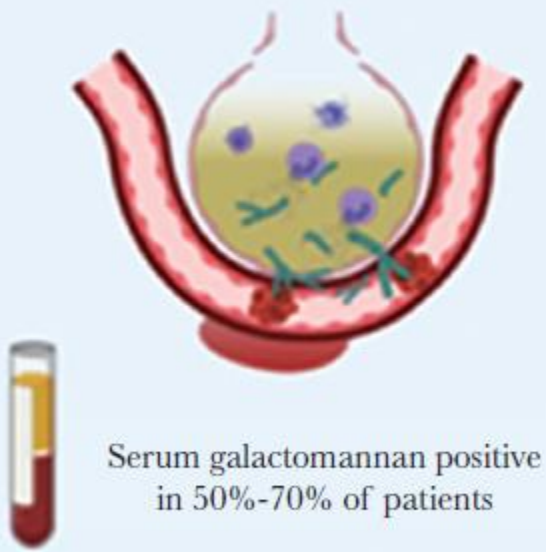
SARS CoV-2 targets ACE2 expression in type 2 pneumocytes and pulmonary endothelial cells

Inflammation → microthrombosis (>50%) → diffuse alveolar damage

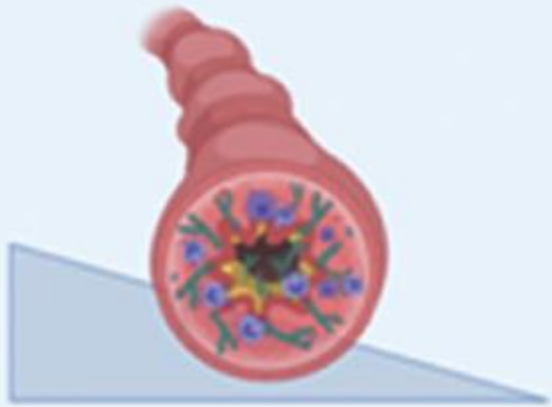
Influenza-associated pulmonary aspergillosis (IAPA)

COVID-19-associated pulmonary aspergillosis (CAPA)

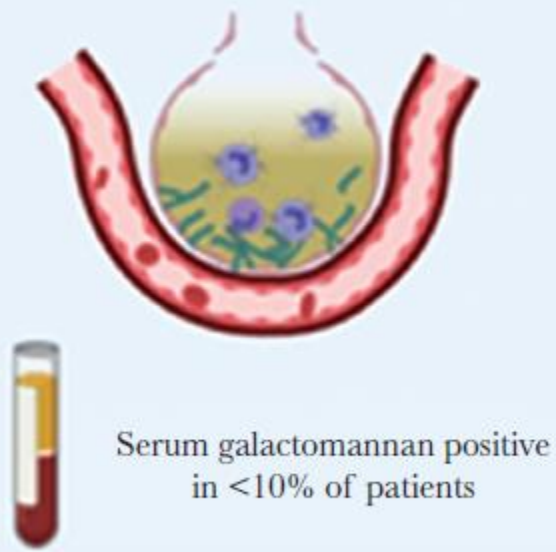
Inflamatory and airway-Invasive aspergillosis



Serum galactomannan positive in 50%-70% of patients



Angioinvasive disease at time of pulmonary aspergillosis diagnosis



Serum galactomannan positive in <10% of patients

Viral pneumonia treatment

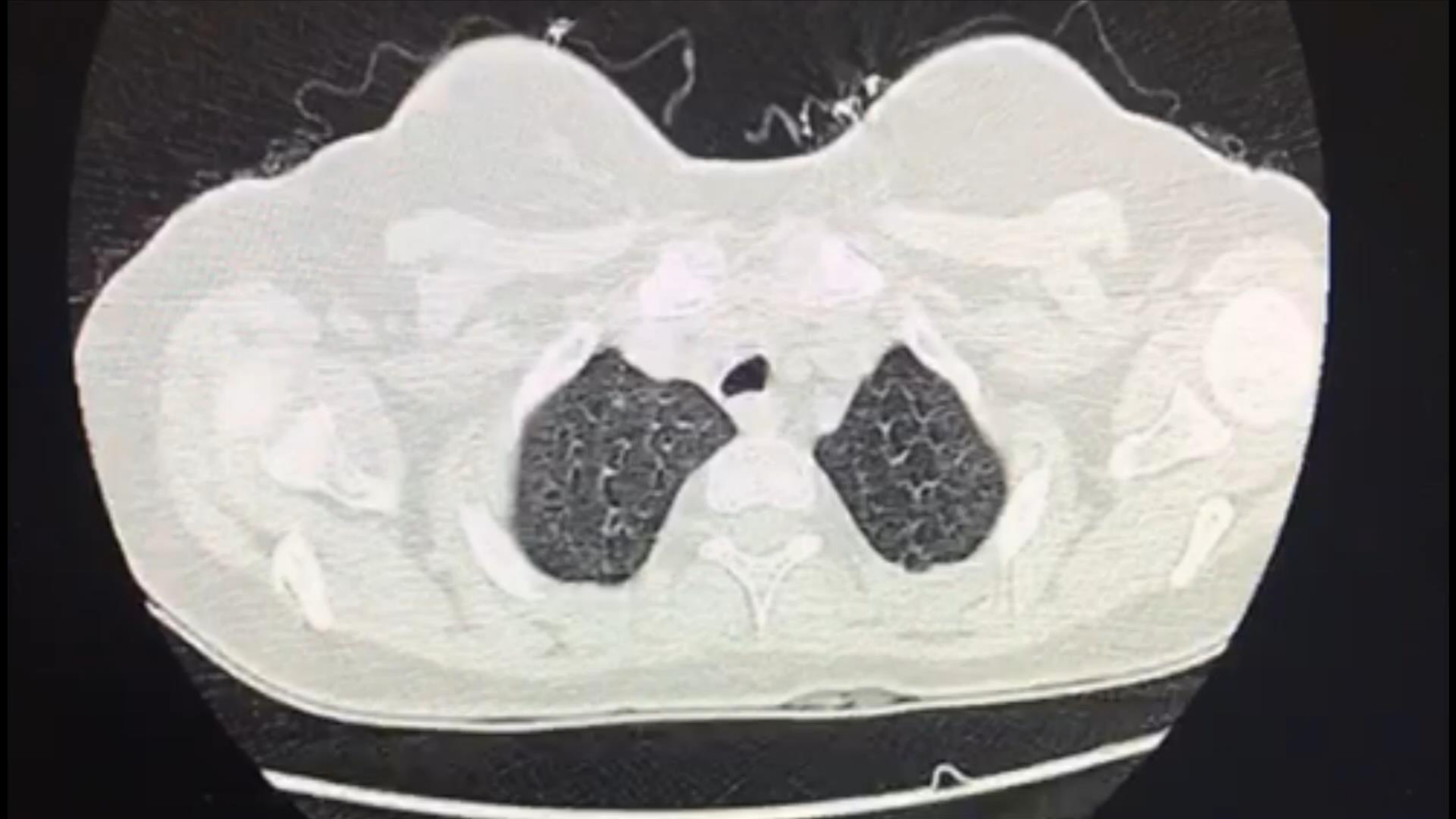
Influenza-associated pulmonary aspergillosis (IAPA)

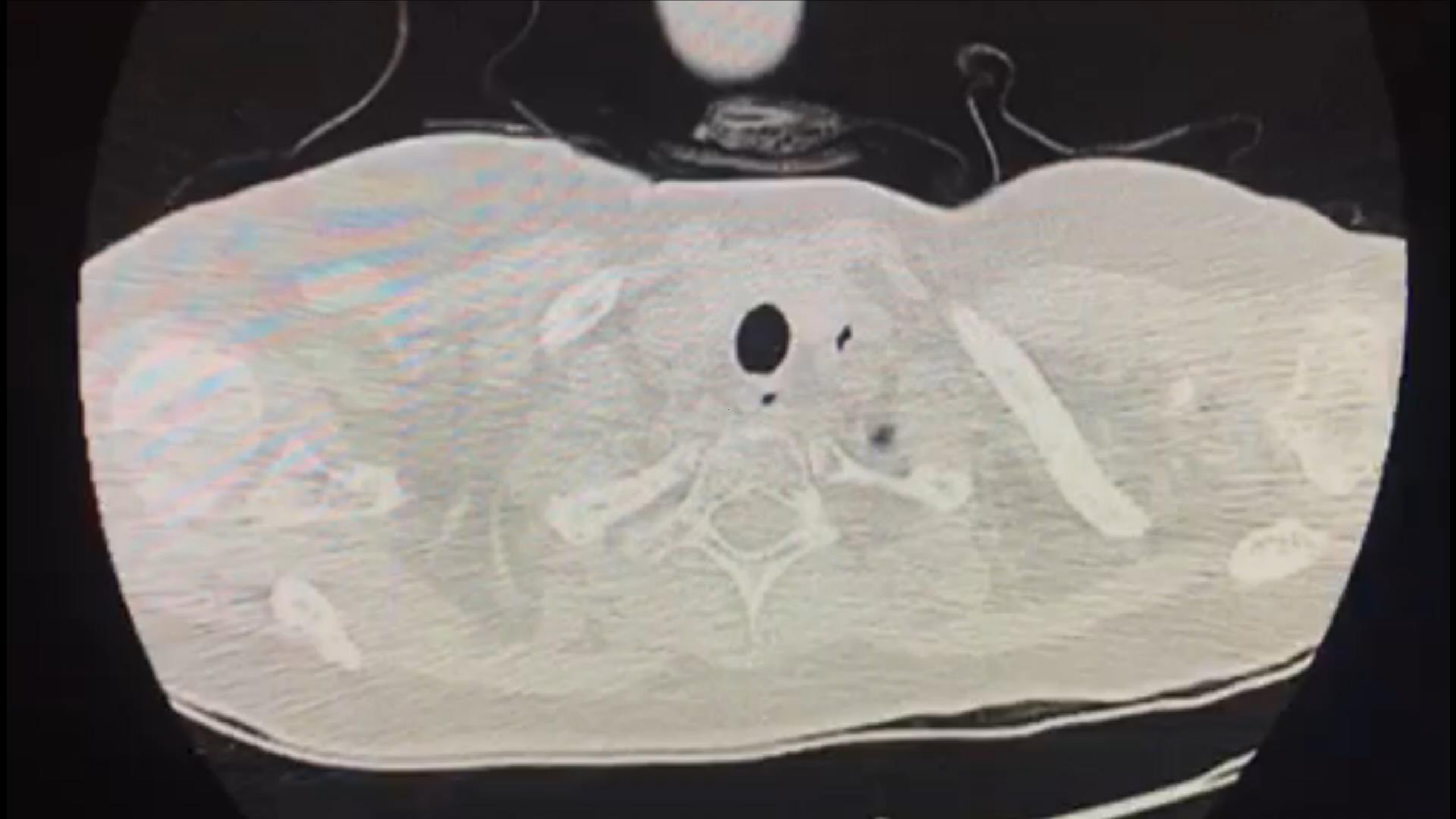
- Antiviral therapy (oseltamivir)
- Corticosteroids: not standard of care (discouraged)

COVID-19-associated pulmonary aspergillosis (CAPA)

- Antiviral therapy (remdesivir)
- Corticosteroids: standard of care
- Other immunomodulatory drugs eg, tocilizumab, anakinra (occasionally used)

Characteristic	IAPA	CAPA
Incidence	Variable (10%–30%)	Variable (4%–35%)
Baseline characteristics of patients	Approximately 25%–30% immunocompromised[a]	<10% immnunocompromised[a] Predominantly male Obesity, hypertension, diabetes
Timing	Early (usually within 3–7 d from ICU admission)	Variable (from 3 to >14 d from ICU admission)
Mycological findings	Positive serum galactomannan in 50%–70% of cases Bronchoscopy and BAL findings in most cases	Positive serum galactomannan in <10% of cases Infrequent use of bronchoscopy, diagnosis relying on non-BAL respiratory samples in some cases
Type of IPA classification[b]	Majority of probable/proven cases (≥60%) Important proportion of tracheobronchitis (30%)	Majority of putative cases (>90%) Unknown proportion of tracheobronchitis
Inflammatory response to viral infection	Potential deleterious role of high IL-10	Potential protective role of high TNF-α/IFN-γ
Bacterial superinfections	Frequent pneumonia due to community-acquired pathogens Nosocomial pneumonia in 10%–20% of influenza ICU cases	Rare pneumonia due to community-acquired pathogens Nosocomial pneumonia in 10%–20% of COVID-19 ICU cases
Role of corticosteroids	Deleterious impact on both overall influenza mortality and IAPA incidence	Benefit for overall COVID-19 survival, unknown impact on CAPA incidence
Impact on outcome	Overall mortality 50%–60% Association of IAPA with increased mortality in some studies [3, 13]	Overall mortality 60%–70% Association of CAPA with increased mortality demonstrated in some but not all studies [5, 16]






THANK YOU FOR
YOUR PATIENCE