Invasive Pulmonary Aspergillosis in Nonimmunocompromised Hosts

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Abstract

Invasive pulmonary aspergillosis (IPA) is a fungal infection that is the hallmark of severe cellular or complex immune alterations. Evidence that IPA can occur in nonimmunocompromised hosts is increasing. Actually, up to 1% of general intensive care unit (ICU) patients present positive samples with *Aspergillus* spp. Both colonization and invasive disease are associated with poor outcome. Unexpected IPA has also been reported in approximately 1% of critically ill patients who underwent postmortem biopsies. In nonimmunocompromised patients with acute respiratory distress syndrome (ARDS), IPA prevalence can reach up to 15% of patients in both clinical and autopsy studies. Factors associated with IPA in nonimmunocompromised critically ill hosts include short and long courses of steroids, broad antibiotic therapy, chronic obstructive pulmonary disease, ARDS, liver failure, and the severity of organ dysfunctions.

This review aims to appraise the prevalence of IPA in nonimmunocompromised hosts, address diagnostic challenges, and outcomes.

Keywords

- *Aspergillus*
- transplant
- COPD
- influenza
- sepsis
- steroids

Aspergillus spp. is involved in a wide range of diseases of the lower respiratory tract (LRT), from colonization to invasive infection. Most of these diseases involve either excessive (e.g., allergy) or insufficient (e.g., invasive pulmonary aspergillosis [IPA]) immune response.

IPA is the disease with the poorest prognosis, achieving up to 50% mortality.[1] Known risk factors for IPA include several immune-suppression conditions such as prolonged neutropenia, T cell defects, hematological malignancies with or without stem cell transplantation, acquired immunodeficiency syndrome (AIDS), chronic granulomatous disease, solid organ transplantation, and prolonged high-dose steroid therapy.[2–4] However, IPA is also increasingly reported in nonimmunocompromised patients. Although the case published by Blum and colleagues in 1978 appeared anecdotal, case reports and case series of IPA are increasing in this setting, especially in critically ill patients.[5–10]

Herein, we aimed to review evidence for IPA in nonimmunocompromised patients, its diagnostic challenge, as well as its prognosis.

Epidemiology

Aspergillosis is ubiquitous. As such, *Aspergillus* studies have suggested that 5 to 7% of IPA cases occurred in critically ill nonimmunocompromised hosts.[11,12] Two kind of studies can be found in the literature: point prevalence studies addressing how often nonneutropenic intensive care unit (ICU) patients have positive respiratory samples to *Aspergillus*, and those addressing the causes of infiltrates from undetermined etiology in nonneutropenic ICU patients. Positive respiratory samples to *Aspergillus* spp. have been reported in approximately 1% of ICU patients receiving mechanical ventilation for more than 2 days; this proportion increases to 2% if patients on long-term steroids are not excluded.[13,14] In the EPIC international prevalence study, Vincent et al[15] reported 1.4% of ICU patients with positive samples with *Aspergillus* spp. infection (vs. 17% of *Candida* infections). Invasive aspergillosis affects up to 0.2 to 0.35% of ICU patients.[14,16] In critically ill patients receiving mechanical ventilation, both colonization and invasive disease remain

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associated with high mortality (50 and 80%, respectively).[13,16,17] Incidence of pathology-documented IPA may be increasing over time from 0.13% up to 0.56%.[16] Whether this increase is related to better knowledge of the disease and improved diagnostic strategies, or to additional opportunities for the mold to become invasive is not established. Autopsy studies suggest that IPA incidence in ICU patients may be underestimated, being at approximately 1 to 3.5% overall,[18–20] but reaching 12.5% in patients affected by acute respiratory distress syndrome (ARDS).[21]

Pathophysiology

Pathophysiology of invasive aspergillosis in reputed immune competent patients remains controversial. On one hand, ICU incidence of IPA could be ascribable to post-aggressive immune system disturbances that have been reported in sepsis survivors.[22] Indeed, reduced tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-6, IL-10 secretion by splenocytes, increased secretion of receptor inhibitors and suppressive cells, $CD4^+$, $CD8^+$, $HLA\text{-}DR^+$ cell and dendritic cell spleen depletion, monocyte deactivation, and reduced expression of ligand for receptor on epithelial alveolar cells have been reported and pathophysiological mechanisms have been suggested.[23–26] On the other hand, critically ill patients with acute illness have never been evaluated for their immune status prior to ICU admission, leaving them with at least, if not more, the same probability of inherited immune deficiency or smoldering hematological malignancies and other sources of acquired immunodeficiency than the general population.[27–29]

Colonization or Infection?

The distinction between *Aspergillus* colonization and invasive pulmonary disease may be challenging in patients with previous pulmonary infiltrates, overload and critical care illness. Isolation of *Aspergillus* spp. in sputa or tracheal aspiration may occur once every month in a general ICU. Similarly, microbiologically undocumented health care-associated pneumonia occurs increasingly. By strictly applying the 2008 European Organization for Research and Treatment of Cancer Mycosis Study Group (EORTC/MSG) criteria for the diagnosis of invasive aspergillosis,[30] not only the underlying host factor may be lacking but also proven IPA might mostly be a postmortem finding unless patients are managed at centers where lung biopsy is easily made. Moreover, positive samples to *Aspergillus* spp. cannot be considered as a simplistic therapeutic target as half these patients are only colonized and should not be treated, whereas other patients might have true IPA requiring antifungal therapy with no more delay. Therefore, as clinical criteria are unspecific and mycological criteria insensitive, alternate classifications dedicated to specific populations such as chronic obstructive pulmonary disease (COPD) or ICU patients have been suggested (►**Table 1**).[31,32]

In the ICU setting, Blot et al suggested the use of alternate criteria.[32] Hence, if proven IPA follow the same diagnostic criteria than those established by the EORTC/MSG experts, possible and probable IPA have been replaced. For instance, they introduced the concept of *putative IPA*, associating both positive LRT sample for *Aspergillus* spp., compatible signs or symptoms, abnormal imaging and either host-related risk factors or bronchoalveolar lavage (BAL) positive culture. If at least one of these criteria is lacking, colonization is concluded. Along the same line, Bulpa et al proposed an algorithm to diagnose putative IPA in COPD patients,[31] including those who become critically ill.[33]

As a matter of fact, isolation of *Aspergillus* spp. in respiratory samples from immune-competent hosts raises the question of its relevance, especially regarding the very low IPA incidence in this setting. It should be however noted that *Aspergillus* spp. colonization still carries prognostic information and remains a risk factor for developing IPA.[34] Mortality rates of patients with *Aspergillus* colonization and IPA are 40 and 70%, respectively.[17]

In the setting of nonneutropenic nonimmunocompromised ICU patients, risk factors for positive *Aspergillus* spp. samples include age, ARDS, steroids, bacterial infection, COPD, and organ failures.[13,35] Though, not all the colonized patients experience IPA. Those with steroids or antibiotic treatment, COPD (notably GOLD IV), or with highest organ failure scores exhibit a higher risk of developing IPA.[12,36,37] Supposedly immune-competent patients with malnutrition, diabetes, or underlying pulmonary disease exhibit up to a 27% risk for developing IPA.[34] However, as mentioned below, severe septic shock and ARDS survivors, most notably after influenza infection, COPD patients exposed to long-term steroids as well as patients with acute liver failure are to be screened very carefully for their probability to develop IPA.

Clinical Picture: Which Patients?

Although without known underlying immune deficit, ICU patients experiencing IPA share several characteristics, such as diabetes, cirrhosis, or COPD (►**Figs. 1** and **2**). These patients exhibit a different clinical picture from neutropenic patients, being less symptomatic and more co-infected with bacteria.[38] Regarding the risk factors associated with IPA, several clinical pictures of patients at risk for IPA can be isolated.

Steroids

High-dose and/or long-term steroid exposure is a known risk factor of invasive fungal infection, notably in an immunosuppressive context such as organ transplant or rheumatic diseases.[39] However, short exposure to steroids also impairs monocyte/macrophage antifungal activity[40–42] and directly enhances *Aspergillus* spp. growth,[43] thereby favoring invasive infection. Hence, case reports/series of patients experiencing IPA under steroid treatment abound, with or without other contributing conditions such as cirrhosis[44] or lung disease.[11,45–48] Agustí et al[49] reported that approximately 30% of the patients with pulmonary infiltrates under long-term steroid therapy exhibited IPA. Noteworthy, up to 80% of the COPD patients with IPA receive underlying steroid therapy.[50] Moreover, short-term steroids sometimes used in COPD exacerbations are associated with an odds ratio (OR) for developing an IPA of 4.56 (95% confidence interval

Table 1 Adapted and modified diagnostic criteria according to EORTC/MSG

A. EORTC/MSG, De Pauw et al (2008)[30]: immunocompromised hosts
Proven
Microscopic analysis on sterile material: histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or sterile biopsy in which hyphae are seen accompanied by evidence of associated tissue damage. Culture on sterile material: recovery of *Aspergillus* by culture of a specimen obtained by lung biopsy
Probable (all three criteria)
1. Host factors (one of the following): recent history of neutropenia (<500 neutrophils/mm^3) for 110 days, receipt of an allogeneic stem cell transplant, prolonged use of corticosteroids at a mean minimum dose of 0.3 mg/kg/d of prednisone equivalent for >3 wk, treatment with other recognized T cell immunosuppressants, inherited severe immunodeficiency. 2. Clinical features (one of the following three signs on CT): dense, well-circumscribed lesion(s) with or without a halo sign, air-crescent sign, cavity. 3. Mycological criteria (one of the following): direct test (cytology, direct microscopy, or culture) on sputum, BAL fluid, bronchial brush indicating presence of fungal elements or culture recovery *Aspergillus* spp., indirect tests (detection of antigen or cell-wall constituents): galactomannan antigen detected in plasma, serum, or BAL fluid.
Possible
Presence of host factors and clinical features (cf. probable) but in the absence of negative mycological findings.
B. Blot et al (2012)[32]: ICU patients
Proven
Idem EORTC/MSG
Putative (all four criteria)
1. *Aspergillus*-positive lower respiratory tract specimen culture (entry criterion). 2. Compatible signs and symptoms (one of the following): fever refractory to at least 3 days of appropriate antibiotic therapy, recrudescent fever after a period of defervescence of at least 48 hours while still on antibiotics and without other apparent cause, pleuritic chest pain, pleuritic rub, dyspnea, hemoptysis, worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support. 3. Abnormal medical imaging by portable chest X-ray or CT scan of the lungs 4. Either a or b: a. Host risk factors (one of the following conditions): neutropenia (absolute neutrophil count < 500 mm^3) preceding or at the time of ICU admission, underlying hematological or oncological malignancy treated with cytotoxic agents, glucocorticoid treatment (prednisone equivalent, >20 mg/d), congenital or acquired immunodeficiency. b. Semi-quantitative *Aspergillus*-positive culture of BAL fluid (+ or ++), without bacterial growth together with a positive cytological smear showing branching hyphae.
Colonization
When >1 criterion necessary for a diagnosis of putative IPA is not met, the case is classified as *Aspergillus* colonization.
C. Bulpa et al (2007)[31]: COPD patients
Probable (one of the two criteria)
1. As for proven IPA but without confirmation that *Aspergillus* is responsible.2. COPD patient, usually treated with steroids and severe according to GOLD (stage III or IV), with recent exacerbation of dyspnea, suggestive chest imaging (radiograph or CT scan <3 months) and one of the following: • Positive culture and/or microscopy for *Aspergillus* from lower respiratory tract (LRT). • Positive serum antibody test for *A. fumigatus* (including precipitins). • Two consecutive positive serum galactomannan tests.
Possible
COPD patient, usually treated by steroids and severe according to GOLD (stage III or IV), with recent exacerbation of dyspnea, suggestive chest imaging (radiograph or CT scan; 3 months plus), but without positive *Aspergillus* culture or microscopy from LRT or serology.
Colonization
COPD patient with positive *Aspergillus* culture from LRT without exacerbation of dyspnea, bronchospasm, or new pulmonary infiltrate.

Abbreviations: BAL: bronchoalveolar lavage; COPD: chronic obstructive pulmonary disease; CT, computed tomography; EORTC/MSG; European Organization for Research and Treatment of Cancer Mycosis Study Group; ICU: intensive care unit; IPA, invasive pulmonary aspergillosis.

[CI]: 2.022–10.324).[51] Furthermore, chronic lung disease patients with IPA are more often treated with steroids than immunocompromised patients,[52] questioning their "immune competent" status. In COPD patients, antibiotic or steroid treatment is a risk factor for putative IPA, which is associated with mortality before organ failures (OR: 7.44).[36]

Pulmonary Diseases

Among nonimmunocompromised patients, those with pulmonary disease exhibit propensity to develop aspergillosis, as suggested by several publications reporting cases of IPA complicating COPD, asthma, or near drowning.[8,9,31] Among colonized patients, severe COPD seems to be a major risk factor for IPA in immune-competent patients.[37,51]

In the specific setting of ARDS, *Aspergillus* spp. in the LRT affects up to 8.3% of patients, without association with outcome.[53] However, in this cohort IPA affected 4% of the patients and was associated with high mortality (OR: 9.58; 95% CI: 1.97–56.52). Regarding postmortem studies, autopsy findings consistent with IPA are found in up to 12.5% of ARDS patients.[21] Finally, in the sickest ARDS patients undergoing extracorporeal membrane oxygenation (ECMO), 8 to 14% of patients are found with colonization and 2.5 to 8% are reported with IPA.[54,55] Expectedly, IPA case fatality in this setting is 70%.[56]

Beside chronic lung disease, with or without steroids, acute pulmonary illnesses like influenza infection predispose to IPA, as suggested in several case series.[57–59] A recent multicenter study cited an IPA incidence of 14% in immune-competent patients admitted for severe influenza as compared with 5% in those admitted for severe community-acquired pneumonia without influenza.[60] Once again, in this population use of steroids is a risk factor for developing IPA.[61]

Liver Failure

Critically ill patients experiencing liver failure are also at risk for aspergillosis, as shown by Zhang et al[62] with an incidence of 5% of IPA in this setting. Steroids, antibiotics, and hepatorenal syndrome are frequent under this condition and each one is an independent risk factor for IPA in this population.

Which Diagnostic Tools in Immune-Competent Patients?

If the gold standard to diagnose IPA remains histopathology, several surrogate markers of invasive fungal infection have shown their utility and are included in diagnostic classifications presented above. However, the diagnostic yield of such techniques remains unclear in nonneutropenic patients. Current evidence is shown in ►**Table 2**.

Table 2 Diagnostic yield of biomarkers in serum and BAL for probable or proven invasive aspergillosis

	Mixed population	Neutropenic patients	Nonneutropenic patients	References
Serum GM				Meersseman et al (2008),[65] Acosta et al (2011),[63] He et al (2011),[64] Rose et al (2014),[68] Zhou et al (2017)[66]
Se	31–77%	–	38–72%	
NPV	77–97%	–	73–88%	
AUC	0.76–0.84	–	0.66–85	
Serum BDG				Acosta et al (2011)[63]
Se	–	–	80%	
NPV	–	–	94%	
AUC	–	–	0.81	
BAL GM				Meersseman et al (2008),[65] Acosta et al (2011),[63] Torelli et al (2011),[67] Rose et al (2014),[68] Eigl et al (2017),[69] Zhou et al (2017)[66]
Se	37–94%	–	76–80	
NPV	77–99%	–	88–95%	
AUC	0.90	–	0.82–0.98	
BAL BDG				Rose et al (2014)[68]
Se	71%	–	–	
NPV	–	–	–	
AUC	–	–	–	
BAL PCR				Torelli et al (2011),[67]
Se	61–94%	30–45%	48–75%	Eigl et al (2017),[69]
NPV	80–99%	–	–	Guegan et al (2018)[71]
AUC	–	–	–	

Abbreviations: AUC, area under the curve; BAL, bronchoalveolar lavage; BDG, 1→ 3 β-D-glucan; GM, galactomannan antigen; NPV, negative predictive value; PCR, polymerase chain reaction; SE, standard error.

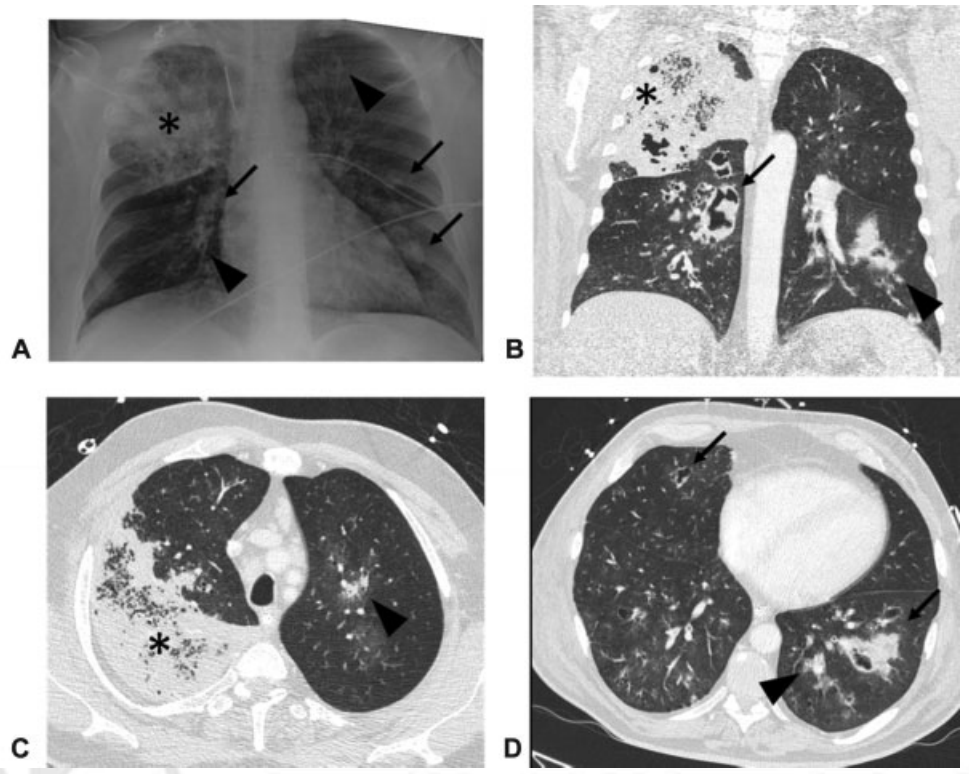

Fig. 1 A 51-year-old patient with no previous medical history admitted to the ICU for ARDS related to severe influenza pneumonia superinfected with *Staphylococcus aureus*. Deterioration at day 9 was ascribed to invasive pulmonary aspergillosis. **(A)** Chest X-ray showing right upper lobe opacity consistent with the initial *Staphylococcus* pneumonia (*asterisk*), and newly appeared cavities (*arrowhead*) and multiple consolidations of the left upper and lower lobes (*arrows*). **(B–D)** Chest CT-scan showing right upper lobe consistent with consolidation (*asterisks*), and multiple newly appeared excavated nodules (*arrows*) and dense nodule with halo sign (*arrowhead*). ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

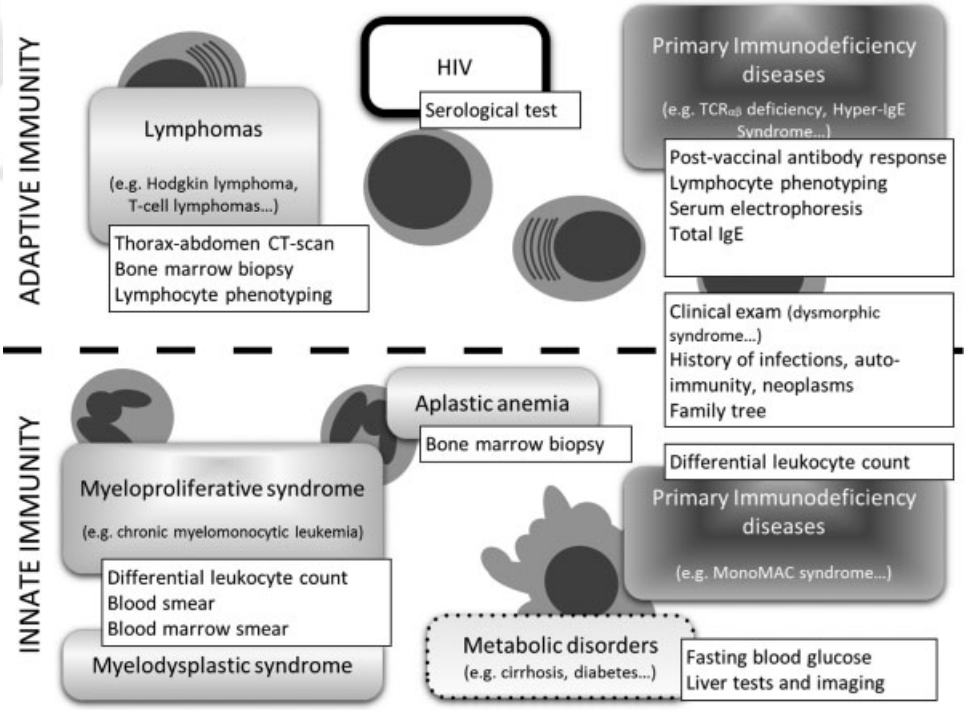

Fig. 2 Diagnostic workup when facing invasive aspergillosis in a patient presumed immunocompetent.

Galactomannan

In nonneutropenic patients the diagnostic yield is less than in neutropenic ones, due to a higher antigen scavenging. In this setting, serum galactomannan (GM) achieves a Sensitivity and negative predictive value (NPV) of 50–58% and 87–88%, respectively.[63,64] In nonneutropenic patients, repetition of GM dosing improves Se and NPV from 58 and 87% to 70 and 89%, respectively. Two positive GM tests improve specificity and positive predictive value from 85 and 55% to 94 and 73%, respectively.[64]

BAL galactomannan (BGM) exhibits higher sensitivity than GM. Notably, in neutropenic patients its Se and NPV are 58–70 and 70–90%, respectively.[64–66] In nonneutropenic patients, Se and NPV are 25–80 and 85–95%, respectively.[63,65,66] Several studies in unselected ICU patients at risk for developing IPA (COPD, steroids-treated, or hematological patients) are difficult to interpret because of the variable proportion of neutropenic patients (►**Table 2**). In this population, BGM achieves a diagnostic yield of Se: 34 to 94% and NPV: 77 to 99%.[67–69] There was no difference in clinical presentation or outcomes in patients diagnosed for IPA with LRT culture or with positive (serum or BAL) GM only.[70]

Polymerized Chain Reaction

As shown in ►**Table 2**, molecular biology techniques increase the diagnosis of aspergillosis with high sensitivity, especially in patients who did not have antifungal therapy.[71] However, these techniques lack standardization and performance varies between the different assays.[67,71]

1→ 3 β-D-Glucan

1–3 β-D-Glucan (BDG) has been widely studied in patients at risk for invasive fungal infections. Data that are available in the nonimmunocompromised population are included in series involving heterogeneous patient population. Notably, BAL-BDG exhibits a Se of 71% for the diagnosis of IPA in a mixed population of neutropenic and nonneutropenic patients.[68] In an ICU population of nonneutropenic patients, serum BDG reaches a Se of 80%, a NPV of 93%, and an area under the curve (AUC) of 0.81.[63]

Conclusion

Aspergillosis occurs in patients without classical host risk factors such as severe immune suppression. Factors associated with IPA are short- or long-term steroids, broad antibiotic therapy, severity of organ failures, chronic or acute pulmonary underlying disease such as COPD or influenza infections, but also ARDS and sepsis survivors. Both colonization and invasive infection are associated with high mortality. Diagnosis relies on alternate classifications dedicated to ICU or COPD patients. Prospective cohorts and post-ICU follow-up studies are needed to enhance the diagnosis and to improve the understanding of the pathophysiology of invasive aspergillosis in such patients.

Conflict of Interest
None declared.

References

1 Herbrecht R, Denning DW, Patterson TF, et al; Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global Aspergillus Study Group. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347(06):408–415
2 Gerson SL, Talbot GH, Hurwitz S, Strom BL, Lusk EJ, Cassileth PA. Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Intern Med 1984;100(03):345–351
3 Soubani AO, Chandrasekar PH. The clinical spectrum of pulmonary aspergillosis. Chest 2002;121(06):1988–1999
4 Segal BH. Aspergillosis. N Engl J Med 2009;360(18):1870–1884
5 Blum J, Reed JC, Pizzo SV, Thompson WM. Miliary aspergillosis associated with alcoholism. AJR Am J Roentgenol 1978;131(04): 707–709
6 Hartemink KJ, Paul MA, Spijkstra JJ, Girbes ARJ, Polderman KH. Immunoparalysis as a cause for invasive aspergillosis? Intensive Care Med 2003;29(11):2068–2071
7 Eckerle I, Ebinger D, Gotthardt D, et al. Invasive Aspergillus fumigatus infection after Plasmodium falciparum malaria in an immuno-competent host: case report and review of literature. Malar J 2009;8:167
8 Dominelli GS, Shaipanich T. Ulcerative tracheobronchitis due to Aspergillus. J Bronchology Interv Pulmonol 2013;20(04):326–329
9 Tavazzi G, Via G, Marzani FC, Mojoli F. Invasive pulmonary aspergillosis after near-drowning. Lancet Infect Dis 2016;16(12):1430
10 Moreno-González G, Ricart de Mesones A, Tazi-Mezalek R, Marron-Moya MT, Rosell A, Mañez R. Invasive pulmonary aspergillosis with disseminated infection in immunocompetent patient. Can Respir J 2016;2016:7984032
11 Meersseman W, Vandecasteele SJ, Wilmer A, Verbeken E, Peetermans WE, Van Wijngaerden E. Invasive aspergillosis in critically ill patients without malignancy. Am J Respir Crit Care Med 2004;170 (06):621–625
12 Vandewoude KH, Blot SI, Depuydt P, et al. Clinical relevance of Aspergillus isolation from respiratory tract samples in critically ill patients. Crit Care 2006;10(01):R31
13 Garnacho-Montero J, Amaya-Villar R, Ortiz-Leyba C, et al. Isolation of Aspergillus spp. from the respiratory tract in critically ill patients: risk factors, clinical presentation and outcome. Crit Care 2005;9(03):R191–R199
14 Bassetti M, Mikulska M, Repetto E, et al. Invasive pulmonary aspergillosis in intensive care units: is it a real problem? J Hosp Infect 2010;74(02):186–187
15 Vincent J-L, Rello J, Marshall J, et al; EPIC II Group of Investigators. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302(21):2323–2329
16 Xu N, Li S, Feng R, Wang D. The clinical monitoring of invasive aspergillosis in surgical intensive care unit during 10 years [in Chinese]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2014;26(09): 634–638
17 Vandewoude KH, Blot SI, Benoit D, Colardyn F, Vogelaers D. Invasive aspergillosis in critically ill patients: attributable mortality and excesses in length of ICU stay and ventilator dependence. J Hosp Infect 2004;56(04):269–276
18 Tejerina E, Esteban A, Fernández-Segoviano P, et al. Clinical diagnoses and autopsy findings: discrepancies in critically ill patients*. Crit Care Med 2012;40(03):842–846
19 Lehrnbecher T, Frank C, Engels K, Kriener S, Groll AH, Schwabe D. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. J Infect 2010;61(03):259–265

20 Dimopoulos G, Piagnerelli M, Berré J, Salmon I, Vincent J-L. Post mortem examination in the intensive care unit: still useful? Intensive Care Med 2004;30(11):2080–2085
21 de Hemptinne Q, Remmelink M, Brimioulle S, Salmon I, Vincent J-L. ARDS: a clinicopathological confrontation. Chest 2009;135 (04):944–949
22 Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. Lancet Infect Dis 2013;13(03):260–268
23 Boomer JS, To K, Chang KC, et al. Immunosuppression in patients who die of sepsis and multiple organ failure. JAMA 2011;306(23): 2594–2605
24 Copland IB, Kavanagh BP, Engelberts D, McKerlie C, Belik J, Post M. Early changes in lung gene expression due to high tidal volume. Am J Respir Crit Care Med 2003;168(09):1051–1059
25 Park WY, Goodman RB, Steinberg KP, et al. Cytokine balance in the lungs of patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2001;164(10, Pt 1):1896–1903
26 Pène F, Courtine E, Ouaaz F, et al. Toll-like receptors 2 and 4 contribute to sepsis-induced depletion of spleen dendritic cells. Infect Immun 2009;77(12):5651–5658
27 Camargo JF, Lobo SA, Hsu AP, Zerbe CS, Wormser GP, Holland SM. MonoMAC syndrome in a patient with a GATA2 mutation: case report and review of the literature. Clin Infect Dis 2013;57(05): 697–699
28 Hsu AP, Johnson KD, Falcone EL, et al. GATA2 haploinsufficiency caused by mutations in a conserved intronic element leads to MonoMAC syndrome. Blood 2013;121(19):3830–3837, S1–S7
29 Picard C, Al-Herz W, Bousfiha A, et al. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015. J Clin Immunol 2015;35(08):696–726
30 De Pauw B, Walsh TJ, Donnelly JP, et al; European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. 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. Clin Infect Dis 2008;46(12):1813–1821
31 Bulpa P, Dive A, Sibille Y. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. Eur Respir J 2007;30(04):782–800
32 Blot SI, Taccone FS, Van den Abeele A-M, et al; AspICU Study Investigators. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. Am J Respir Crit Care Med 2012;186(01):56–64
33 Huang L, He H, Jin J, Zhan Q. Is Bulpa criteria suitable for the diagnosis of probable invasive pulmonary aspergillosis in critically ill patients with chronic obstructive pulmonary disease? A comparative study with EORTC/ MSG and ICU criteria. BMC Infect Dis 2017;17(01):209
34 Perfect JR, Cox GM, Lee JY, et al; Mycoses Study Group. The impact of culture isolation of Aspergillus species: a hospital-based survey of aspergillosis. Clin Infect Dis 2001;33(11):1824–1833
35 Lugosi M, Alberti C, Zahar J-R, et al. Aspergillus in the lower respiratory tract of immunocompetent critically ill patients. J Infect 2014;69(03):284–292
36 Delsuc C, Cottereau A, Frealle E, et al. Putative invasive pulmonary aspergillosis in critically ill patients with chronic obstructive pulmonary disease: a matched cohort study. Crit Care 2015;19:421
37 Barberán J, García-Pérez F-J, Villena V, et al; working group on Infectious Diseases from the Spanish Society of Internal Medicine. Development of aspergillosis in a cohort of non-neutropenic, non-transplant patients colonised by Aspergillus spp. BMC Infect Dis 2017;17(01):34
38 Cornillet A, Camus C, Nimubona S, et al. Comparison of epidemiological, clinical, and biological features of invasive aspergillosis in neutropenic and nonneutropenic patients: a 6-year survey. Clin Infect Dis 2006;43(05):577–584
39 Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. Lancet 2003;362(9398):1828–1838
40 Diamond RD. Inhibition of monocyte-mediated damage to fungal hyphae by steroid hormones. J Infect Dis 1983;147(01):160
41 Diamond RD, Huber E, Haudenschild CC. Mechanisms of destruction of Aspergillus fumigatus hyphae mediated by human monocytes. J Infect Dis 1983;147(03):474–483
42 Schaffner A. Therapeutic concentrations of glucocorticoids suppress the antimicrobial activity of human macrophages without impairing their responsiveness to gamma interferon. J Clin Invest 1985;76(05):1755–1764
43 Ng TT, Robson GD, Denning DW. Hydrocortisone-enhanced growth of Aspergillus spp.: implications for pathogenesis. Microbiology 1994;140(Pt 9):2475–2479
44 Prodanovic H, Cracco C, Massard J, et al. Invasive pulmonary aspergillosis in patients with decompensated cirrhosis: case series. BMC Gastroenterol 2007;7:2
45 Palmer LB, Greenberg HE, Schiff MJ. Corticosteroid treatment as a risk factor for invasive aspergillosis in patients with lung disease. Thorax 1991;46(01):15–20
46 Ader F, Nseir S, Le Berre R, et al. Invasive pulmonary aspergillosis in chronic obstructive pulmonary disease: an emerging fungal pathogen. Clin Microbiol Infect 2005;11(06):427–429
47 He H, Ding L, Sun B, Li F, Zhan Q. Role of galactomannan determinations in bronchoalveolar lavage fluid samples from critically ill patients with chronic obstructive pulmonary disease for the diagnosis of invasive pulmonary aspergillosis: a prospective study. Crit Care 2012;16(04):R138
48 He H, Jiang S, Zhang L, et al. Aspergillus tracheobronchitis in critically ill patients with chronic obstructive pulmonary diseases. Mycoses 2014;57(08):473–482
49 Agustí C, Rañó A, Filella X, et al. Pulmonary infiltrates in patients receiving long-term glucocorticoid treatment: etiology, prognostic factors, and associated inflammatory response. Chest 2003; 123(02):488–498
50 Patel DA, Gao X, Stephens JM, Forshag MS, Tarallo M. US hospital database analysis of invasive aspergillosis in the chronic obstructive pulmonary disease non-traditional host. J Med Econ 2011;14 (02):227–237
51 Guinea J, Torres-Narbona M, Gijón P, et al. Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome. Clin Microbiol Infect 2010;16(07):870–877
52 Wessolossky M, Welch VL, Sen A, Babu TM, Luke DR. Invasive Aspergillus infections in hospitalized patients with chronic lung disease. Infect Drug Resist 2013;6:33–39
53 Contou D, Dorison M, Rosman J, et al. Aspergillus-positive lower respiratory tract samples in patients with the acute respiratory distress syndrome: a 10-year retrospective study. Ann Intensive Care 2016;6(01):52
54 Aubron C, Pilcher D, Leong T, et al. Aspergillus sp. isolated in critically ill patients with extracorporeal membrane oxygenation support. Scand J Infect Dis 2013;45(09):715–721
55 Rodriguez-Goncer I, Thomas S, Foden P, et al. Invasive pulmonary aspergillosis is associated with adverse clinical outcomes in critically ill patients receiving veno-venous extracorporeal membrane oxygenation. Eur J Clin Microbiol Infect Dis 2018;37(07): 1251–1257
56 Garcia X, Mian A, Mendiratta P, Gupta P, Rycus P, Prodhan P. Aspergillus infection and extracorporeal membrane oxygenation support. J Intensive Care Med 2013;28(03):178–184
57 Hasejima N, Yamato K, Takezawa S, Kobayashi H, Kadoyama C. Invasive pulmonary aspergillosis associated with influenza B. Respirology 2005;10(01):116–119

58 Wauters J, Baar I, Meersseman P, et al. Invasive pulmonary aspergillosis is a frequent complication of critically ill H1N1 patients: a retrospective study. Intensive Care Med 2012;38(11):1761–1768
59 Vanderbeke L, Spriet I, Breynaert C, Rijnders BJA, Verweij PE, Wauters J. Invasive pulmonary aspergillosis complicating severe influenza: epidemiology, diagnosis and treatment. Curr Opin Infect Dis 2018;31(06):471–480
60 Schauwvlieghe AFAD, Rijnders BJA, Philips N, et al; Dutch-Belgian Mycosis study group. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med 2018;6(10):782–792
61 Huang L, Zhang N, Huang X, et al. Invasive pulmonary aspergillosis in patients with influenza infection: a retrospective study and review of the literature. Clin Respir J 2019;13(04):202–211
62 Zhang X, Yang M, Hu J, Zhao H, Li L. Epidemiology of invasive pulmonary aspergillosis in patients with liver failure: clinical presentation, risk factors, and outcomes. J Int Med Res 2018;46(02):819–827
63 Acosta J, Catalan M, del Palacio-Peréz-Medel A, et al. A prospective comparison of galactomannan in bronchoalveolar lavage fluid for the diagnosis of pulmonary invasive aspergillosis in medical patients under intensive care: comparison with the diagnostic performance of galactomannan and of (1→ 3)-β-d-glucan chromogenic assay in serum samples. Clin Microbiol Infect 2011;17(07):1053–1060
64 He H, Ding L, Chang S, Li F, Zhan Q. Value of consecutive galactomannan determinations for the diagnosis and prognosis of invasive pulmonary aspergillosis in critically ill chronic obstructive pulmonary disease. Med Mycol 2011;49(04):345–351
65 Meersseman W, Lagrou K, Maertens J, et al. Galactomannan in bronchoalveolar lavage fluid: a tool for diagnosing aspergillosis in intensive care unit patients. Am J Respir Crit Care Med 2008;177 (01):27–34
66 Zhou W, Li H, Zhang Y, et al. Diagnostic value of galactomannan antigen test in serum and bronchoalveolar lavage fluid samples from patients with nonneutropenic invasive pulmonary aspergillosis. J Clin Microbiol 2017;55(07):2153–2161
67 Torelli R, Sanguinetti M, Moody A, et al. Diagnosis of invasive aspergillosis by a commercial real-time PCR assay for Aspergillus DNA in bronchoalveolar lavage fluid samples from high-risk patients compared to a galactomannan enzyme immunoassay. J Clin Microbiol 2011;49(12):4273–4278
68 Rose SR, Vallabhajosyula S, Velez MG, et al. The utility of bronchoalveolar lavage beta-D-glucan testing for the diagnosis of invasive fungal infections. J Infect 2014;69(03):278–283
69 Eigl S, Hoenigl M, Spiess B, et al. Galactomannan testing and Aspergillus PCR in same-day bronchoalveolar lavage and blood samples for diagnosis of invasive aspergillosis. Med Mycol 2017; 55(05):528–534
70 Schroeder M, Simon M, Katchanov J, et al. Does galactomannan testing increase diagnostic accuracy for IPA in the ICU? A prospective observational study. Crit Care 2016;20(01):139
71 Guegan H, Robert-Gangneux F, Camus C, et al. Improving the diagnosis of invasive aspergillosis by the detection of Aspergillus in broncho-alveolar lavage fluid: comparison of non-culture-based assays. J Infect 2018;76(02):196–205