FungaDia-Aspergillus – Selected References

Published Articles and Guidelines

Author(s)	Journal	Year	Title
D'Haese et al.	*J Clin Microbiol.*	*2012*	*Detection of galactomannan in bronchoalveolar lavage fluid samples of patients at risk for invasive pulmonary aspergillosis: analytical and clinical validity*

Summary:
We examined the analytical and clinical validity of galactomannan (GM) testing of bronchoalveolar lavage (BAL) fluid in diagnosing IPA in a mixed population by retrospectively reviewing records of 251 consecutive at risk patients for whom BAL fluid GM testing was ordered. The performance of the enzyme immunoassay was evaluated by using a range of index cutoffs to define positivity. Using a BAL fluid GM index of ≥0.8 (optimal optical density [OD] index cutoff identified by a receiver operating characteristic curve), **the sensitivity in diagnosing proven and probable IPA was 86.4%, and the specificity was 90.7%**. At this cutoff, positive and negative predictive values were 81% and 93.6%, respectively.
Detection of GM in BAL fluid samples of patients at risk of IPA has an excellent diagnostic accuracy provided results are interpreted in parallel with clinico-radiological findings and pretest probabilities.

Author(s)	Journal	Year	Title
Gupta et al.	*J Lab Physicians*	*2017*	*Comparative evaluation of galactomannan test with bronchoalveolar lavage and serum for the diagnosis of invasive aspergillosis in patients with hematological malignancies*

Summary:
Invasive pulmonary aspergillosis (IPA) is a major cause of morbidity and mortality in patients with hematological malignancies. In recent years, testing for values of galactomannan (GM) in serum and bronchoalveolar lavage (BAL) fluid has been investigated as a diagnostic test for IPA. We performed a prospective case–control study to determine an optimal BAL GM OD cutoff for IPA in at-risk patients. Cases were subjects with hematological diagnoses who met established revised definitions for proven or probable IPA established by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC/MSG, 2008), without the use of BAL GM results. Cases had higher BAL fluid GM OD indices (ODIs) (mean: 1.27 and range: 0.4–3.78) compared with controls (mean: 0.26 and range: 0.09–0.35). Receiver operating characteristic analysis demonstrated an optimum ODI cutoff of 1.0, **with high specificity (100%) and sensitivity (87.5%) for diagnosing IPA.**
Our results support BAL GM testing as a reasonably safe test with higher sensitivity compared to serum GM testing in at risk patients with hematological diseases. A higher OD cutoff is necessary to avoid overdiagnosis of IPA.

Author(s)	Journal	Year	Title
Lass-Flörl et al.	*Medical Mycology*	*2019*	*How to make a fast diagnosis in invasive aspergillosis*

Summary:
Aspergillosis is more common among immunocompromised patients with neutropenia or immunosuppression due to corticosteroid use, and infections are typically of the lung or sinuses. For diagnosis, broncholaveolar lavages (BALs) and lung biopsies are the specimens of choice. Culture and microscopic examinations are a must have and laboratory results should immediately be reported to the clinic. Fungal elements (hyphae) display the proof of an infection if present in primarily steril specimens, independent of culture results. Microscopy should be performed preferably using optical brighteners and histopathology using Gomori's methenamine silver stain or Periodic acid–Schiff. **Serum and BAL galactomannan assays are recommended as markers for the diagnosis of invasive aspergillosis**, PCR should be considered in conjunction with other diagnostic tests. Antifungal treatment decreases GM sensitivity.

Lehrnbecher et al.	*Frontiers in Microbiology*	*2018*	*Diagnostic Approaches for Invasive Aspergillsis Specific Considerations in the Pediatric Population*

Summary:
Invasive aspergillosis (IA) is a major cause of morbidity and mortality in children with hematological malignancies and those undergoing hematopoietic stem cell transplantation. Similar to immunocompromised adults, clinical signs, and symptoms of IA are unspecific in the pediatric patient population. As early diagnosis and prompt treatment of IA is associated with better outcome, imaging and non-invasive antigen-based such as galactomannan or ß-D-glucan and molecular biomarkers in peripheral blood may facilitate institution and choice of antifungal compounds and guide duration of therapy. In patients in whom imaging studies suggest IA or another mold infection, invasive diagnostics such as bronchoalveolar lavage and/or bioptic procedures should be considered. Here we review the current data of diagnostic approaches for IA in the pediatric setting and highlight the major differences of performance and clinical utility of the tests between children and adults

Park et al	*Clinical Infectious Diseases*	*2011*	*Serum and Bronchoalveolar Lavage Fluid Galactomannan Assays in Patients with Pulmonary Aspergilloma*

Summary:
The **sensitivities of the serum and bronchoalveolar lavage galactomannan (GM) assays in 48 patients with pulmonary aspergilloma were 38% (13 of 34; 95% confidence interval [CI], 22%–56%) and 92%** (33 of 36; 95% CI, 78%–98%), respectively. The positivity of serum GM assays was significantly higher in patients with hemoptysis than in those without hemoptysis (52% vs 9%; P = 0.02).

Pfeiffer et al.	*Clinical Infectious Diseases*	*2006*	*Diagnosis of Invasive Aspergillosis Using a Galactomannan Assay: A Meta-Analysis*

Summary:
Twenty-seven studies from 1966 to 28 February 2005 were included. Overall, the galactomannan assay had a **sensitivity of 0.71** (95% confidence interval [CI], 0.68–0.74) and **specificity of 0.89** (95% CI, 0.88–0.90) for proven cases of invasive aspergillosis. The Youden index, mean D, and Q* were 0.54 (95% CI, 0.41–0.65), 2.74 (95% CI, 21.12–3.36), and 0.80 (95% CI, 0.74–0.86), respectively, indicating moderate accuracy. Subgroup analyses showed that the performance of the test differed by patient population and type of reference standard used. Significant heterogeneity was present.
The galactomannan assay has moderate accuracy for diagnosis of invasive aspergillosis in immunocompromised patients. The test is more useful in patients who have hematological malignancy or who have undergone hematopoietic cell transplantation than in solid-organ transplant recipients.

Sehgal et al.	*Journal of Clinical Microbiology*	*2019*	*Utility of Serum and Bronchoalveolar Lavage Fluid Galactomannan in Diagnosis of Chronic Pulmonary Aspergillosis*

Summary:
The value of serum and bronchoalveolar lavage fluid galactomannan (BALF-GM) in diagnosing chronic pulmonary aspergillosis (CPA) remains unclear. Here, we study the diagnostic efficacy of GM in the diagnosis of CPA.
We enrolled 243 consecutive treatment-naive subjects (53.5% males) of CPA with a mean (standard deviation) age of 43.6 (14.7) years. Forty-five (60% males; age, 46.7 [15.7] years) and 27 (59.3% males; age, 52.6 [12.8] years) subjects served as controls for serum and BALF-GM, respectively. The best cutoff value for serum and BALF-GM was 0.55 (area under the ROC curve [AUROC], 0.605; **sensitivity, 38%; specificity, 87%)** and 1.375 (AUROC, 0.836; **sensitivity, 68%; specificity, 93%),** respectively. At a cutoff value of 2.5, BALF-GM had a sensitivity and specificity of 50% and 100%, respectively. BALF-GM performs better than serum GM and may be helpful in the diagnosis of CPA in selected patients.

Ullmann et al.	*Clinical Microbiology and Infection*	*2018*	*Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline*

Summary:
The European Society for Clinical Microbiology and Infectious Diseases, the European Confederation of Medical Mycology and the European Respiratory Society Joint Clinical Guidelines focus on diagnosis and management of aspergillosis. Of the numerous recommendations, a few are summarized

here. Chest computed tomography as well as bronchoscopy with bronchoalveolar lavage (BAL) in patients with suspicion of pulmonary invasive aspergillosis (IA) are strongly recommended. For diagnosis, direct microscopy, preferably using optical brighteners, histopathology and culture are strongly recommended. Serum and BAL galactomannan measures are recommended as markers for the diagnosis of IA.

Wu et al.	*Diagnostic Microbiology and Infectious Disease*	*2021*	*Diagnostic value of galactomannan in serum and bronchoalveolar lavage fluid for invasive pulmonary aspergillosis in non-neutropenic patients*

Summary:
To evaluate the diagnostic performance of galactomannan (GM) detection in serum and bronchoalveolar lavage fluid (BALF) for invasive pulmonary aspergillosis (IPA) in non-neutropenic patients. A total of 291 non-neutropenic patients in the Second Xiangya Hospital of Central South University were included. According to the 2019 EORTC/MSG guidelines, all cases were divided into an IPA group (n = 24) and a non-IPA group (n = 267). Receiver operating characteristic (ROC) curves were drawn to compare the diagnostic efficiency of GM detection in BALF and serum. According to the receiver operating characteristic curves of BALF and serum GM, the areas under the curve were 0.961 and 0.699, respectively. The optimal BALF GM detection was found when the cutoff value was set to 0.87, **whereas the sensitivity and specificity were 91.7% and 92.5%, respectively.**
BALF GM detection is more sensitive than serum GM detection for diagnosing IPA, and the optimal cutoff value for BALF GM is 0.87.

Hoenigl et al.	*Open Forum Infect Dis.*	*2019*	*Aspergillus Galactomannan Lateral Flow Assay for Rapid Diagnosis of Invasive Aspergillosis in Bronchoalveolar Lavage*

Summary:
The Aspergillus Galactomannan LFA was retrospectively performed according to the manufacturer's instructions in 106 previously frozen bronchoalveolar lavage fluid (BAL) samples from 106 patients at risk for IPA (23% with underlying hematological malignancies). Samples were collected between September 2016 and September 2018 at the University of California, San Diego. Performance of the LFA was compared with Galactomannan, BAL culture and the Aspergillus-specific LFD (another rapid test for IPA). IPA was classified according to revised EORTC/MSG criteria.
Sensitivity of the **Apergilllus Galactomanann LFA for probable/proven IPA was 77%** (17/22). Sensitivity was similar to BAL GM (77% with a cutoff of 1.0 ODI), but higher compared with the Aspergillus-specific LFD (59%), and BAL culture (23%). The LFA resulted negative in 7/9 cases with possible IPA and 47/73 cases without IPA (overall specificity 66%, 54/82). The less than perfect specificity was driven particularly by non-neutropenic patients (specificity 62%, 43/69), while specificity was 85% among patients with underlying hematological malignancies. **Lower specificity among non-neutropenic patients was also observed for the BAL GM (overall 77%, non-neutropenic patients 72%), the Aspergillus-specific LFD (overall 70%, non-neutropenic patients 67%) and BAL culture (overall 90%, non-neutropenic 88%).**

Linder et al.	*Journal of Fungi*	*2020*	*Performance of Aspergillus Galactomannan Lateral Flow Assay on Bronchoalveolar Lavage Fluid for the Diagnosis of Invasive Pulmonary Aspergillosis*

Summary:
Twenty patients with proven/probable IPA (EORTC/MSGERC criteria) were matched by age and underlying disease with 20 patients without IPA. Bronchoalveolar lavage fluid (BALF) was analyzed in duplicate using the Aspergillus GM-LFA. Results were read visually by two blinded observers, and the optical density index (ODI) was obtained digitally with a cube reader.
Using a cutoff of ≥0.5 ODI, the Aspergillus GM-LFA had a sensitivity of 40%, specificity of 80%, positive predictive value (PPV) of 67% and negative predictive value (NPV) of 57%. When the cutoff was increased to ≥1.0 ODI, **sensitivity remained at 40%, specificity rose to 95%, PPV was 89%, and NPV was 61%.** Excellent agreement was found when duplicate samples were read either visually (κ = 1) or with the cube reader (κ = 0.89). Correlation of results obtained by visual inspection and those obtained using the cube reader was excellent (κ = 0.82). **The Aspergillus GM-LFA had poor sensitivity but excellent specificity for proven/probable IPA in BALF.** The assay was easy to interpret, and there was high concordance between results obtained visually and with a cube reader.

Salzer et al.	*Front. Microbiol*	*2018*	*Evaluation of Galactomannan Testing, the Aspergillus-Specific Lateral-Flow Device Test and Levels of Cytokines in Bronchoalveolar Lavage Fluid for Diagnosis of Chronic Pulmonary Aspergillosis*

Summary:
Patients with CPA (n = 27) and controls (n = 27 with underlying respiratory diseases but without CPA, and n = 27 healthy volunteers) were recruited at the Medical University of Graz, Austria and the Research Center Borstel, Germany between 2010 and 2018. GM, LFD and cytokine testing was performed retrospectively at the Research Center Borstel.
Sensitivity and specificity of GM testing from BALF with a cut off level of ≥0.5 optical density index (ODI) was 41 and 100% and 30 and 100% with a cut off level of ≥1.0 ODI. ROC curve analysis showed an AUC 0.718 (95% CI 0.581–0.855) for GM for differentiating CPA patients to patients with other respiratory diseases without CPA. The LFD resulted positive in only three patients with CPA (7%) and was highly specific. CPA patients did not differ significantly in the BALF cytokine profile compared to patients with respiratory disorders without CPA, but showed significant higher values for IFN-γ, IL-1b, IL-6, IL-8, and TNF-α compared to healthy individuals.
Both GM and LFD showed insufficient performance for diagnosing CPA, with sensitivities of BALF GM below 50%, and sensitivity of the LFD below 10%. The high specificities may, however, result in a high positive predictive value and thereby help to identify semi-invasive or invasive disease.

Mercier et al.	*Crit Care*	*2020*	*Point of care aspergillus testing in intensive care patients*

Summary:
Invasive pulmonary aspergillosis (IPA) is an increasingly recognized complication in intensive care unit (ICU) patients, especially those with influenza, cirrhosis, chronic obstructive pulmonary disease, and other diseases. The diagnosis can be challenging, especially in the ICU, where clinical symptoms as well as imaging are mostly non- specific. Recently, Aspergillus lateral flow tests were developed to decrease the time to diagnosis of IPA. Several studies have shown promising results in bronchoalveolar lavage fluid (BALf) from hematology patients. We therefore evalu- ated a new lateral flow test for IPA in ICU patients.
Using left-over BALf from adult ICU patients in two university hospitals, we studied the performance of the Aspergillus galactomannan lateral flow assay (LFA) by IMMY (Norman, OK, USA). Patients were classified according to the 2008 EORTC-MSG definitions, the AspICU criteria, and the modified AspICU criteria, which incorporate galac- tomannan results.
We included 178 patients, of which 55 were classified as cases (6 cases of proven and 26 cases of probable IPA according to the EORTC-MSG definitions, and an additional 23 cases according to the modified AspICU criteria). Depending on the definitions used, the **sensitivity of the LFA was 0.88–0.94, the specificity was 0.81, and the area under the ROC curve 0.90–0.94, indicating good overall test performance. In ICU patients, the LFA performed well on BALf and can be used as a rapid screening test while waiting for other microbiological results.**

Jenks et al.	*Current Fungal Infection Reports*	*2020*	*The Aspergillus Lateral Flow Assay for the Diagnosis of Invasive Aspergillosis: an Update*

Summary:
Aspergillus spp. cause a wide spectrum of disease with invasive aspergillosis (IA) as its most severe manifes- tation. Early and reliable diagnosis of disease is crucial to decrease associated morbidity and mortality, and enable prompt initiation of treatment for IA. Most recently, non-culture-based tests, such as Aspergillus galactomannan (GM), have been useful in early identification and treatment of patients with IA. However, cost, turnaround time, and variable performance indifferent populations at risk for IA remain significant drawbacks to the use of this test. Several diagnostic tests for IA have been developed, including the soͅna Aspergillus GM Lateral flow assay (GM-LFA) rapid test.
The GM-LFA has shown excellent performance for the diagnosis of IA in patients with hematologic malignancy and may be a viable option for settings where ELISA GM testing is not feasible. Further evaluation of the GM-LFA in the non- hematology setting is ongoing, including in solid organ transplant recipients and patients in the intensive care unit.

Chamroen-sakchai et al.	*Kidney Int Rep*	*2020*	*Serum Galactomannan Index for the Rapid Diagnosis of Fungal Peritonitis in Patients With Peritoneal Dialysis*

Summary:
There were no significant differences among patients with fungal peritonitis (n 1/4 23), bacterial peritonitis (n 1/4 21), and no peritonitis (n 1/4 19) with respect to age, sex, PD vintage, residual kidney function, and comorbidities. Serum GMI in patients with fungal peritonitis was significantly higher than that in patients with bacterial peritonitis and controls without peritonitis (median, 0.85 [interquartile range, 0.43–1.75] vs 0.45 [inter- quartile range, 0.35–0.79] vs. 0.43 [interquartile range, 0.34–0.47], respectively; P 1/4 0.036).
Serum GMI cutoff value of 0.56
provided the best diagnostic accuracy with **65.2% sensitivity, 85.0% specificity,** 4.35 positive likelihood ratio, and 0.41 negative likeli- hood ratio.

Koehler et al.	*Mycoses*	*2020*	*COVID-19 associated pulmonary aspergillosis*

Summary:
A retrospective chart review of all patients with COVID-19 associated ARDS admitted to the medical or surgical intensive care unit at the University Hospital of Cologne, Cologne, Germany. COVID-19 associated invasive pulmonary aspergillosis was found in five of 19 consecutive critically ill patients with moderate to severe ARDS. Clinicians caring for patients with ARDS due to COVID-19 should con- sider invasive pulmonary aspergillosis and subject respiratory samples to compre- hensive analysis to detect co-infection.

Koehler et al.	*Lancet Infect Dis*	*2020*	*Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance*

Summary:
Severe acute respiratory syndrome coronavirus 2 causes direct damage to the airway epithelium, enabling aspergillus invasion. Reports of COVID-19-associated pulmonary aspergillosis have raised concerns about it worsening the disease course of COVID-19 and increasing mortality. Additionally, the first cases of COVID-19-associated pulmonary aspergillosis caused by azole-resistant aspergillus have been reported. This article constitutes a consensus statement on defining and managing COVID-19-associated pulmonary aspergillosis, prepared by experts and endorsed by medical mycology societies. COVID-19-associated pulmonary aspergillosis is proposed to be defined as possible, probable, or proven on the basis of sample validity and thus diagnostic certainty. Recommended first-line therapy is either voriconazole or isavuconazole. If azole resistance is a concern, then liposomal amphotericin B is the drug of choice. Our aim is to provide definitions for clinical research and up-to-date recommendations for clinical management of the diagnosis and treatment of COVID-19-associated pulmonary aspergillosis.

Van Arkel et al.	*American Journal of Respiratory and Critical Care Medicine*	*2020*	*COVID-19–associated Pulmonary Aspergillosis*

Summary:
In the first 3 weeks of the outbreak, 135 adult patients with laboratory-confirmed COVID-19 were admitted to the Amphia Hospital Breda, a 700-bed teaching hospital. Of these patients, 31 (23%) required mechanical ventilation on ICU. Eleven ICU patients with COVID-19 developed a secondary infection, of whom six (19.4%) were presumed to have IPA. We identified Aspergillus fumigatus in five patients, and in three patients, the Aspergillus antigen galactomannan (GM) (Platelia Aspergillus; Biorad) was found positive on BAL fluid

Lahmer et al.	*PLOS ONE*	*2021*	*Invasive pulmonary aspergillosis in critically ill patients with severe COVID-19 pneumonia: Results from the prospective AspCOVID-19 study*

Summary:
We prospectively screened 32 critically ill patients with severe COVID-19 pneumonia for a time period of 28 days using a standardized study protocol for oberservation of developement of COVID-19 associated invasive pulmonary aspergillosis (CAPA). We collected laboratory, microbiological, virological and clinical parameters at defined timepoints in combination with galactomannan-

antigen-detection from nondirected bronchial lavage (NBL). We used logistic regression analyses to assess if COVID-19 was independently associated with IPA and compared it with matched controls.
CAPA was diagnosed at a median of 4 days after ICU admission in 11/32 (34%) of critically ill patients with severe COVID-19 pneumonia as compared to 8% in the control cohort. In the COVID-19 cohort, mean age, APACHE II score and ICU mortality were higher in patients with CAPA than in patients without CAPA (36% versus 9.5%; p<0.001). ICU stay (21 versus 17 days; p = 0.340) and days of mechanical ventilation (20 versus 15 days; p = 0.570) were not different between both groups. In regression analysis COVID-19 and APACHE II score were independently associated with IPA. CAPA is highly prevalent and associated with a high mortality rate. COVID-19 is independently associated with invasive pulmonary aspergillosis.

Lai et al.	*J Microbiol Immunol Infect*	*2021*	*COVID-19 associated with pulmonary aspergillosis: A literature review*

Summary:
Bacterial or virus co-infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been reported in many studies, however, the knowledge on Aspergillus co-infection among patients with coronavirus disease 2019 (COVID-19) was limited. This literature review aims to explore and describe the updated information about COVID-19 associated with pulmonary aspergillosis. We found that Aspergillus spp. can cause co-infections in patients with COVID-19, especially in severe/critical illness. The incidence of IPA in COVID-19 ranged from 19.6% to 33.3%. Acute respiratory distress syndrome requiring mechanical ventilation was the common complications, and the overall mortality was high, which could be up to 64.7% (n = 22) in the pooled analysis of 34 reported cases. The conventional risk factors of invasive aspergillosis were not common among these specific populations. Fungus culture and galactomannan test, especially from respiratory specimens could help early diagnosis. Aspergillus fumigatus was the most common species causing co-infection in COVID-19 patients, followed by Aspergillus flavus. Although voriconazole is the recommended anti-Aspergillus agent and also the most commonly used antifungal agent, aspergillosis caused by azole-resistant Aspergillus is also possible. Additionally, voriconazole should be used carefully in the concern of complicated drug-drug interaction and enhancing cardiovascular toxicity on anti-SARS-CoV-2 agents. Finally, this review suggests that clinicians should keep alerting the possible occurrence of pulmonary aspergillosis in severe/critical COVID-19 patients, and aggressively microbiologic study in addition to SARS-CoV-2 via respiratory specimens should be indicated.

Chong et al	*The Journal of Hospital Infection*	*2021*	*Incidence, diagnosis and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review*

Summary:
COVID-19-associated pulmonary aspergillosis (CAPA) is defined as invasive pulmonary aspergillosis occurring in COVID-19 patients. The purpose of this review was to discuss the incidence, characteristics, diagnostic criteria, biomarkers, and outcomes of hospitalized patients diagnosed with CAPA. A literature search was performed through Pubmed and Web of Science databases for articles published up to 20th March 2021. In 1421 COVID-19 patients, the overall CAPA incidence was 13.5% (range 2.5–35.0%). The majority required invasive mechanical ventilation (IMV). The time to CAPA diagnosis from illness onset varied between 8.0 and 16.0 days. However, the time to CAPA diagnosis from intensive care unit (ICU) admission and IMV initiation ranged between 4.0–15.0 days and 3.0–8.0 days. The most common diagnostic criteria were the modified AspICU–Dutch/Belgian Mycosis Study Group and IAPA-Verweij et al. A total of 77.6% of patients had positive lower respiratory tract cultures, other fungal biomarkers of bronchoalveolar lavage and serum galactomannan were positive in 45.3% and 18.2% of patients. The CAPA mortality rate was high at 48.4%, despite the widespread use of antifungals. Lengthy hospital and ICU stays ranging between 16.0–37.5 days and 10.5–37.0 days were observed. CAPA patients had prolonged IMV duration of 13.0–20.0 days. The true incidence of CAPA likely remains unknown as the diagnosis is limited by the lack of standardized diagnostic criteria that rely solely on microbiological data with direct or indirect detection of Aspergillus in respiratory specimens, particularly in clinical conditions with a low pretest probability. A well-designed, multi-centre study to determine the optimal diagnostic approach for CAPA is required.