



How to lose resistance to *Aspergillus* infections

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SPOTLIGHT

Tentative title:

How to Lose Resistance to Aspergillus Infections

Alternative titles (at your convenience):

- *How to Lose Resistance to Aspergillus Infections if your Neutrophils are Intact*
- *Unravelling the Mechanism of Aspergillosis in non-Neutropenic ICU Patients*

Jean-Pierre Gangneux^{1,2*}, Martin Hoenigl^{3,4,5}, Nicolas Papon⁶

¹ Inserm, EHESP, IRSET (Institut de Recherche en Santé, Environnement et Travail)-UMR_S 1085, CHU Rennes, Univ Rennes, F-35000 Rennes, France.

² Laboratory of Parasitology and medical mycology, European Confederation of Medical Mycology (ECMM) Excellence Center, Rennes Teaching Hospital, F-35000 Rennes, France.

³ Division of Infectious Diseases, Department of Internal Medicine, Medical University of Graz, Graz, Austria.

⁴ BioTechMed-Graz, Graz, Austria.

⁵ Translational Medical Mycology Research Unit, European Confederation of Medical Mycology (ECMM) Excellence Center, Medical University of Graz, Graz, Austria.

⁶ Univ Angers, Univ Brest, IRF, SFR ICAT, F-49000 Angers, France.

Correspondence: jean-pierre.gangneux@univ-rennes1.fr (JP. Gangneux)

ORCID:

JP. Gangneux: <https://orcid.org/0000-0002-4974-5607>

M. Hoenigl: <https://orcid.org/0000-0002-1653-2824>

N. Papon: <https://orcid.org/0000-0001-6265-7321>

Twitter:

JP. Gangneux: @GangneuxJp

M. Hoenigl: @martinhoenigl

N. Papon: @NicolasPapon49

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Abstract

The distinct risk factors to deadly infections by *Aspergillus fumigatus* in ICU patients are well known, however, the mechanistic link between these predisposing conditions was unknown so far. Sarden et al. recently unraveled a shared B1a lymphocytes-natural antibodies-neutrophils defense pathway to *A. fumigatus*, opening new perspectives in diagnostics and therapeutics.

48 Fungal infections represent a global burden worldwide. While superficial fungal infections
49 account for a large proportion of the overall worldwide prevalence of mycoses and fortunately are
50 rarely fatal, invasive fungal infections are characterized by dramatic high morbidity, mortality, and
51 economic burden. Invasive fungal infections are killing approximately 1.5 million people annually
52 [1]. To tackle the steady increase of invasive fungal infections, the WHO provided recently a first
53 global response to identify and prioritize fungal pathogens according to their impact on global public
54 health for considering the unmet research and development needs [2].

55 Among the list of four fungal species of critical importance topping the WHO Fungal Priority
56 Pathogens List stands *Aspergillus fumigatus* (*Af*), one of the most ubiquitous of the airborne
57 saprophytic fungi [3]. By filtering more than 10,000 liters of unsterile air daily, our lungs inhale
58 thousands of *Af* spores. Although mucociliary clearance ensures an efficient mechanical expulsion of
59 a significant amount of these particles, the small spores of *Af* can easily get stuck in alveoli gaps.
60 Yet it is intriguing that most humans do not develop any illness attributable to *Af* and do not display
61 any evidence of antibody- or cell-mediated acquired immunity to this microorganism in case of
62 asymptomatic carriage. This teaches us that, for most healthy individuals, the local and innate
63 immune response is sufficient to clear the organism without requiring intervention of an acquired
64 immunity [4].

65 Risk factors predisposing to *Af* infections are now well-recognized, in particular defective or
66 deficient neutrophils, underlying the central role of these white cells as first line defense for naturally
67 combating *Af*. However, the fact that non-neutropenic intensive care unit (ICU) patients receiving
68 long-term systemic corticosteroid therapy and even immunocompetent people once affected by
69 acute respiratory failure driven by influenza A virus (IAV) and acute respiratory syndrome
70 coronavirus 2 (SARS-CoV-2) can also develop life-threatening *Af* infections suggest that other
71 contributors than neutrophils may act to maintaining essential pulmonary host resistance to this
72 mold [5-8]. While the diverse risk factors to losing defenses to *Af* and the essential role of neutrophils
73 in killing this fungal pathogen are well ingrained in the literature, the mechanistic relationship that
74 could link and explain the diverse predisposing conditions to losing resistance to deadly *Af* infections
75 remains unknown. In such perspective, unprecedented insights into a shared host resistance
76 pathway disrupted during viral and steroid-associated aspergillosis were gained recently through a
77 remarkable report by the research group of Bryan G. Yipp published in *Science Translational Medicine*
78 [9].

79
80 In a first series of investigations, Sarden and colleagues demonstrated that sera from
81 individuals with either severe IAV or SARS-CoV-2 infection had decreased concentrations of specific
82 anti-*A. fumigatus* IgG (anti-*Af* IgG). By developing an IAV/*Af* coinfection mouse model, the
83 pathophysiological relevance was further underscored by revealing that these viral infections trigger
84 a decrease in circulating anti-*Af* IgG and impair resistance to *Af in vivo*. In addition, by taking
85 advantage of an *Af* fluorescent reporter strain, Sarden et al. provided evidence that lung neutrophils
86 are hampered in their capacity to capture fungal spores while neutrophil recruitment was found
87 unchanged in the context of a IAV/*Af* co-infection.

88 Because healthy people display innate resistance to *Af* in the absence of prior infection or
89 immunization, the research group of Bryan G. Yipp then postulated that natural antibodies produced
90 by B1 innate lymphocytes may regulate neutrophil-mediated phagocytosis *in vivo*. In this respect,
91 by combining different models of infection in various mice genetic backgrounds, serum transfer

experiments, monoclonal antibody administration, and transcriptional profiling of donor samples, investigators elegantly validated this hypothesis. It is noteworthy that decrease in anti-*Af*IgG stands out as a common and conserved mechanism of acquired host susceptibility to invasive aspergillosis since steroid treatment also diminished these specific antibodies in mice. Importantly, further experiments revealed that this decreased serum concentration in anti-*Af*IgG during viral infection (IAV or SARS-CoV-2) or following corticosteroid treatment commonly derived from the depletion of circulating B1 lymphocytes in patients.

In a last series of experimentations, Sarden and colleagues aimed at identifying the essential host resistance pathway that is impaired during SARS-CoV-2 for explaining the high prevalence of COVID-19-associated pulmonary aspergillosis (CAPA) [6,7]. Following the observation that SARS-CoV-2 spike (S) protein triggers B1a apoptosis *in vivo*, investigators engineered a Vesicular stomatitis virus expressing the SARS-CoV-2 S protein (VSV-GS pseudovirus) for developing a mouse model mimicking CAPA. Co-infection of wild-type mice by VSV-GS pseudovirus and *Af* resulted in high mortality associated to a marked decrease in serum anti-*Af*IgG levels, similarly to that observed in the IAV-aspergillosis model. This added string evidence that the break in *Af*resistance during CAPA is conditioned by a loss in B1a cells and natural antibodies.

Overall, all the data compiled in this enlightening article converge toward the unifying evidence that during infection with IAV or SARS-CoV-2 or following corticosteroid treatment, *Af* innate immunity is disrupted and results from the death of B1a lymphocytes leading in turn to depletion of anti-*Af* IgG thereby allowing the fungus to remain concealed from recruited lung neutrophils, leaving the door open for fungal germination and tissue invasion (**Figure 1**).

To summarize, Sarden and colleagues findings highlight a new B1a lymphocytes - natural anti-*Af* IgG - neutrophils axis governing the innate resistance to one of the most critical fungal pathogens (**Figure 1**) [9]. Above all, it is important to applaud the Bryan G. Yipp research group for having focused their investigations toward a putative role of B-cells in the defense toward *Af* infection. This approach contrasted most of the existing literature on antifungal immunity, focusing primarily on T-cells [10]. The identification of B1a cells and anti-*Af*IgG as essential components of the host innate immunity to *Af* that are lost during IAV and SARS-CoV-2 but also after corticosteroid treatment nicely complement the established knowledge on neutrophils as a key cell population for host defense against *Af* (**Figure 1**). In fact, the relevance of neutrophils for protection against fatal aspergillosis was inferred in early descriptions of invasive pulmonary aspergillosis because of its prevalence in individuals with impaired neutrophil numbers or functions such as neutropenic patients, those with inherited immune deficiency or chronic granulomatous disease, and those receiving allogeneic stem cell transplants (**Figure 1**). The seminal study by Sarden et al. provides original mechanistic explanation for resistance breakdown to aspergillosis in at least three distinct clinical contexts. The identification of new actors adding to neutrophils and the discovery of an essential cooperative pathways involved in natural defense against *Af* now unveils the functional relationship that could link and explain a multitude of diverse risk factors predisposing to this life-threatening fungal infection. Finally, this groundbreaking work not only opens exciting perspectives for diagnostics considering the possibility to stratify the risk of fatal aspergillosis by determining the concentration of anti-*Af*IgG in the serum of patients but also propels future hope in therapeutics by using pooled sera from healthy donors or biotechnologically-produced anti-*Af*IgG.

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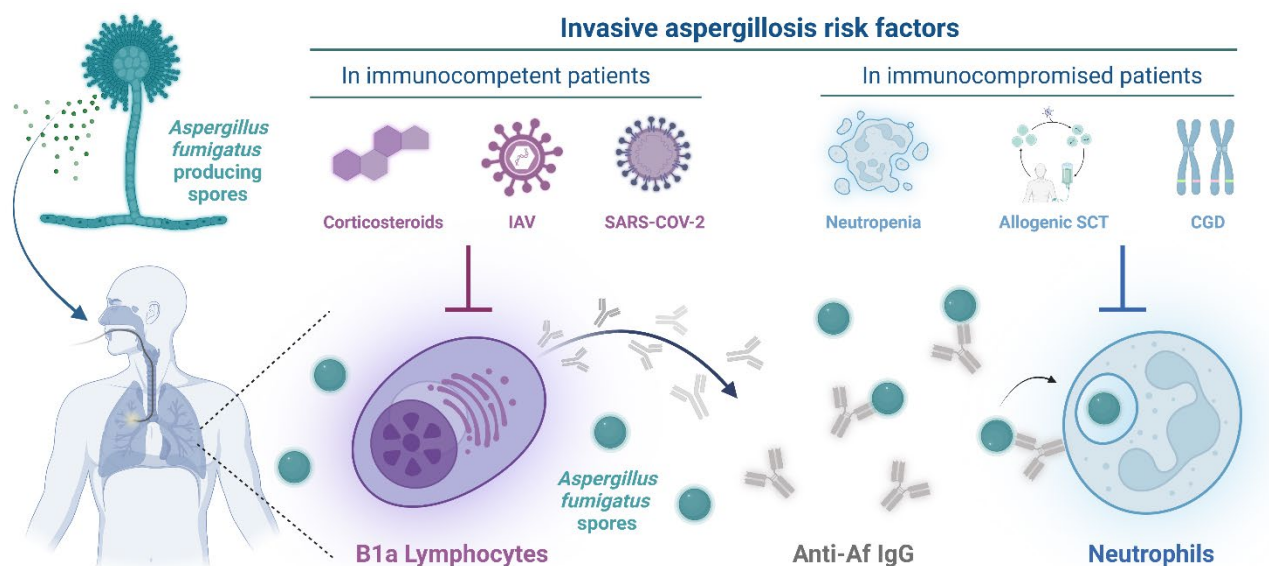


Figure 1. A new core resistance pathway to *Aspergillus fumigatus* (Af) infections. Lungs inhale thousands of Af spores daily. However, healthy humans do not develop any illness attributable to Af. Risk factors predisposing to Af infections are now well-categorized and include primarily immunosuppressed patients such as those for instance with neutropenia, undergoing allogeneic stem cell transplantation (SCT), or with chronic granulomatous disease (CGD) (right upper panel). T-cell suppression may also play a role in other patient groups (not shown). Immunocompetent patients receiving long-term systemic corticosteroid therapy or affected by pneumonia driven by SARS- IAV and CoV-2 (left upper panel) can also develop life-threatening Af infections. In their new report, Sarden and colleagues detailed the mechanistic relationship that explain the diverse predisposing conditions to losing resistance to deadly Af infections by highlighting a B1a lymphocytes - natural anti-Af IgG - neutrophils axis (lower panel) governing the innate resistance to this prominent fungal pathogen.