



Decoding the Guidelines of Invasive Pulmonary Aspergillosis in Critical Care Setting: Imaging Perspective

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Abstract

Invasive pulmonary aspergillosis (IPA) is a common, life-threatening opportunistic fungal infection seen in susceptible individuals especially those admitted in critical care units. Multiple guidelines have been promulgated for the diagnosis of IPA, some of which are all inclusive, while others cater to specific patient groups. Microbiology forms the crux of the majority of the diagnostic tests/criteria; however, results take a considerable amount of time. Radiology can play an important role by bridging the gap to reach at an early diagnosis. Thus, the role of a radiologist cannot be over-emphasized to recognize the typical and atypical imaging manifestations of invasive aspergillosis and aid in the swift management of these cases. This review decodes the terminology and various diagnostic criteria for IPA relevant to imaging studies. Further, the differences in imaging manifestations of IPA in neutropenic and non-neutropenic patients are also discussed.

Keywords

- ▶ invasive pulmonary aspergillosis
- ▶ chest CT
- ▶ fungal lung disease
- ▶ aspergillosis
- ▶ galactomannan

Introduction

Invasive pulmonary aspergillosis (IPA) is an opportunistic infection that often affects immunocompromised patients and significantly escalates their morbidity and mortality. Neutropenia is the classical risk factor; however, IPA is also common in non-neutropenic immunocompromised hosts and even immunocompetent critically ill patients in intensive care units (ICUs). Multiple studies have estimated the mortality rates reaching up to 50% in patients of influenza and COVID-19 with *Aspergillus* superinfection.^{1–3} Compounding the problem is the nonspecific presentation of this entity, which is often difficult to differentiate clinically and radiologically from nosocomial pneumonia and pulmonary complications of mechanical ventilation in ICU settings. The radiological manifes-

tations also differ according to the immune status of the patient, with non-neutropenic patients seldom showing the typical imaging findings of invasive fungal pneumonia. Various guidelines have been proposed to facilitate diagnosis of IPA in different vulnerable patient groups with serology and microbiology forming the core supplemented by imaging. This article attempts to decode the myriad guidelines with special emphasis on radiological manifestations in patients with traditional and nontraditional risk factors for IPA.

Terminology

Before elaborating on the imaging manifestations, a clarification of basic terminology is essential.

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Invasive Pulmonary Aspergillosis

It involves the presence of *Aspergillus* species in lung tissue or respiratory samples with associated clinical, radiological or bronchoscopic features.⁴ The most common *Aspergillus* species causing invasive fungal infection in lungs is *A. fumigatus* followed by *A. flavus*.

Angioinvasive Aspergillosis

Angioinvasion (as relevant to the lungs) refers to invasion of branches of pulmonary arteries by fungal hyphae, leading to coagulative necrosis and hemorrhagic infarction of the pulmonary parenchyma.

Airway Invasive Aspergillosis

Airway invasion is said to occur when there is invasion by *Aspergillus* organisms beyond the airway basement membrane. It can affect both large (tracheobronchitis) and small airways (bronchiolitis).⁵

Influenza-Associated Pulmonary Aspergillosis

Influenza-associated pulmonary aspergillosis (IAPA) is defined as radiological and microbiological evidence of *Aspergillus* superinfection in a patient with influenza infection, (proven with influenza-positive polymerase chain reaction [PCR]/rapid antigen test) presenting with severe respiratory distress.⁶

COVID-19-Associated Pulmonary Aspergillosis

Similarly, in the backdrop of COVID-19 infection, a diagnosis of IPA by radiological and microbiological criteria is termed as COVID-19-associated pulmonary aspergillosis (CAPA).⁷

AspICU (Aspergillosis in ICU) Criteria for IPA

Given by Blot et al in 2012, these guidelines are used to diagnose *Aspergillus* infection in ICU patients.^{8,9}

Risk Factors for Invasive Aspergillosis

Various conditions predispose to invasive aspergillosis. The “high-risk factors” include neutropenia (neutrophil count $<500/\text{mm}^3$), hematological malignancy, and allogeneic bone marrow transplantation (BMT). BMT patients can have a bimodal peak. The first peak occurs within a month due to neutropenia and if they are subsequently treated with immunosuppressive drugs for graft versus host disease, the second one occurs 2 to 4 months after transplantation. “Intermediate-risk factors” for the development of IPA include prolonged treatment with corticosteroids (>3 weeks), lung transplantation, chronic obstructive pulmonary disease (COPD), chronic liver/kidney disease, solid organ malignancies, congenital and acquired immunodeficiencies like human immunodeficiency virus (HIV) infection and chronic granulomatous disease (CGD) and treatment with immunosuppressive/cytotoxic drugs. On the other hand, severe burns, diabetes mellitus, solid organ transplants other than lung transplant, prolonged ICU admission (>3 weeks), malnutrition, and cardiac surgery are considered “low-risk factors” for IPA.¹⁰ Recently viral infections like H1N1 and

COVID-19 have been associated with IPA probably as a result of infection-induced immune paralysis.^{6–8}

Guidelines for Diagnosis and Management of IPA

Based on the clinical, microbiological, and imaging findings, various criteria have been defined by different societies, based on the level of confidence. These are summarized in **Table 1**.

The various terms used in the guidelines to diagnose IPA are stated below in decreasing order of the level of confidence.

Proven Invasive Pulmonary Aspergillosis

Proven IPA is when there is evidence of tissue invasion by septate hyphae in lung biopsy specimens or detection of *Aspergillus* species from a clinically or radiologically involved site that is normally sterile, irrespective of the immune status of the patient.¹¹

As obtaining biopsy samples from critically ill patients is rarely feasible, management decisions are guided by “probable” or “possible” criteria with a lower level of certainty than proven IPA.

Probable IPA/Putative IPA

The revised European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) consensus guidelines “probable” case definition pertain mainly to neutropenic patients with hematological malignancy or history of BMT, who must have typical radiological features and collaborative microbiological evidence, for diagnosis. Although this provides increased specificity of diagnosis for research purposes, a large subset of patients who are not neutropenic are excluded.¹¹

All the recent guidelines, however, are applicable to the entire gamut of critically ill patients, including non-neutropenic individuals with milder degrees of immunocompromise due to COPD, post-viral infection, etc. In these patients, a positive laboratory evidence of *Aspergillus* species (by direct microscopy, culture, PCR and/or galactomannan in [GM] antigen in serum and/or BAL) supplemented by any nonspecific lung infiltrate is sufficient justification to initiate antifungal treatment.

Possible Invasive Pulmonary Aspergillosis

In the absence of mycological confirmation or reliable sampling methods (like non-BAL fluid used in suspected covid patients), a diagnosis of “possible IPA” is rendered by some of the guidelines (EORTC/MSG, CAPA, etc.).^{7,11}

Colonization

Colonization is isolation of fungus from respiratory secretions in a subject without any symptoms, radiological or bronchoscopic findings. It may be indicative of saprophytic infection in patients with localized lung disease, or a harbinger of invasive disease especially in lung transplant patients, but does not imply any active infection.²

Table 1 List of guidelines for diagnosis of IPA

Guideline	Groups to which it is applicable/entry criteria	Categories suggested
Revised definitions of invasive fungal disease from European Organization for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) consensus group (2019) ¹¹	<ul style="list-style-type: none"> • Neutropenic patients • Hematological malignancy • Stem cell transplant • Solid organ transplant 	Proven IFD Probable IFD Possible IFD
AspICU (2012) by Blot et al ⁹	All patients with <i>Aspergillus</i> species positive lower respiratory tract specimen including those with the following: <ul style="list-style-type: none"> • Neutropenia • Hematological/solid organ malignancy • Glucocorticoid treatment • Immunodeficiency 	Proven IPA Putative IPA Respiratory tract colonization
Modified AspICU/BM-AspICU (Biomarker-AspICU) (2021) by Réseau de Surveillance des Infections Fongiques (RESSIF group) ⁸	No risk factors required	Proven IPA Probable IPA
IAPA (2020) by expert panel ⁶	No risk factors required	Proven Probable
CAPA (2020) by expert panel ⁷	No risk factors required	Proven Probable Possible
Special case: guidelines for COPD patients (2007) by Bulpa et al ²¹	No other risk factors required	Proven Probable Possible Colonization
International Society for Heart and Lung Transplantation (ISHLT) consensus statements (2010) for recipients of cardiothoracic transplants ⁴	No other risk factors required	Proven Probable Colonization
Recipients of other solid organ transplants (SOT) ⁵	No specific guidelines: EORTC/AspICU followed	

Abbreviations: BM, biomarker; CAPA, Covid-associated pulmonary aspergillosis; COPD, chronic obstructive pulmonary disease; EORTC, European Organization for Research and Treatment of Cancer; IAPA, influenza-associated pulmonary aspergillosis; IFD, invasive fungal disease; IPA, invasive pulmonary aspergillosis; ISHLT, International Society for Heart and Lung Transplantation; MSGERC, Mycoses Study Group Education and Research Consortium; RESSIF, Réseau de Surveillance des Infections Fongiques; SOT, solid organ transplant.

When to Suspect Invasive Pulmonary Aspergillosis?

Although the entry criteria differ among the various guidelines, broadly, all patients admitted in the ICU having respiratory symptoms like dyspnea, hemoptysis, chest pain, persistent fever despite 3 days of antibiotics, or new, enlarging or persistent chest infiltrates on imaging despite antibiotic therapy should be suspected of having superimposed fungal infection. In severely neutropenic individuals, however, due to blunting of inflammatory responses, a temperature elevation for even 1 hour raises concern for IPA and warrants further workup (►Fig. 1).

Imaging Findings of IPA

Although the guidelines for IPA emphasize the role of serology/mycology for diagnosis, various factors like cardiorespiratory compromise, deranged coagulation, and fear of iatrogenic infection often preclude invasive sampling, especially

in nonintubated ICU patients. Frequent respiratory colonization by *Aspergillus* and inflammatory response due to simultaneous ongoing rejection in lung transplant recipients may further jeopardize laboratory results. Moreover, it may not be pragmatic to wait for laboratory confirmation in critical care settings and prompt treatment is often commenced empirically. Imaging can facilitate this decision-making by detecting typical imaging findings leading to a specific and early diagnosis of IPA in appropriate clinical settings. Further, imaging also aids in monitoring disease progression and detecting complications with prognostic implications.¹²⁻¹⁵

IPA can involve the peripheral airways or lung parenchyma in the form of nodules and consolidation. Pleural effusion and mediastinal lymphadenopathy are uncommon and should prompt investigation into a different etiology like mucor. The radiological manifestations of IPA can be divided under two broad groups: neutropenic and non-neutropenic patients. Although they have overlapping manifestations, some differences are noted due to their varied pathophysiology (►Table 2).

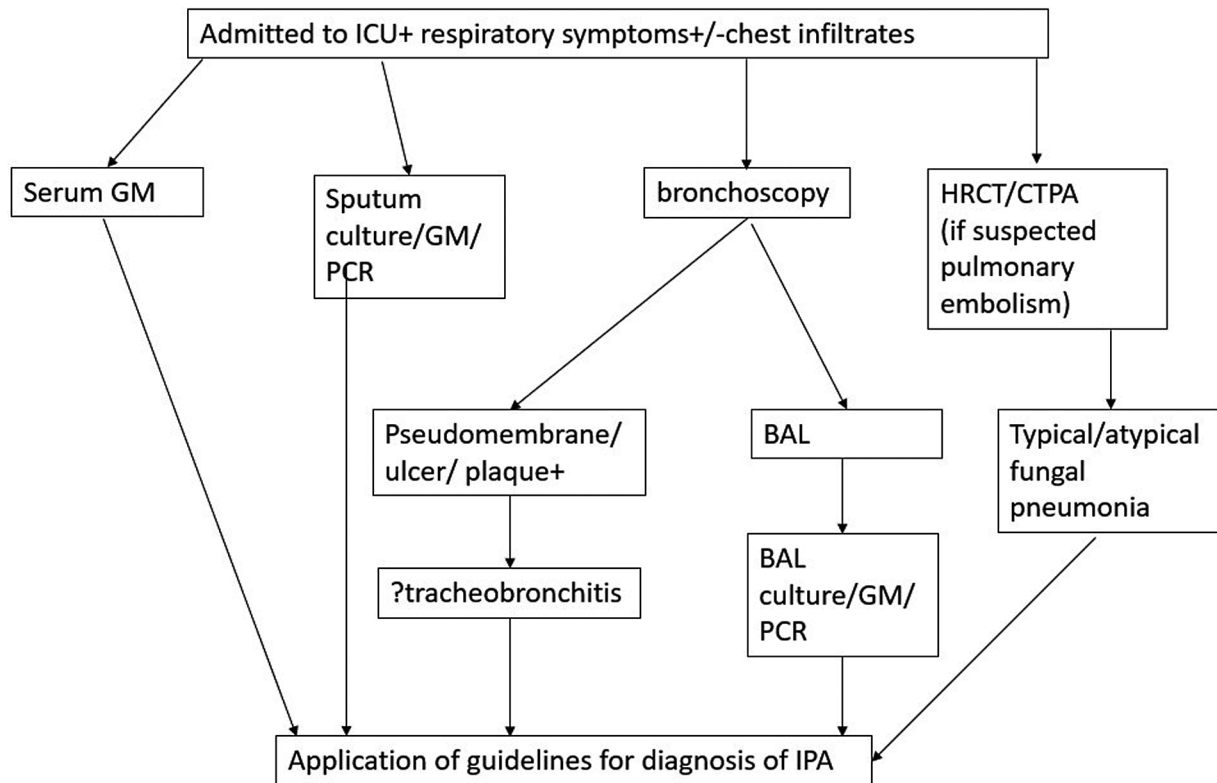


Fig. 1 Algorithmic approach to diagnose aspergillosis in ICU patients (BAL, bronchoalveolar lavage; CTPA, computed tomography pulmonary angiography; GM, serum galactomannan antigen; HRCT, high-resolution computed tomography; ICU, intensive care unit; IPA, invasive pulmonary aspergillosis; PCR, polymerase chain reaction)

Table 2 Comparison of pathological and radiological manifestations of IPA in neutropenic and non-neutropenic patients²²

Categories of ICU patients	Neutropenic patients	Non-neutropenic immunosuppressed/critically ill immunocompetent patients
Pathophysiology	<i>Aspergillus</i> becomes angioinvasive within hours	Prolonged airway invasive phase prior to angioinvasion
Pathology	Lung lesions represent coagulative necrosis, hemorrhagic infarction, and angioinvasion	Lung lesions represent pyogranulomatous inflammation and necrosis with no angioinvasion initially
Radiology	Typical findings: <ul style="list-style-type: none"> • Scattered nodules most common • Peripheral GGO halo • Air crescent • Hypodense sign • Peripheral wedge-shaped infarcts and consolidations 	Atypical findings: <ul style="list-style-type: none"> • Tracheal/bronchial wall thickening (large airways) • Tree-in-bud opacities (small airways) • Consolidations and nodules ± cavitation and GGOs with predominant peribronchial distribution (most common) • Nonspecific infiltrates (most common)
Microbiology	Serum galactomannan (GM) positivity	Serum GM unreliable (prolonged airway invasive phase)

Abbreviations: GGO, ground glass opacity; ICU, intensive care unit; IPA, invasive pulmonary aspergillosis.

Chest radiographs are not preferred in ICU settings due to low yield of portable radiography and chest computed tomography (CT) remains the primary modality for both diagnosis and follow-up. The imaging features of IPA on chest CT are discussed below.

- **Pulmonary nodules:** Ill-defined round nodules that tend to enlarge and coalesce over time are among the most common

manifestations of IPA and are more often seen in fungal vis-à-vis bacterial infection. These are present in both neutropenic and non-neutropenic individuals, although these are more common in the former. A predominant centrilobular distribution suggests airway invasive pattern, whereas peripheral random nodules are seen predominantly in angioinvasive infection in neutropenic individuals. These nodules may be associated with the following features:

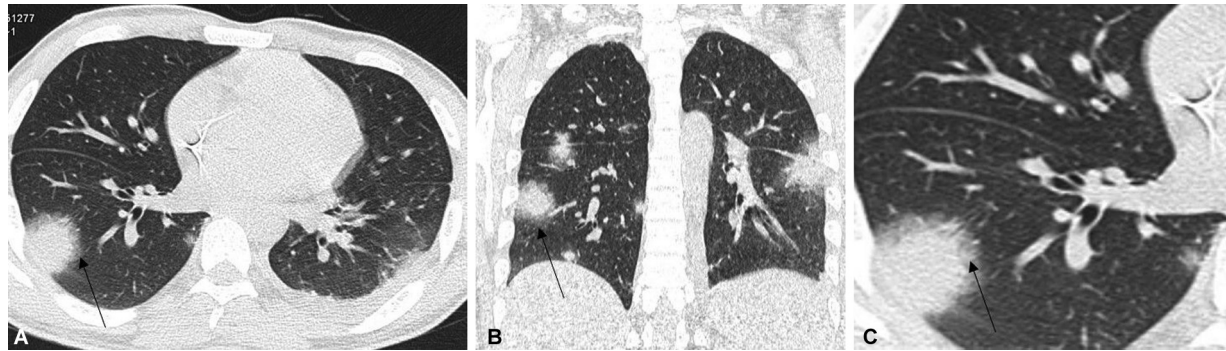


Fig. 2 Halo sign. A 24-year-old patient of acute promyelocytic leukemia complained of cough and dyspnea. High-resolution computed tomography (HRCT) of the thorax was performed 2 days after symptom onset. Lung window (A) axial and (B) coronal images depict multiple nodules and rounded dense areas of consolidation with surrounding ground glass opacity giving “halo sign” (arrow). (C) Zoomed in image depicting the “halo sign” (arrow). In the presence of risk factors, CT halo sign strongly indicates invasive pulmonary aspergillosis (IPA) and antifungals can be initiated even before mycological confirmation. Hence, early CT is important in patients with invasive fungal pulmonary infection.

- **Halo sign:** Halo sign refers to a rim of ground glass opacity (GGO) around a dense parenchymal nodule. It occurs in the early stages of infection (within a week) and disappears thereafter. Hence, early CT scan is essential to capture this finding (→ Fig. 2). Its presence also correlates with the degree of immunosuppression. However, it is a nonspecific sign and can also be seen in many other conditions like mucormycosis, septic emboli, hemorrhagic metastasis, and granulomatosis polyangiitis (GPA). Nevertheless, in the setting of traditional risk factors like neutropenia, it is highly suggestive of the angioinvasive form of IPA. Pathologically, it represents infarct like necrosis with surrounding hemorrhage. It has been associated with good prognosis, probably as a result of early disease detection and treatment.
- **Cavitation/air crescent sign:** On improvement of neutropenia, there is decrease in the surrounding GGO but with the appearance of internal breakdown and formation of a crescent of air (“air crescent sign”; → Fig. 3) separating the wall of cavity from infarcted, contracting lung tissue. Hence, it occurs late in the course of the disease (after 2–3 weeks) and heralds immune reconstitution and improved survival. As the necrotic debris is expelled into an adjoining bronchus, a rounded irregular area of cavitation appears within the fungal

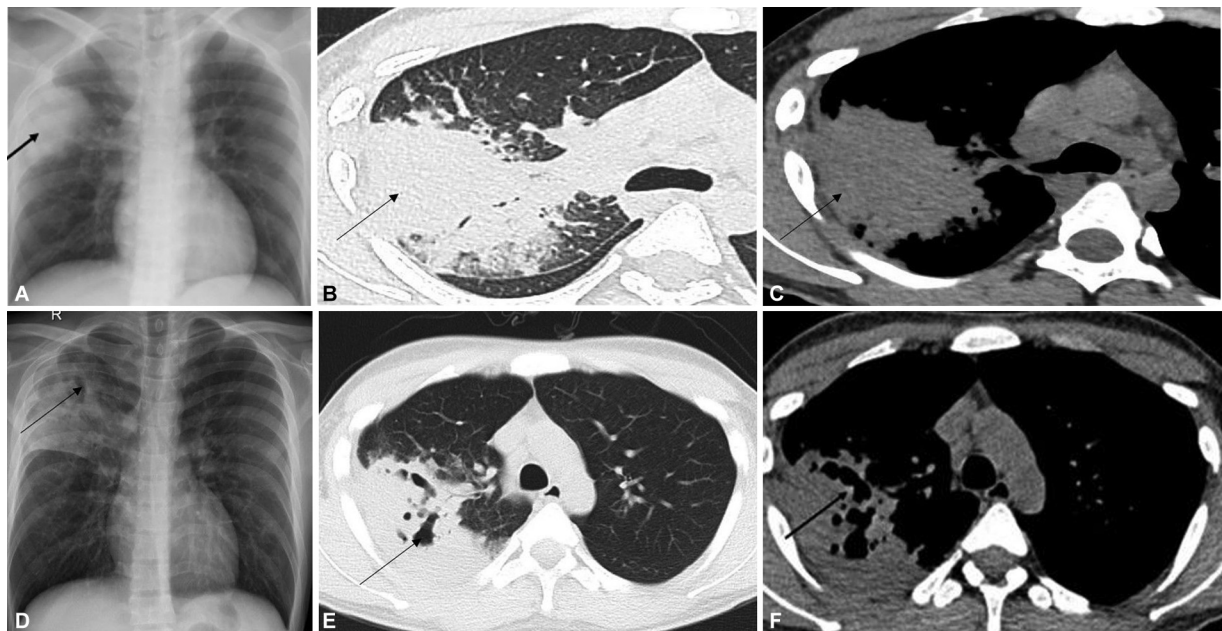


Fig. 3 Air crescent sign: A young patient post renal transplantation presented with fever, dyspnea, and cough not responding to antibiotics. Top row: (A) chest radiograph, (B) high-resolution computed tomography (HRCT) of the chest lung window, and (C) mediastinal window show dense consolidation in the right upper lobe with air bronchograms (arrow). The patient was started on voriconazole on presumptive diagnosis of invasive pulmonary aspergillosis (IPA). Bronchoalveolar lavage (BAL) galactomannan was positive. Imaging was repeated after 2 weeks. Bottom row: (D) chest radiograph, (E) HRCT of the chest lung window, and (F) mediastinal window show eccentric cavitation within the consolidation s/o “air crescent sign” (arrow).

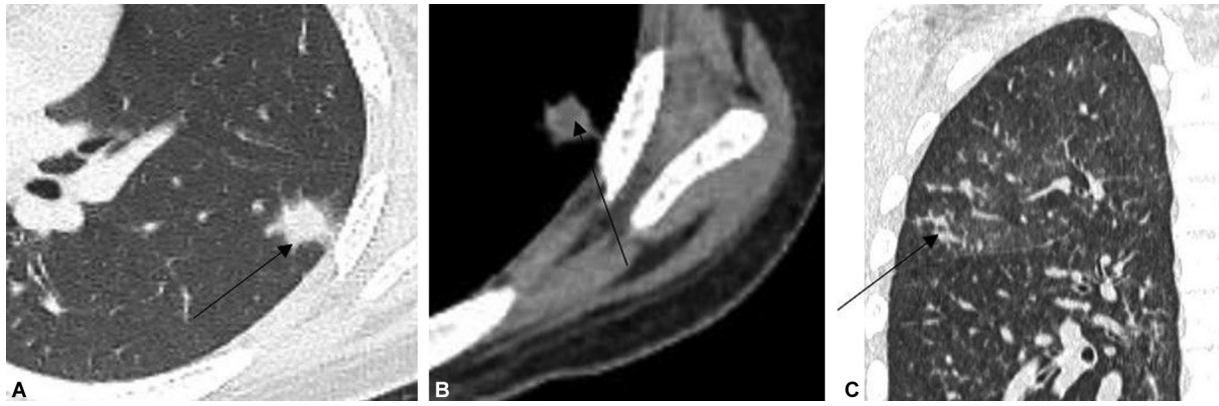


Fig. 4 Hypodense sign: A young female with acute myeloid leukemia (AML) presented with febrile neutropenia after induction chemotherapy. (A) Contrast-enhanced computed tomography (CECT) of the thorax axial view section in lung window shows an irregular nodule (arrow) in the anterior segment of left lower lobe. (B) On zoomed mediastinal window, the nodule is showing nonenhancing hypodensity (arrow) within the central portion of the nodule. “Hypodense sign.” Fungal etiology was strongly considered. (C) Coronal lung window section reveals multifocal centrilobular nodules (arrow) with patchy ground glass opacities (GGOs) in both lungs (fungal bronchopneumonia). Hence, both angioinvasive and bronchoinvasive components were present on imaging.

nodule/opacity. Although infarction of lung tissue is seen mainly in angioinvasive infection in neutropenic individuals, cavitation is also commonly encountered in consolidations seen in non-neutropenic cases due to necrosis.

- **Hypodense sign:** A parenchymal nodule may transiently show a central hypodensity signifying ischemic necrosis (hypodense sign; ▶Fig. 4) with subsequent cavitation due to communication with an adjoining bronchus/bronchiole. This is a highly specific sign (specificity of 90–100%) of angioinvasion and has not been reported in bacterial/viral infection.¹⁶

Thus, the chronological sequence of appearance of the hypodense sign in a pulmonary nodule within a week, followed by air crescent sign and subsequent cavitation is highly suggestive of IPA.¹⁵

- **Transfissural extension:** The nodules may show pleural, mediastinal, and chest wall invasion and transfissural extension (▶Fig. 5).

Miliary aspergillosis is a rare form of angioinvasive IPA seen in neutropenic hosts and is characterized by innumerable 1- to 3-mm discrete nodules in random distribution.

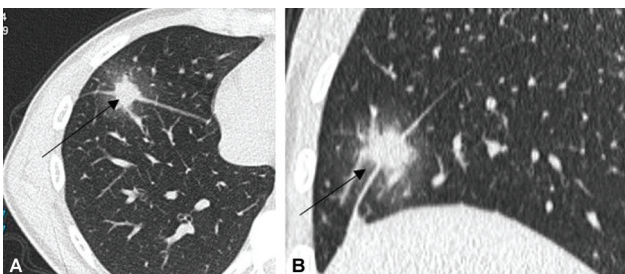


Fig. 5 Transfissural sign: high-resolution computed tomography (HRCT) chest lung window (A) axial and (B) sagittal images in a patient of acute myeloid leukemia (AML) and febrile neutropenia depict a dense nodule with surrounding ground glass halo in the right middle lobe showing “transfissural extension” across the oblique fissure (arrow).

- **Consolidation:** Diffuse lobar or segmental areas of consolidation may be seen with/without surrounding GGOS and cavitation. In neutropenic individuals, they represent changes due to angioinvasion with subsequent pulmonary infarction and are generally seen as pleural-based wedge-shaped consolidations (▶Fig. 6).

Predominant peribronchial and multisegmental distribution suggests airway invasive fungal bronchopneumonia (▶Fig. 7). The airway invasive form persists for a prolonged time in a non-neutropenic patient with subsequent invasion of vessels. In neutropenic patients, however, *Aspergillus* species becomes angioinvasive within hours, accounting for the varied radiological presentation.

- **Reverse halo sign/atoll sign:** There is central GGO surrounded by crescentic denser consolidation (▶Fig. 8). It is a nonspecific imaging finding seen most commonly in mucormycosis, organizing pneumonia, COVID infection, and infarction. Infrequently, it may be encountered in IPA as a delayed finding in contrast to mucor where it occurs at an earlier stage.

- **Vascular occlusion sign:** This sign is also seen more frequently in mucormycosis and rarely in the angioinvasive form of IPA in neutropenic hosts. It refers to interruption of a vessel at the border of a nodule/consolidation without opacification of the vessel within the lesion.

- **Acute fungal tracheobronchitis:** It usually shows no radiological findings. Occasionally, tracheal or bronchial wall thickening may be seen. It is unique to lung transplant recipients where it generally occurs at the anastomotic site within 3 months of transplant. It may lead to anastomotic dehiscence. Bronchoscopic findings include superficial invasion causing ulceration and pseudomembrane formation and deep invasion in the form of plaques and nodules with peribronchial infiltration.

- **Bronchiolitis:** It is seen as bronchial wall thickening, centrilobular nodules, and branching linear opacities

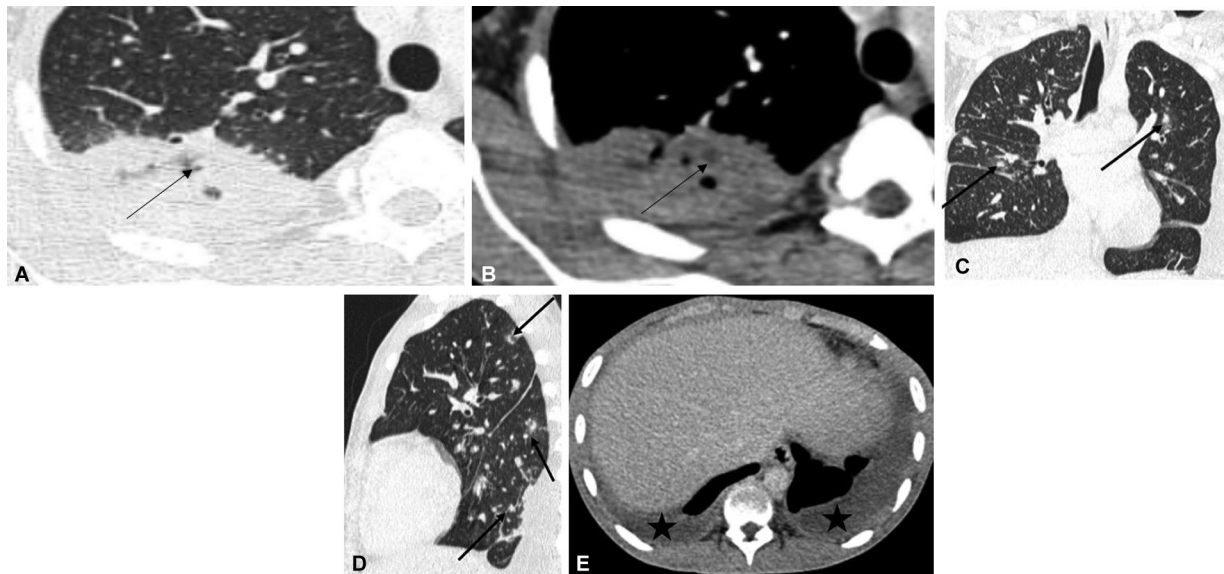


Fig. 6 Infarct like peripheral consolidation: Adolescent male suffering from severe aplastic anemia presented with febrile neutropenia. Bronchoalveolar lavage (BAL) galactomannan and GeneXpert were positive suggesting mixed fungal and tubercular infection. Contrast-enhanced computed tomography (CECT) of the chest (A) axial sections in the lung and (B) mediastinal windows show wedge-shaped subpleural consolidation in the right upper lobe with a small nonenhancing focus within “hypodense sign” (arrow). (C) Coronal and (D) sagittal images in the lung window show multiple random nodules in both lungs (arrows in C and D), many with surrounding ground glass opacities (GGOs). (E) Axial soft-tissue window reveals peripherally enhancing pleural collections in the bilateral hemithorax s/o empyema (stars). Subsequently, antituberculosis therapy (ATT) and antifungals were initiated and follow-up high-resolution computed tomography (HRCT; not shown) showed improvement.

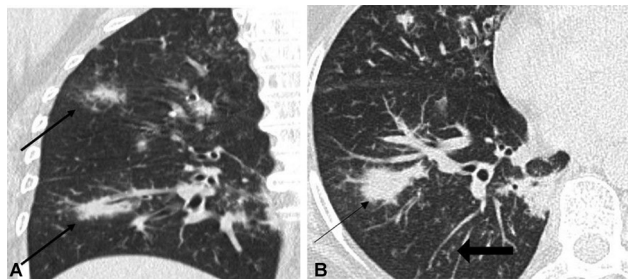


Fig. 7 (a,b) Bronchopneumonia pattern: Elderly non-neutropenic diabetic presented with fever and dyspnea. Ill-defined nodules (arrow) in predominant peribronchovascular distribution with smaller centrilobular nodules (thick arrow) are seen in bilateral lungs. Presumptive diagnosis of fungal bronchopneumonia was suggested and treatment started. Bronchoalveolar lavage (BAL) galactomannan antigen was subsequently positive.

having a “tree-in-bud” appearance in patchy distribution (→Fig. 9). It is a nonspecific feature, also seen in tuberculosis, aspiration, etc. So clinical correlation is paramount.

- **Nonspecific patterns:** These include bilateral multilobar segmental and lobar consolidations with/without breakdown, masslike consolidation, single or multiple nodules with/without halo sign and cavitation, diffuse GGO, and mosaic attenuation frequently seen in non-neutropenic patients and critically ill immunocompetent subjects (→Fig. 10). They appear indistinguishable from other bacterial pneumonia especially due to gram-negative bacteria. The differences in imaging appearance of IPA among neutropenic and nonneutropenic patients are summarized in →Figs. 11 and 12.

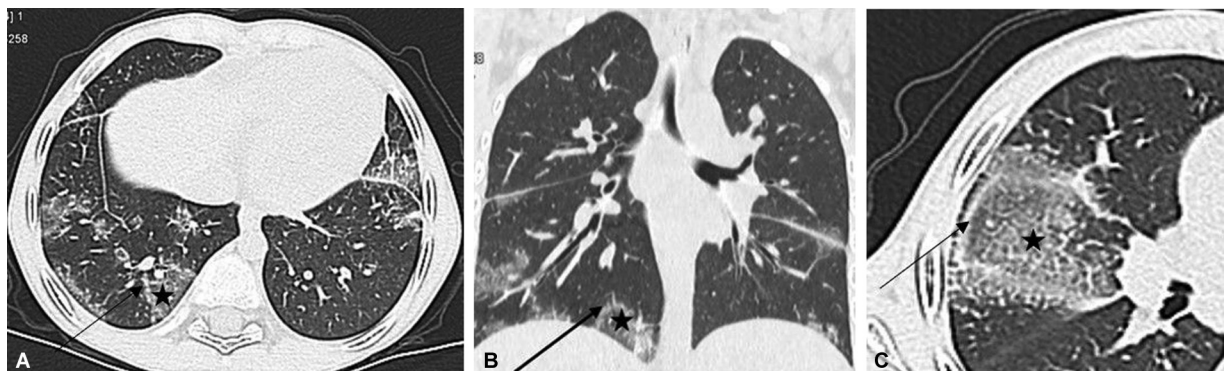


Fig. 8 Reverse halo sign: high-resolution computed tomography (HRCT) chest (A) axial, (B) coronal, and (C) magnified sections in lung window in a patient of pancytopenia and febrile neutropenia who presented after 10 days show areas of ground glass opacities (GGOs; star) with surrounding denser curvilinear bands of consolidation (arrow) randomly distributed in both lungs—“atoll sign.” Invasive pulmonary aspergillosis (IPA) was confirmed with bronchoalveolar lavage (BAL) galactomannan.



Fig. 9 Tree-in-bud pattern: a 26-year-old female patient of acute myeloid leukemia (AML) post induction therapy with severe neutropenia and fever unresponsive to antibiotics. High-resolution computed tomography (HRCT) of the chest was done to look for evidence of fungal infection. (A,B) Axial HRCT of the chest sections in the lung window show clustered centrilobular nodules with surrounding ground glass opacities (GGOs) in the right middle lobe and bilateral lower lobes forming a “tree-in-bud” pattern (arrow). (C) This is better depicted in zoomed image.

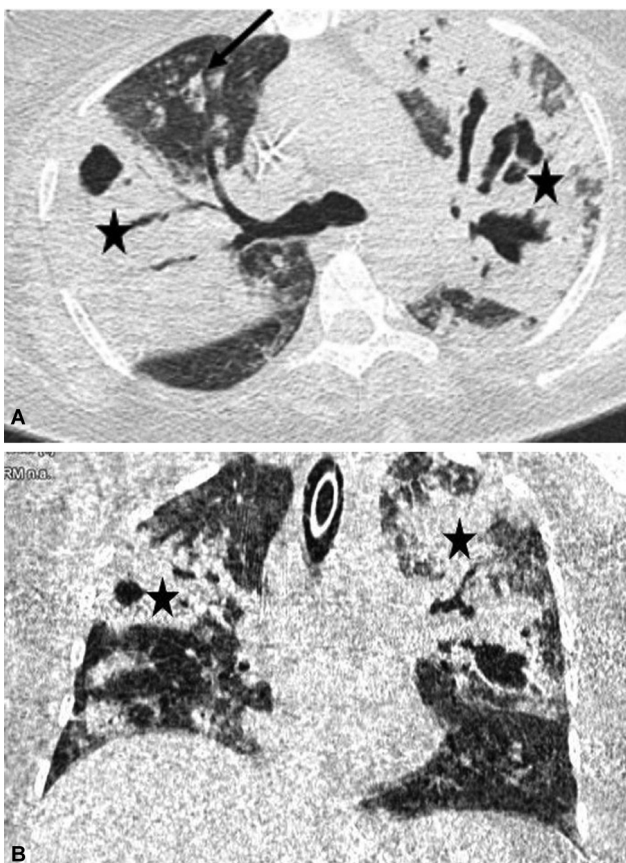


Fig. 10 A 43-year-old diabetic female patient presented with shortness of breath, fever, and productive cough. High-resolution computed tomography (HRCT) of the chest lung window (A,B) axial and (C) coronal sections reveal multifocal consolidations (star) and nodules (arrow) in bilateral lungs with internal areas of cavitation and breakdown. Imaging appearances were nonspecific. Gram-negative bacterial and fungal etiology were both considered differentials and empirically treated. Culture from mini-bronchoalveolar lavage (mini-BAL) done subsequently showed the *Aspergillus* species.

IPA is the most common pulmonary mycoses in critical care settings; however, invasive pulmonary mucormycosis (IPM) is also sometimes encountered as during the recent SARS pandemic. The imaging appearances are often similar, but it would be worthwhile to highlight certain differentiating markers. Multiple pulmonary nodules (>10), pleural effusion, concom-

itant fungal sinusitis, and progression of disease despite voriconazole therapy suggest IPM. Also as noted earlier, the “reverse halo sign” is observed more commonly and earlier during the course in mucor. Another related sign described is “bird nest sign,” which is specific for IPM. It consists of intersecting irregular lines within an area of ground glass with surrounding halo of consolidation. However, invasive sampling might be required for definitive diagnosis.^{13,17}

Although this review is concerned entirely with the diagnosis of IPA in ICU patients, it would be interesting to note here the imaging manifestations of aspergillosis in noncritical care settings. The clinicroadiological presentations in this population relies on the balance between host immunity and pathogenicity of the organism with some role played by genetic susceptibility. The profoundly neutropenic individuals as well those with lesser degrees of immunosuppression, who are being managed in noncritical hospital care/outpatient basis, generally manifest a similar spectrum of typical and atypical IPA (as discussed earlier) depending on their ability to resist angioinvasion. The subjects with improving immune function may evolve into a more subacute form of aspergillosis with less dramatic clinical course. Immunocompetent individuals with chronic fibrocavitary lung lesions usually suffer from the chronic form of pulmonary aspergillosis in contrast to hypersensitive/atopic hosts who are prone to develop allergic bronchopulmonary aspergillosis (ABPA). However, they may sometimes progress to IPA in the event of ongoing immunosuppression by corticosteroids, etc. Curiously, there are sporadic case reports of healthy humans who succumbed to IPA post massive fungal spore exposure. Thus, there is an ongoing dynamic interconversion of one form to another based on the current immunity of the patient, termed *Aspergillus* overlap syndrome. Further discussion on this topic is beyond the scope of this article and is available in more detailed manuscripts.^{18–20}

To summarize, the imaging criteria of IPA cited by various guidelines have been enumerated (– Table 3). It is prudent to realize that imaging manifestations of invasive aspergillosis in non-neutropenic patients do not follow the conventional patterns of fungal pneumonia so that lack of the typical features should not delay further workup for aspergillosis. Microbiology supplemented by radiology can expedite the diagnosis and

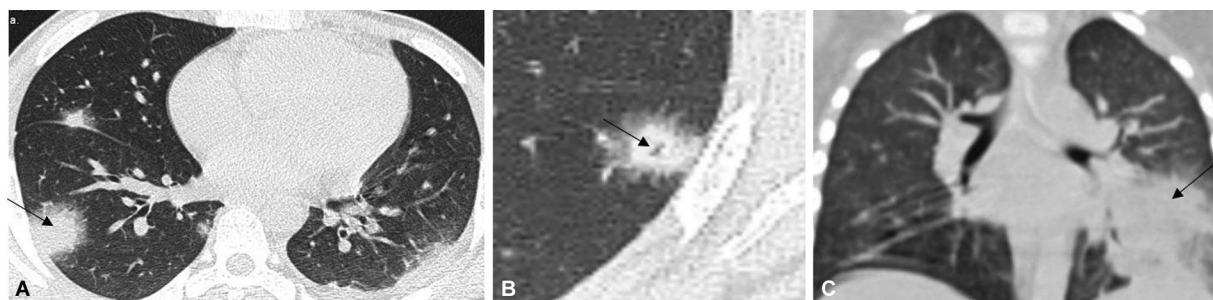


Fig. 11 Image dataset consisting of high-resolution computed tomography (HRCT) of the chest axial sections and zoomed-in view in different patients presenting with febrile neutropenia and invasive pulmonary aspergillosis (IPA) depict (A) multiple peripherally based nodules with surrounding ground glass opacities (GGOs; arrow), (B) peripheral nodules with internal cavitation (arrow) and GGO halo, (C) pleural-based cavitating consolidations (arrow). These features are more preponderant in angioinvasive forms of IPA.

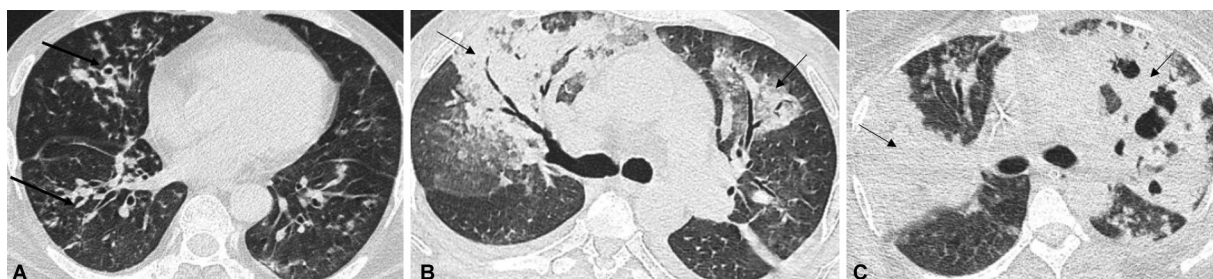


Fig. 12 Image dataset consisting of high-resolution computed tomography (HRCT) chest axial sections in lung window in different non-neutropenic immunosuppressed patients with IPA reveal (A) peribronchial thickening and centrilobular nodules in both lungs (arrow), (B) peribronchial consolidations with surrounding ground glass opacities (GGOs; arrow), and (C) nonspecific cavitating consolidations in both lungs (arrows). These features are more commonly seen in non-neutropenic patients.

Table 3 Comparison of imaging criteria for invasive pulmonary aspergillosis among the various guidelines⁸

Imaging criteria	Modified EORTC	AspICU	BM-AspICU	IAPA	CAPA
Air crescent sign	X	X	X	X	X
Cavity	X	X	X	X	X
Nodule ± halo sign	X	X	X	X	X
Wedge-shaped consolidation/infarct	X	X	X	X	X
Chest infiltrates		X	X	X	X
Cavitating consolidation/nodule	X	X	X	X	X
Tree-in-bud opacities		X	X	X	X
Bronchopneumonia pattern		X	X	X	X

Abbreviations: AspICU, Aspergillosis in ICU; BM, biomarker; EORTC, European Organization for Research and Treatment of Cancer; CAPA, COVID-associated pulmonary aspergillosis; IAPA, influenza-associated pulmonary aspergillosis; ICU, intensive care unit.

treatment of invasive aspergillosis and subsequently reduce morbidity and mortality in vulnerable patients.

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Conflict of Interest

None declared.

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