Invasive fungal diseases in patients with autoimmune diseases: a case series from the French RESSIF network

Simon Galmiche, Benjamin Thoreau, Stéphane Bretagne, Alexandre Alanio, André Paugam, Valérie Letscher-Bru, Sophie Cassaing, Jean-Pierre Gangneux, Hélène Guegan, Loïc Favennec, et al.

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Invasive fungal diseases in patients with autoimmune diseases: a case series from the French RESSIF network

Simon Galmiche ,[1,2] Benjamin Thoreau,[3,4] Stéphane Bretagne,[5,6] Alexandre Alanio,[5,6] André Paugam,[7] Valérie Letscher-Bru,[8,9] Sophie Cassaing,[10,11] Jean-Pierre Gangneux,[12] Hélène Guegan,[12] Loïc Favennec,[13,14] Alida Minoza,[15,16] Florent Morio,[17,18] Julie Bonhomme,[19] Guillaume Desoubeaux,[20,21] Odile Eloy,[22] Lilia Hasseine,[23] Milène Sasso,[24] Laurence Millon,[25,26] Anne-Pauline Bellanger,[25] Philippe Poirier,[27,28] Maxime Moniot,[27] Taieb Chouaki,[29] Antoine Huguenin,[30] Frédéric Dalle,[31,32] Bernard Bouteille,[33] Muriel Nicolas,[34] Nicole Desbois-Nogard,[35] Marie-Elisabeth Bougnoux,[36,37] François Danion,[38,39] Vincent Poindron,[40] Antoine Néel,[41,42] Karine Boukris-Sitbon,[6] Fanny Lanternier,[6,43] Benjamin Terrier ,[3,44] French Mycoses Study Group

To cite: Galmiche S, Thoreau B, Bretagne S, *et al*. Invasive fungal diseases in patients with autoimmune diseases: a case series from the French RESSIF network. *RMD Open* 2023;**9**:e003281. doi:10.1136/rmdopen-2023-003281

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2023-003281).

Received 3 May 2023
Accepted 28 July 2023

For numbered affiliations see end of article.

Correspondence to
Dr Simon Galmiche;
simon.galmiche@pasteur.fr

ABSTRACT

Objectives We aimed to describe patients with autoimmune diseases (AID) developing invasive fungal disease (IFD) and identify factors associated with short-term mortality.

Methods We analysed cases of IFD associated with AID from the surveillance network of invasive fungal diseases (Réseau de surveillance des infections fongiques invasives, RESSIF) registry of the French national reference centre for invasive mycoses. We studied association of AID-specific treatments with 30-day mortality. We analysed total lymphocyte and CD4-T cell counts in patients with *Pneumocystis jirovecii* pneumonia (PCP).

Results From 2012 to 2018, 549 individuals with IFD and AID were included, mainly with PCP (n=227, 41.3%), fungemia (n=167, 30.4%) and invasive aspergillosis (n=84, 15.5%). Rheumatoid arthritis (RA) and anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) were the most frequent AID in PCP (n=55 and 25, respectively) and invasive aspergillosis (n=15 and 10, respectively), inflammatory bowel diseases (IBDs) were predominant in fungemia (n=36). At IFD diagnosis, 365 (66.5%) patients received glucocorticoids (GCs), 285 (51.9%) immunosuppressants, 42 (7.7%) tumor necrosis factor (TNF)-α blockers, 75 (13.7%) other biologics. Mortality at 30 days was 28.1% (143/508). Fungemia and high-dose GCs were independently associated with higher 30-day mortality. In PCP patients, lymphopenia <1500/mm^3 was frequent (132/179, 73.7%) even if CD4+T cell count exceeded 200/mm^3 in 56/78 patients (71.8%) (median 472.5/mm^3, IQR 160–858).

Conclusion IFD associated with AID occurs primarily in RA, AAV and IBD, especially when treated with GCs and immunosuppressants. Mortality is high, especially for patients on high-dose GCs. Lymphopenia may help identify risk of PCP, but normal CD4+T cell count does not rule out the risk. Further studies are needed to assess the individual risk factors for IFD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Invasive fungal diseases can occur in patients with autoimmune diseases but evidence on profiles of patients at risk and prognosis remains scarce.

WHAT THIS STUDY ADDS

⇒ *Pneumocystis jirovecii* pneumonia (PCP) is the most frequent invasive fungal disease in patients with autoimmune diseases (often in patients with CD4−T cell counts above 200/mm^3), ahead of fungemia and invasive aspergillosis. Most frequently associated autoimmune diseases are rheumatoid arthritis, anti-neutrophil cytoplasmic antibodies (ANCA-associated vasculitides, sarcoidosis and inflammatory bowel diseases. Mortality is high, particularly in cases of fungemia and patients who received high doses of glucocorticoids.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings will help raise physicians' awareness to guide diagnostic investigations in clinical practice and will contribute to inform individual PCP prophylaxis indications.

INTRODUCTION

Invasive fungal diseases (IFD) are rare but potentially severe opportunistic infections that can occur in patients with autoimmune diseases (AID) treated with glucocorticoids (GCs), immunosuppressants and/or biologics such as anti-CD20 agents or tumor necrosis factor (TNF)-α blockers. The most frequently reported IFD in patients with AID is *Pneumocystis jirovecii* pneumonia

(PCP). In case series, systemic GCs and immunosuppressive agents were frequently reported,[1 2] suggesting iatrogenic contribution in the occurrence of PCP. PCP-related mortality is higher in patients with AID than in people living with HIV,[3] ranging between 34% and 46%.[1 2 4] The most frequent AID associated with IFD are rheumatoid arthritis, mainly treated with biologics,[5 6] systemic lupus erythematosus (SLE)[4] and anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV).[2 4 7] Other predisposing AID have been reported, mainly dermatomyositis,[2 4] inflammatory bowel diseases (IBD)[8] or giant cell arteritis.[9] Comparative estimates suggest that patients with granulomatosis with polyangiitis (GPA) and dermatomyositis may be at the highest risk among patients with AID.[10 11]

Data on fungemia or invasive candidiasis in patients with AID are scarcer. Apart from a case series of *Candida* spp bloodstream infections,[12] most studies included both non-invasive and invasive candidiasis.[8 13] Invasive aspergillosis has been mostly reported in patients with SLE[14] or AAV,[15] and cryptococcosis in patients with sarcoidosis[16] and SLE,[17–19] the latter being also the main AID in patients with mucormycosis.[20]

However, a comprehensive description with multicentre enrolment of all IFD and AID is still lacking. This could provide representative data, minimising centre and publication bias and identify the scope of AID particularly affected by a particular IFD. The latter may be crucial for the design of targeted prophylaxis strategies, such as PCP prophylaxis (often based on trimethoprim-sulfamethoxazole, TMP-SMX), for which evidence-based recommendations in patients with AID exist but mostly fail to take into account the type of underlying AID or antirheumatic drug due to lack of evidence.[21] The strongest indication recommended by the American Thoracic Society is based on the prescription of GCs over 20 mg/day for over a month, but this recommendation does not take into account the type of AID.[22] Furthermore, while the monitoring of CD4+T cells to estimate the risk of PCP is recommended in some AID, there is little evidence in patients with AID specifically to support this practice, which is largely based on studies in people living with HIV.[22 23]

The surveillance network of invasive fungal diseases (Réseau de surveillance des infections fongiques invasives, RESSIF) has been prospectively collecting all cases of IFDs in a number of centres in France since 2012.[24] Our objectives were to describe the population of patients with an AID who developed an IFD and to determine how the treatment of the AID affects the IFD-related mortality.

METHODS

Patients

The RESSIF network was started in 2012 by the French National Reference Center for Invasive Mycoses and Antifungals (NRCMA, Institut Pasteur, Paris, France).[24] It is an active surveillance system involving 29 participating secondary and tertiary centres across metropolitan France and overseas French territories, with 21 centres who were active between 2013 and 2018 (and 13 centres in 2012). All IFDs occurring in these centres are prospectively and manually notified. These 21 university hospitals cover approximately 45% of hospitalisation days of all French university hospitals and cover 15/18 French regions, including overseas territories. Each collaborative centre aggregates several hospitals or wards, including adults and paediatric patients. A referent medical mycologist is responsible for the accuracy and completeness of the records based on local diagnosis in collaboration with clinicians and all data are monitored at National Reference Center by a senior physician. Participating centres are not only responsible for fungal identification but also send their isolates for central characterisation at the NRCMA except for the common species unless the isolate exhibited an unusual antifungal susceptibility profile. We applied diagnostic criteria as defined in the paper by Bretagne *et al*,[24] reporting the complete data of the RESSIF network, that is, those defined in 2008 by the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium,[25] except for PCP for which no criteria were defined during the study period: cases of PCP were declared in the registry relying on mycological evidence (microscopical detection or *Pneumocytis jirovecii* PCR) and a clinical context consistent with PCP diagnosis. Proven and probable invasive aspergillosis were defined according to the criteria mentioned above with the addition of positive PCR tests only that were also included as probable, in line with the 2020 update.[25 26] Further methods on diagnostic classification, the surveillance system structure and the information system for case notification have been described before.[24]

We identified patients in the registry for whom a diagnosis of systemic disease was reported. We included patients with an episode of IFD between 1 January 2012 and 31 December 2018. We excluded patients for whom the nature of the underlying AID could not be confirmed in the medical record or for whom the underlying systemic disease was not autoimmune (eg, genetic, amyloidosis).

Clinical and laboratory assessment

Notification data include demographic, diagnostic and therapeutic information, details on underlying conditions and concomitant medications. We retrieved further data using local access to electronic health records, including the nature of the AID, year of diagnosis, dose of GCs at the time of IFD diagnosis and latest total lymphocyte and CD4+T cell counts (if measured within the previous 3 months) for patients with PCP.

We described the population of patients with AID affected by IFD, by breaking down the population according to the main IFD categories (PCP, fungemia,

invasive aspergillosis) and reporting patients with several IFDs or another IFD in separate groups.

For the analysis on how the treatment of the AID affected the mortality, the outcome was mortality at 30 days.

Statistical analysis

Comparisons were made using non-parametric Kruskal-Wallis test for quantitative variables and the χ^2 or Fisher's exact test as appropriate for qualitative parameters. We investigated the association of various AID-specific treatments (GCs, immunosuppressants, TNF-α blockers, other biologics) with 30-day mortality in a multivariable logistic regression model adjusted for demographic characteristics (sex as binary variable, age in years as continuous variable), underlying conditions (solid cancer, haematological malignancy, solid organ transplantation, cirrhosis, renal or respiratory failure), co-occurring bacterial or viral infection, type of IFD (PCP, fungemia, invasive aspergillosis, multiple IFD, other IFD) and underlying AID (rheumatoid arthritis, other chronic inflammatory rheumatism, other connective tissue disease, IBD, sarcoidosis, systemic vasculitis, other AID). We also described separately the patients who did not have any other risk factor for IFD among malignancy, solid organ transplantation and recent surgery. We calculated the age-standardised and sex-standardised estimates for the main characteristics of the study population for the three main IFDs (PCP, fungemia, invasive aspergillosis) as well as across the 12 most frequent AIDs in the study, using the data on the French population (in 5-year age categories) provided by the World Bank for 2015.[27] Data were analysed using Stata/IC V.15.1 (College Station, Texas).

RESULTS

From 1 January 2012, to 31 December 2018, we identified 660 patients presenting an IFD with an underlying AID, among which 111 patients were excluded for the following reasons: non-confirmed AID (n=107), IFD diagnosis subsequently excluded (n=3), aspergillosis identified as chronic and not invasive (n=1). In total, 549 patients with a confirmed AID and at least one IFD were collected.

Characteristics of IFD

Main characteristics of the study population are presented in table 1. IFDs were mainly PCP (n=227, 41.3%), fungemia (n=167, 30.4%) and invasive aspergillosis (n=84, 15.3%), and less frequently other IFD (n=58, 10.6%) including cryptococcosis (n=20, 3.6%), deep-seated tissue candidiasis (n=19, 3.5%) or another IFD (n=19, 3.5%).

The cases of fungemia were due to *Candida* spp in 155 (92.8%), including *C. albicans* (n=81, 48.5%), *C. glabrata* (n=28, 16.8%), *C. parapsilosis* (n=20, 12.0%) and *C. tropicalis* (n=12, 7.2%). Further details on infection sites as well as species responsible for fungemia, description of population with fungemia comparing *Candida* spp fungemia and non-*Candida* spp fungemia, deep-seated tissue candidiasis and other IFD are available in online supplemental materials (online supplemental tables S1–S4). Thirteen patients (2.4%) presented several concomitant IFD, including seven with both PCP and invasive aspergillosis (online supplemental table S5). Most cases of invasive aspergillosis were probable (n=73, 86.9%) while 11 (13.1%) were proven. Seventy-five (89.3%) were pulmonary infections (online supplemental table S6). When documented (n=52, 61.9%), the most frequent species responsible for invasive aspergillosis was *Aspergillus fumigatus* (n=44, 84.6%).

Additional risk factors for IFD were common. One hundred and fifty-nine patients (29.0%) had at least one risk factor among haematological malignancy (n=74, 13.5%), solid cancer (n=63, 11.5%) or solid organ transplantation (n=34, 6.2%). Solid cancer was frequent in patients with fungemia (19.8%), while haematological malignancy (35.7%) and solid organ transplantation (14.5%) were common in patients with invasive aspergillosis (table 1). Among cases of fungemia, use of central catheters (n=111, 66.5%) and recent surgical procedure (n=55, 32.9%) were frequent.

When restricted to patients without malignancy, solid organ transplantation or recent surgery, 342 patients were identified, including 189 with PCP, 70 with fungemia and 39 with invasive aspergillosis. This subpopulation was largely comparable with the overall study population in terms of demographics, underlying AID, or associated treatments (online supplemental tables S7 and S8).

Characteristics of AIDs

Rheumatoid arthritis was the most frequent underlying AID, both overall (n=113, 20.6%), and among cases of PCP (n=55, 24.2%) and invasive aspergillosis (n=15, 17.9%) (table 2). Crohn's disease (n=29, 17.4%) and rheumatoid arthritis (n=28, 16.8%) were the most represented AID among fungemia. Other diseases highly represented in PCP included AAV (n=25, 11.0%), dermatomyositis (n=21, 9.3%) and sarcoidosis (n=19, 8.4%), in cases of invasive aspergillosis AAV and sarcoidosis (n=10 each, 11.9%), and SLE (n=9, 10.7%), and in cases of fungemia SLE (n=12, 7.2%). Details on the less frequent AID are available in online supplemental materials (online supplemental table S9). Ninety patients (16.4%) presented at least two concomitant AID. The most frequent combination was rheumatoid arthritis and Sjögren's syndrome (n=9, including one patient with associated primary biliary cholangitis) (details available in online supplemental table S10). The population description by AID, including comorbidities, treatments and mortality, is available in online supplemental table S11 as well as the age-standardised and sex-standardised proportions in online supplemental table S12.

The year of AID diagnosis was available in 409 (74.5%) patients. IFD occurred in median 4 years (IQR 1–12) after diagnosis of AID. Median interval between AID diagnosis

Table 1 Patients with autoimmune disease presenting an episode of invasive fungal disease (IFD)

	Pneumocystis pneumonia (227)	Fungemia (167)*	Invasive aspergillosis (84)	Other IFD (58)	Multiple IFD (13)	Total (549)	P value†
Age (years) (median (IQR))	68 (59–76)	64 (52–74)	59.5 (49.5–70)	64 (54–72)	67 (58–69)	65 (55–74)	**<0.001**
Female sex	117 (51.5)	86 (51.5)	32 (38.1)	31 (53.5)	9 (69)	275 (50.1)	0.08
Solid cancer	16 (7.1)	33 (19.8)	6 (7.1)	8 (13.8)	0	63 (11.5)	**<0.001**
Haematological malignancy	13 (5.7)	21 (12.6)	30 (35.7)	6 (10.3)	4 (31)	74 (13.5)	**<0.001**
Solid organ transplantation	8 (3.5)	9 (5.4)	12 (14.5)	3 (5.2)	2 (15)	34 (6.2)	**0.01**
Diabetes mellitus	42 (18.5)	27 (16.2)	14 (16.7)	6 (10.3)	2 (15)	91 (16.6)	0.82
Central catheter	12 (5.3)	111 (66.5)	18 (21.4)	8 (13.8)	3 (23)	152 (27.7)	**<0.001**
Neutropenia	0	10 (6.0)	14 (16.7)	2 (3.5)	3 (23)	29 (5.3)	**<0.001**
Chronic renal failure	27 (11.9)	32 (19.2)	12 (14.3)	3 (5.2)	3 (23)	77 (14.1)	0.13
Chronic respiratory failure	13 (5.7)	21 (12.6)	7 (8.3)	3 (5.2)	2 (15)	46 (8.4)	0.06
Cirrhosis	9 (4.0)	6 (3.6)	9 (10.7)	0 (0)	1 (8)	25 (4.6)	0.05
Recent surgery	3 (1.3)	55 (32.9)	6 (7.1)	9 (15.5)	0 (0)	73 (13.3)	**<0.001**
Intensive care unit	67 (29.5)	72 (43.1)	31 (36.9)	9 (15.5)	7 (54)	186 (33.9)	**0.02**
Mortality at 30 days‡	42/207 (20.3)	66/151 (43.7)	23/81 (28.4)	6/50 (10.7)	6/13 (46)	143/508 (28.1)	**<0.001**
Mortality at 90 days§	54/183 (29.5)	73/140 (52.1)	31/79 (39.2)	8/55 (14.6)	8/13 (62)	174/470 (37.0)	**<0.001**

Results are presented as n (%).
*Including *Candida spp*. fungemia in 155 (92.8%) (see online supplemental table S2) for further details), excluding two cases of *Cryptococcus neoformans* fungemia which are presented with the 'other IFD'.
†P-value: test applied to the three main IFD categories (PCP, fungemia, IA).
‡Missing data for 41 patients, 7.5%.
§Missing data for 79 patients, 14.4%.
PCP, *Pneumocystis jirovecii* pneumonia.

and IFD was 2 years (IQR 0–11) for PCP, 5 (IQR 1–11) for fungemia and 5 (IQR 1–17) for invasive aspergillosis.

At the time of IFD diagnosis, most patients were receiving GCs (n=365, 66.5%), at a dose greater than 0.3 mg/kg/day within the previous month in 254 (46.3%) (table 3). The proportion of patients treated with GCs was especially high in patients with PCP (n=178, 78.4%). Immunosuppressants were common (n=285, 51.9%), most of all methotrexate (n=114, 20.8%), particularly in patients with PCP (n=135, 59.5%) or invasive aspergillosis (n=50, 59.5%). TNF-α blockers (n=42, 7.7%) and other biologics (n=75, 13.7%) were more rarely reported. Most common biologics were rituximab (n=46, 8.4%) and infliximab (n=15, 2.7%). Only a few patients (n=75, 13.7%) did not receive any GCs, immunosuppressants, biologics, or chemotherapy.

Findings were comparable when restricted to the patients without any other risk factor for IFD among malignancy, solid organ transplantation or recent surgery (online supplemental table S7). Among the 29 patients who had none of those other risk factors for IFD and received no treatment among GCs, immunosuppressants, biologics or chemotherapy, we identified 21 patients with fungemia, including four with rheumatoid arthritis, three with Crohn's disease, three with systemic sclerosis and three with Sjögren's syndrome.

Age-standardised and sex-standardised estimates are reported in online supplemental table S13, with a lower proportion of patients with PCP and invasive aspergillosis on GCs or immunosuppressive agent in the adjusted estimates compared with the crude estimates, whereas the adjusted estimates are higher for TNF-α blocker in fungemia.

Mortality and factors associated with mortality

At 30 days after IFD diagnosis, 143/508 patients had died (28.1%) (missing data for 41 patients, 7.5%) (online supplemental table S14). After 90 days, 174/470 (37.0%) had died (missing data for 79 patients, 14.4%) (table 1). Mortality differed between the types of IFD (Fisher test,

Table 2 Autoimmune diseases (AID) in patients presenting an episode of invasive fungal disease (IFD)

	Pneumocystis pneumonia (227)	Fungemia (167)	Invasive aspergillosis (84)	Other IFD (58)	Multiple IFD (13)	Total (549)
Rheumatoid arthritis	55 (24.2)	28 (16.8)	15 (17.9)	13 (22.4)	2 (15)	113 (20.6)
Inflammatory bowel disease (IBD)	13 (5.7)	36 (21.6)	2 (2.4)	3 (5.2)	0 (0)	54 (9.8)
Crohn's disease	9 (4.0)	29 (17.4)	2 (2.4)	2 (3.4)	0 (0)	42 (7.7)
Ulcerative colitis	4 (1.8)	6 (3.6)	0 (0)	1 (1.7)	0 (0)	11 (2.0)
Unclassified IBD	0 (0)	1 (0.6)	0 (0)	0 (0)	0 (0)	1 (0.2)
Sarcoidosis	19 (8.4)	10 (6.0)	10 (11.9)	6 (10.3)	1 (8)	46 (8.4)
ANCA-associated vasculitis	25 (11.0)	7 (4.2)	10 (11.9)	2 (3.4)	2 (15)	46 (8.4)
Granulomatosis with polyangiitis	11 (4.8)	4 (2.4)	5 (6.0)	0 (0)	0 (0)	20 (3.6)
Microscopic polyangiitis	11 (4.8)	1 (0.6)	5 (6.0)	0 (0)	1 (8)	18 (3.3)
Eosinophilic granulomatosis with polyangiitis	1 (0.4)	2 (1.2)	0 (0)	2 (3.4)	0 (0)	5 (0.9)
Unclassified ANCA-associated vasculitis	2 (0.9)	0 (0)	0 (0)	0 (0)	1 (8)	3 (0.5)
Systemic lupus erythematosus	6 (2.6)	12 (7.2)	9 (10.7)	7 (12.1)	2 (15)	36 (6.6)
Dermatomyositis	21 (9.3)	7 (4.2)	1 (1.2)	4 (6.9)	0 (0)	33 (6)
Systemic sclerosis	12 (5.3)	12 (7.2)	1 (1.2)	3 (5.2)	0 (0)	28 (5.1)
Giant-cell arteritis	11 (4.8)	0 (0)	1 (1.2)	4 (6.9)	0 (0)	16 (2.9)
Spondylarthritis	2 (0.9)	4 (2.4)	7 (8.3)	3 (5.2)	0 (0)	16 (2.9)
Sjögren's syndrome	7 (3.1)	4 (2.4)	1 (1.2)	2 (3.4)	0 (0)	14 (2.6)
Autoimmune hepatitis	0 (0)	6 (3.6)	2 (2.4)	1 (1.7)	2 (15)	11 (2.0)
Polymyalgia rheumatica	5 (2.2)	3 (1.8)	1 (1.2)	1 (1.7)	0 (0)	10 (1.8)
Autoimmune haemolytic anaemia	5 (2.2)	2 (1.2)	0 (0)	2 (3.4)	0 (0)	9 (1.6)
Myasthenia gravis	4 (1.8)	1 (0.6)	2 (2.4)	1 (1.7)	0 (0)	8 (1.5)
Multiple sclerosis	0 (0)	7 (4.2)	1 (1.2)	0 (0)	0 (0)	8 (1.5)
Psoriasis	4 (1.8)	0 (0)	3 (3.6)	0 (0)	0 (0)	7 (1.3)
Psoriatic arthritis	5 (2.2)	0 (0)	2 (2.4)	0 (0)	0 (0)	7 (1.3)
Immune thrombocytopenic purpura	4 (1.8)	1 (0.6)	1 (1.2)	0 (0)	0 (0)	6 (1.1)
Other	29 (12.8)	27 (16.2)	15 (17.9)	6 (10.3)	4 (31)	81 (14.8)

Results are presented as n (%); only one AID per patient reported: 82 patients had at least two concomitant AIDs (most frequent combination: rheumatoid arthritis and Sjögren's syndrome in 9 patients), 10 had three concomitant AIDs (further details in online supplemental table S9).

p<0.001 for both 30-day and 90-day mortality) and was particularly high in patients with fungemia (66/151, 43.7% at 30 days and 73/140, 52.1% at 90 days). In a multivariable logistic regression model, we found increased odds of 30-day mortality for people receiving high-dose GCs (adjusted OR (aOR) 1.9, 95% CI 1.2 to 3.1), but not immunosuppressants (aOR 1.6, 95% CI 0.9 to 2.6), TNF-α blockers (aOR 1.0, 95% CI 0.4 to 2.6) or other biologics (aOR 0.9, 95% CI 0.5 to 1.8) (figure 1, see online supplemental table S14 for further model description). Fungemia was also associated with increased odds of 30-day mortality (aOR 5.4, 95% CI 3.0 to 9.8 compared with PCP). When restricted to the patients without any other major risk factor for IFD, we found a persistent effect for high-dose GCs (aOR 2.9, 1.5–5.8) (online supplemental table S14).

Pneumocystis jirovecii pneumonia

Patients with rheumatoid arthritis presenting PCP (n=56) differed from the others with PCP (n=171). They were older (median 75 years, IQR 66.5–80 vs 66 years, IQR 58–74, p<0.001), received less frequently high-dose GCs (30.8% vs 63.2%, p<0.001; median dose among those on GCs 10 mg/day, IQR 5–20 vs 30 mg/day, IQR 17.5–50, p<0.001) but more frequently immunosuppressants (85.7% vs 50.9%, p<0.001), mostly methotrexate (for 90% of them). Time from AID diagnosis to PCP was significantly longer in rheumatoid arthritis than in other

Table 3 Treatments of patients with autoimmune disease at the time of diagnosis of the invasive fungal disease (IFD)

Treatments	*Pneumocystis* pneumonia (227)	Fungemia (167)	Invasive aspergillosis (84)	Other IFD (58)	Multiple IFD (13)	Total (549)	P value*
Glucocorticoids	178 (78.4)	89 (53.3)	49 (58.3)	41 (70.7)	8 (62)	365 (66.5)	**<0.001**
High dose†	125 (55.1)	63 (37.7)	36 (42.9)	25 (43.1)	5 (38)	254 (46.3)	**0.002**
Median daily dose (IQR)‡	22.5 (10–45)	25 (10–40)	35 (10–60)	15 (10–37.5)	20 (5–60)	20 (10–45)	0.77
Immunosuppressant§	135 (59.5)	67 (40.1)	50 (59.5)	27 (46.6)	6 (46)	285 (51.9)	**<0.001**
Methotrexate	82 (36.1)	15 (9.0)	6 (7.1)	10 (17.2)	1 (8)	114 (20.8)	–
Azathioprine	16 (7.0)	11 (6.6)	5 (6.0)	4 (6.9)	1 (8)	37 (6.7)	–
Cyclophosphamide	14 (6.2)	2 (1.2)	8 (9.5)	3 (5.2)	0	27 (4.9)	–
Mycophenolate	5 (2.2)	5 (3.0)	8 (9.5)	3 (5.2)	1 (8)	22 (4.0)	–
Other	18 (7.9)	34 (20.4)	24 (28.6)	9 (15.5)	3 (23)	88 (16.0)	–
TNF-α blocker¶	14 (6.2)	11 (6.6)	11 (13.1)	5 (8.6)	1 (8)	42 (7.7)	0.10
Infliximab	4 (1.8)	4 (2.4)	3 (3.6)	3 (5.2)	1 (8)	15 (2.7)	–
Adalimumab	3 (1.3)	4 (2.4)	4 (4.8)	1 (1.7)	0	12 (2.2)	–
Other	2 (0.9)	2 (1.2)	1 (1.2)	1 (1.7)	0	6 (1.1)	–
Other biologic	33 (14.5)	20 (12.0)	16 (19.1)	4 (6.9)	2 (15)	75 (13.7)	0.32
Rituximab	26 (11.5)	9 (5.4)	9 (10.7)	1 (1.7)	1 (8)	46 (8.4)	–
Chemotherapy**	1 (0.4)	9 (5.4)	12 (14.3)	1 (1.7)	2 (15)	25 (4.6)	**<0.001**
None of the above	18 (7.9)	41 (24.6)	7 (8.3)	8 (13.8)	1 (8)	75 (13.7)	**<0.001**

Results are presented as n (%).
*P value: test applied to the three main IFD categories (*Pneumocystis* pneumonia, fungemia, invasive aspergillosis).
†High-dose: over 0.3 mg/kg/day prednisone-equivalent dose for at least month.
‡Prednisone-equivalent dose among those on GCs, missing data for the detailed dose: 88/365 (24.1%).
§35 patients had a combination of at least two immunosuppressants (including 1 patient with invasive aspergillosis, on azathioprine and mycophenolate, and 2 patients with another IFD, on azathioprine combined respectively with methotrexate and cyclophosphamide; they are included in the totals for each immunosuppressive agent).
¶Missing detail on type of TNF-α blocker in 9 patients.
**For patients with a solid cancer or a haematological malignancy in addition to the AID.
AID, autoimmune diseases; GC, glucocorticoids; TNF-α, Tumor necrosis factor alpha.

AID (9 years, IQR 3–18 vs 1 year, IQR 0–10, p<0.001) (description by AID in online supplemental table S15). Mortality at 30 days did not differ: n=12/48, 25.0% in patients with rheumatoid arthritis, n=30/159, 18.9% for other cases of PCP (p=0.413).

Total lymphocyte count was available for 179 (75.5%) of the 237 patients with PCP (including 10 additional patients with another co-occurring IFD). Median lymphocyte count was 890/mm^3 (IQR 450–1580). Total lymphocyte count was <1000/mm^3 in 97 patients (54.2%) and <1500/mm^3 in 132 patients (73.7%). CD4+T cell count was available within the previous 3 months in 78 patients (32.9%). Median CD4+T cell count was 472.5/mm^3 (IQR 160–858), median percentage was 48% (IQR 35.9–63.7) and median CD4/CD8 ratio was 2.2 (IQR 1.3–4.3). CD4+T cell count was >200/mm^3 in 56 patients (71.8%) and >300/mm^3 in 47 (60.3%). Only seven patients (3.0%) were receiving PCP prophylaxis before diagnosis (six with TMP-SMX and one with pentamidine). No data were available on compliance with prescription.

Fungemia

Among the 167 patients with fungemia, patients with IBDs (n=37) differed from other AID (n=130). Patients with IBDs were younger (55 years, IQR 38–67 vs 65 years, IQR 55–75, p=0.015) and received more frequently TNF-α blockers (27.0% vs 0.8%, p<0.001). They also had a better overall prognosis: 4/31 patients with IBD had died by day 30 (12.9%) compared with 62/120 patients with other AID (51.7%) (p<0.001). Mortality was 50% (n=12/24) in rheumatoid arthritis, 58% (n=7/12) in systemic lupus erythematosus and 46% (n=6/13) in systemic sclerosis.

DISCUSSION

The RESSIF prospective nationwide registry provides novel description of IFD occurring in patients with AID. We report here the predominance of PCP over all other IFD, highlighting that patients with AID are susceptible to this opportunistic infection, whereas cases of fungemia were predominant in the overall population covered

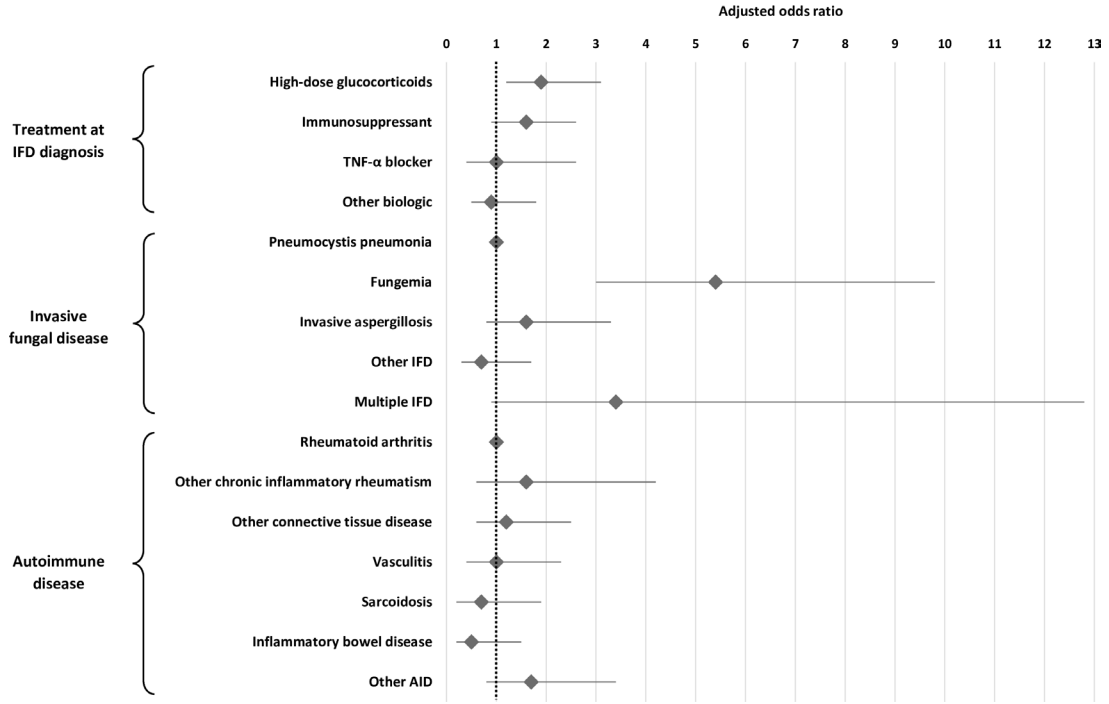

Figure 1 Forest plot of factors associated with 30-day mortality following diagnosis of invasive fungal disease (IFD) in patients with autoimmune diseases (AID) (France, 2012–2018). ORs in a fitted multivariable logistic regression model. Beyond variables presented in the figure, the model also includes age (in years), sex, underlying comorbidities (solid cancer, haematological malignancy, solid organ transplantation, cirrhosis, chronic kidney failure, chronic respiratory failure), co-occurring bacterial of viral infection. High-dose glucocorticoids: over 0.3 mg/kg/day for over 1 month. Further results of the model, as well as the univariable effects, are presented in online supplemental table S14. Results in a population restricted to the 322 without any other major risk factor for IFD (solid cancer, haematological malignancy, solid organ transplantation, recent surgery) are also reported in online supplemental table S14.

by the RESSIF network.[24] PCP was most common in patients with rheumatoid arthritis, AAV or dermatomyositis, often treated with GCs and immunosuppressants. Lymphopenia was common but CD4+T cell count was most often greater than 200/mm^3 or even 300/mm^3. In contrast, fungemia often occurred long after the diagnosis of AID, especially in patients with IBD with central catheter or recent surgery, which are known risk factors for invasive candidiasis[28] and could occur in patients who were not receiving specific treatment for AID. Fungemia was associated with a high mortality, except in IBD patients. Invasive aspergillosis often occurred, but not exclusively, in patients with other risk factors for infection such as haematological malignancy or solid organ transplantation. Further investigation is warranted to describe more accurately the clinical forms of invasive aspergillosis occurring in patients with AID, including imaging.

We report here some associations of AID and IFD that have rarely been documented, if at all, such as PCP in patients with sarcoidosis, giant cell arteritis or systemic sclerosis, fungemia in patients with IBD or invasive aspergillosis in patients with rheumatoid arthritis or AAV. These findings should help raise physicians' awareness during diagnostic evaluation.

The occurrence of fungemia in patients with IBD has not been previously reported,[8] despite evidence of high intestinal colonisation with *Candida* spp,[29] which may then translocate in patients with an altered intestinal barrier.[28] Central catheters, a documented risk factor for invasive candidiasis, also probably contributed to fungemia in patients with IBD.[28] Younger age and a high proportion of patients on TNF-α blockers may reflect differences in the source population and therapeutic practices in IBD compared with other AID. The better prognosis of these patients compared with others with fungemia suggests differences in determinants and natural history of fungemia in this specific population.

We found relatively few patients receiving TNF-α blockers or other biologics, whereas risk has been well documented in other studies for some conditions, particularly in patients with rheumatoid arthritis. In the UK, Bruce *et al* have documented a higher risk of PCP in patients on TNF-α blockers than in patients on traditional synthetic DMARDs.[5] Our findings may reflect changes in prophylaxis practice given previous documentation of risk for those patients or simply the comparatively low prevalence of patients receiving biologics among all patients with AID. The risk may also vary across populations. It is considered high in Japan for patients with rheumatoid arthritis receiving TNF-α blockers, where the incidence ranged from 49 to 88/10 000 patient-years in early postmarketing surveillance,[30 31] whereas it was only 2.0/10 000 patient-years in the UK study by Bruce *et al*.[5]

Recent development of several biologics with growing use in patients with AID may explain the increasing importance of patients with AID observed in the overall RESSIF population: they represented 4.7% of cases in 2013 and 6.8% in 2018, while overall incidence of IFD increased slightly.[24]

Our study lacks a control arm to identify risk factors for the occurrence of IFD in patients with AID. The number of PCP should be interpreted in the light of widespread availability of prophylaxis for patients with AID in France, whereas no prophylactic approach existed for other IFDs during the study period. The individual risk should not be minimised by our findings on patients with AID for whom the risk of PCP has already been well documented and who were likely frequently on prophylaxis during the study period. This includes for instance patients with AAV or dermatomyositis, who were nonetheless still quite highly represented in our findings.[10 11] Occurrence of PCP in those patients may reflect insufficient physician awareness of the risk and the need for prophylaxis. This study also provides some insights into the profile of patients whose risk of PCP was not considered high enough to justify prophylaxis and suggests leads as to who could further benefit from it. Our findings show that the risk cannot be excluded in patients with other types of AID such as sarcoidosis, systemic sclerosis or giant cell arteritis. The low representation of relatively common AID such as SLE or spondylarthritis suggests low risk in these populations.[32 33] Assessing PCP incidence for the different AID represents an important next step to guide the indication of prophylaxis based on the type of AID.[34]

Beyond the type of AID, older age, lymphopenia, GCs and immunosuppressants have been repeatedly associated with the risk of PCP in patients with AID.[11 35–40] This is consistent with the high prevalence of these factors in our study population. Furthermore, we showed that high-dose GCs were associated with a high mortality. Our findings, together with existing evidence, suggest that patients receiving high-dose GCs could benefit from PCP prophylaxis as recommended by EULAR and the American Thoracic Society,[21 22] especially when combined with other factors such as an associated immunosuppressant, age >60 years (75% of PCP cases in our study were older than 60 years) or lymphopenia. Indications for prophylaxis after tapering of GCs also warrant further investigation. Our findings suggest that patients who combine several of these frailty factors may be an interesting target population to evaluate this practice. PCP appears to be more common early after AID diagnosis, which may simply reflect the increased risk induced by high-dose GCs and immunosuppressants but nonetheless suggests a window of opportunity when prophylaxis may most be beneficial.

Our findings on CD4+T cell count suggest that CD4+T cells above the commonly accepted cut-offs of 200/mm^3 or 300/mm^3 should not be used to rule out the risk or diagnosis of PCP in patients with AID. Similar findings were reported in a French series of 20 cases of PCP in patients with AID where the median CD4+T cell count was 302/mm^3.[41]

Patients with rheumatoid arthritis who developed PCP had a remarkable profile in our study. They were older, received somewhat lower doses of GCs (but most often above 5 mg/day) and were often treated with methotrexate alone. This situation is quite common in France, given the high prevalence of the disease and the major role of methotrexate as a first-line treatment in rheumatoid arthritis.[42] PCP could occur many years after diagnosis, hence it is difficult to define a period of vulnerability during which patients could benefit from prophylaxis, but it highlights the need to taper GCs particularly in the elderly. This late onset of PCP has already been documented in a French study, in which five of the six PCP had a diagnosis of rheumatoid arthritis between 69 and 342 months prior to PCP.[41] This finding probably reflects some concerns of physicians regarding the combination of TMP-SMX and methotrexate and the potential risk of myelosuppression. However, data on the safety of combination therapy are quite reassuring when TMP-SMX is given at prophylactic doses.[43] Experience in Japan and South Korea also supports good safety of the combination.[44 45] Further pharmacoepidemiological data on the safety of coprescribing could help inform physicians and scientific societies in determining the indications for PCP prophylaxis. Other approaches to PCP prophylaxis exist. In Japan, a negative beta-D-glucan and a lymphocyte count >1000/mm^3 are recommended before starting TNF-α blockers in patients with rheumatoid arthritis.[46] This approach needs to be evaluated in the French setting, where the incidence of PCP may be significantly lower.

Limitations of this study include the retrospective collection of some data, including those on total and CD4+T cells, leading to a high number of missing data. Given the lack of a control arm of patients with AID who did not develop any IFD, our findings on the scope of AID affected by a specific IFD should be interpreted very cautiously, as this is at least partly a consequence of differences in prevalence between AID: rheumatoid arthritis is, for instance, more than twice as prevalent as AAV, thus the individual risk of PCP may be much higher for patients with AAV than patients with rheumatoid arthritis.[47] Furthermore, it is possible that the differences in age between IFD may lead to an overrepresentation of specific AID: it is, for instance, possible that older age played a role in the onset of PCP, and given that rheumatoid arthritis is more frequent in the elderly, the association between PCP and rheumatoid arthritis may partly be caused by age. The age-standardised and sex-standardised estimates underline the differences of profiles according to age: as standardisation tended to give less weight to older patients, we observed an overall reduction in the prevalence of comorbidities, GCs, immunosuppressive

agents (particularly in cases of rheumatoid arthritis and sarcoidosis), as those exposures were more common in older patients. Further studies including patients with AID who did not develop an IFD are needed to disentangle the effects of demographic factors as age and sex from those of the AID and its associated treatments. We could not measure cumulative therapeutic pressure in patients who may have received consecutive immunosuppressive agents or biologics, which may have impacted the risk of IFD and mortality. We could not distinguish patients who were admitted to the intensive care unit because of the IFD from those who developed the IFD in the intensive care unit. The latter probably included some of the patients with fungemia, as this often occurs during an ICU stay. We also cannot rule out that some cases of IFDs were missed by our surveillance system, despite the notification by a trained physician and the central monitoring by a senior physician. Finally, we do not have long-term follow-up data to assess further impact on morbidity (eg, on AID flares) or mortality, although most of the deaths that occurred did so within the first 30 days after IFD diagnosis.

Overall, this nationwide prospective study provides a comprehensive and novel description of the profile of patients with AID who develop IFD. It should help guide diagnostic investigations in clinical practice, as well as define upcoming prophylactic strategies, particularly for PCP, based on the type of AID, age, total lymphocyte count, administration of GCs and immunosuppressants. The risk of PCP cannot be excluded on the absence of CD4+T cell lymphopenia. Fungemia is associated with high mortality, except in patients with IBD.

Author affiliations
[1]Emerging Diseases Epidemiology Unit, Institut Pasteur, Université Paris Cité, Paris, Île-de-France, France
[2]Ecole doctorale Pierre Louis de santé publique, Sorbonne Université, Paris, France
[3]National Referral Center for Rare Systemic Autoimmune Diseases, Department of Internal Medicine, Cochin Hospital, AP-HP, Université Paris Cité, Paris, Île-de-France, France
[4]INSERM U1016, Cochin Institute, Paris, Université Paris Cité, CNRS UMR 8104, Paris, Île-de-France, France
[5]Parasitologie - Mycologie, Hôpital St Louis, APHP, Paris, Île-de-France, France
[6]Institut Pasteur, Université Paris Cité, CNRS, National Reference Center for Invasive Mycoses and Antifungals, Translational Mycology Research Group, Mycology Department, Paris, Île-de-France, France
[7]Parasitologie - Mycologie, Université Paris Cité, Cochin Hospital, APHP, Paris, Île-de-France, France
[8]Laboratoire de Parasitologie et Mycologie Médicale, Les Hôpitaux Universitaires de Strasbourg, Strasbourg, France
[9]Institut de Parasitologie et Pathologie Tropicale, UR7292 Dynamique des interactions hôte pathogène, Fédération de Médecine Translationnelle, Université de Strasbourg, Strasbourg, France
[10]Parasitologie - Mycologie, Université de Toulouse, CHU Toulouse, Toulouse, Occitanie, France
[11]PharmaDev, Faculté de Pharmacie, Université de Toulouse, UPS, IRD, Toulouse, Occitanie, France
[12]Université de Rennes, CHU, INSERM, Irset: Institut de Recherche en Santé, Environnement et Travail, UMR_S 1085, Rennes, France
[13]French National Cryptosporidiosis Reference Center, CHU de Rouen, Rouen, Normandie, France
[14]EA 7510, UFR Santé, University of Rouen Normandy, Normandy University, Rouen, France
[15]Faculté de Médecine et Pharmacie, Université de Poitiers, Poitiers, Nouvelle-Aquitaine, France
[16]Département des agents anti-infectieux, Service de Mycologie-Parasitologie, CHU Poitiers, Poitiers, France
[17]Parasitologie - Mycologie, CHU Nantes, Nantes, Pays de la Loire, France
[18]UR 1155 IICiMed, Institut de Recherche en Santé 2, Université de Nantes, Nantes, Pays de la Loire, France
[19]Microbiologie, CHU de Caen, ToxEMAC-ABTE Unicaen, Caen, Normandie, France
[20]Centre d'Étude des Pathologies Respiratoires - Inserm UMR1100, Université de Tours, Tours, France
[21]Parasitologie - Mycologie - Médecine tropicale, CHU de Tours, Tours, Centre-Val de Loire, France
[22]Microbiologie, CH Versailles, Le Chesnay, Île-de-France, France
[23]Parasitologie - Mycologie, hôpital de l'Archet, CHU Nice, Nice, Provence-Alpes-Côte d'Azur, France
[24]Laboratoire de Parasitologie - Mycologie, CHU Nîmes, Université de Montpellier, CNRS, IRD, MiVEGEC, Nimes, Occitanie, France
[25]Laboratoire de Parasitologie - Mycologie, CHU de Besançon, Besançon, Bourgogne-Franche-Comté, France
[26]UMR 6249 CNRS Chrono-Environnement, Université Bourgogne Franche-Comté, Besançon, Bourgogne - Franche-Comté, France
[27]Parasitologie - Mycologie, CHU Clermont-Ferrand, Clermont-Ferrand, France
[28]Microbes, Intestin, Inflammation et Susceptibilité de l'Hôte (M2iSH), UMR Inserm/Université Clermont Auvergne U1071, USC INRA 2018, Clermont-Ferrand, Auvergne-Rhône-Alpes, France
[29]Mycologie - parasitologie, CHU Amiens-Picardie, Amiens, Hauts-de-France, France
[30]Parasitologie - Mycologie, hôpital Maison-Blanche, CHU de Reims, Reims, France
[31]Parasitologie - Mycologie, Plateforme de Biologie Hospitalo-Universitaire Gérard Mack, Dijon, Bourgogne-Franche-Comté, France
[32]UMR PAM Univ Bourgogne Franche-Comté - AgroSup Dijon - Equipe Vin, Aliment, Microbiologie, Stress, Université Bourgogne Franche-Comté, Dijon, Bourgogne-Franche-Comté, France
[33]Parasitologie - Mycologie, Centre de Biologie et de Recherche en Santé, CHU Limoges, Limoges, Nouvelle-Aquitaine, France
[34]Mycologie - Parasitologie, Centre Hospitalier Universitaire Pointe-à-Pitre Abymes, Pointe-à-Pitre, Guadeloupe
[35]Parasitologie - Mycologie, CHU de Martinique, Fort-de-France, Martinique
[36]Laboratoire de Parasitologie - Mycologie, Service de Microbiologie, Necker-Enfants Malades University Hospital, APHP, Paris, Île-de-France, France
[37]Institut Pasteur, Université Paris Cité, Unité Biologie et Pathogénicité Fongiques, Département Mycologie, Paris, Île-de-France, France
[38]Maladies infectieuses et tropicales, Les Hôpitaux Universitaires de Strasbourg, Strasbourg, Grand Est, France
[39]Laboratoire d'Immuno-rhumatologie moléculaire UMR_S 1109, INSERM, Strasbourg, Grand Est, France
[40]Service d'Immunologie clinique, Hopitaux universitaires de Strasbourg, Strasbourg, France
[41]CRTI UMR 1064, INSERM, Université de Nantes, Nantes, France
[42]Service de Médecine interne, CHU Nantes, Nantes, Pays de la Loire, France
[43]Infectious Diseases Unit, Necker-Enfants Malades University Hospital, AP-HP, Paris, France
[44]Université Paris Cité, U970, PARCC, INSERM, Paris, Île-de-France, France

Twitter Benjamin Terrier @TerrierBen

Acknowledgements We wish to thank Françoise Dromer at the French National Reference Center for Invasive Mycoses and Antifungals, as well as all practitioners in participating centers who contributed to the registry.

Collaborators The French Mycoses Study Group: Eric Bailly (Microbiologie, CHU de Caen, ToxEMAC-ABTE Unicaen, Caen, France); Caroline Mahinc (Parasitology—Mycology, Department of Infectious Agents and Hygiene, CHU de Saint-Etienne, France); Marc Pihet (Parasitologie - Mycologie, Institut de Biologie en Santé, CHU d'Angers, France; Groupe d'Etude des Interactions Hôte-Pathogène, UPRES-EA 3142, l'UNAM Université, Université d'Angers, Angers, France); Magalie Demar (Laboratoire Hospitalo-Universitaire de Parasitologie-Mycologie, Centre Hospitalier

Andrée Rosemon, Cayenne, Guyane Française; Ecosystèmes Amazoniens et Pathologie Tropicale (EPaT), EA 3593, Université de Guyane, Cayenne, Guyane Française); Lilia Merabet (CHNO des Quinze-Vingts, Inserm-DGOS CIC 1423, IHU ForeSight, Paris, France); Valery Salle (Médecine interne, CHU Amiens, France); Céline Damiani (Mycologie - Parasitologie, CHU Amiens, France); Marie-Fleur Durieux (Parasitologie - Mycologie, Centre de Biologie et de Recherche en Santé, CHU Dupuytren, Limoges, France); Nassim Kamar (Néphrologie et transplantation d'organe, CHU Toulouse, France); Elena Charpentier (Parasitologie - Mycologie, CHU de Bordeaux - Hôpital Pellegrin, France); François Maillot (Médecine interne et immunologie clinique, CHRU Tours, France - Université de Tours, France); Cécile Nourrisson (Parasitologie - Mycologie, CHU Clermont-Ferrand, 3IHP, France; Microbes, Intestin, Inflammation et Susceptibilité de l'Hôte (M2iSH), UMR Inserm / Université Clermont Auvergne U1071, USC INRA 2018, France); Benoit Suzon (Rhumatologie - Médecine interne, CHU de la Martinique, France).

Contributors SG, SB, KBS, FL and BTe designed the investigation. SG, SB, AA, AP, BV, SC, J-PG, HG, LF, AM, FM, JB, GD, OE, LH, MS, LM, A-PB, PP, MM, TC, AH, FD, BB, MN, NDN, MD, M-EB, FD, VP, AN, KB-S and members of the French Mycoses Study Group managed the data collection on research sites. SG, BTh and BTe performed the statistical analyses. SG, BTh, FL and BTe drafted the first versions of the manuscript. SG acts as guarantor for this study. All authors critically reviewed and approved the final version of the manuscript.

Funding SG if funded by the INCEPTION program (grant number Investissement d'Avenir ANR-16-CONV-0005). This work was supported by recurrent financial support from Santé Publique France and Institut Pasteur.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Institut Pasteur Institutional Review Board 1 (2009-34/IRB). The surveillance of the NRCMA, for which written informed consent of patient was not necessary, was approved by the Institut Pasteur Institutional Review Board 1 (2009-34/IRB) and the 'Commission Nationale de l'Informatique et des Libertés' according to the French regulation. Physicians provided information to patients regarding data collection and ensured absence of opposition.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data are collected by the National Reference Center for Invasive Mycoses and Antifungals within surveillance activity under authorisation of the French data protection authority 'Commission Nationale de l'Informatique et des Libertés' (CNIL). Access to these pseudonymised data would require prior authorisation by the CNIL.

ORCID iDs
Simon Galmiche http://orcid.org/0000-0002-1691-1744
Benjamin Terrier http://orcid.org/0000-0001-6612-7336

REFERENCES

1 Liu Y, Su L, Jiang S-J, *et al*. Risk factors for mortality from Pneumocystis carinii pneumonia (PCP) in non-HIV patients: a meta-analysis. *Oncotarget* 2017;8:59729–39.
2 Godeau B, Coutant-Perronne V, Le Thi Huong D, *et al*. Pneumocystis carinii pneumonia in the course of connective tissue disease: report of 34 cases. *J Rheumatol* 1994;21:246–51.
3 Roux A, Canet E, Valade S, *et al*. Pneumocystis Jirovecii pneumonia in patients with or without AIDS, France. *Emerg Infect Dis* 2014;20:1490–7.
4 Ward MM, Donald F. Pneumocystis carinii pneumonia in patients with connective tissue diseases: the role of hospital experience in diagnosis and mortality. *Arthritis Rheum* 1999;42:780–9.
5 Bruce ES, Kearsley-Fleet L, Watson KD, *et al*. Risk of Pneumocystis Jirovecii pneumonia in patients with rheumatoid arthritis treated with inhibitors of tumour necrosis factor A: results from the British society for rheumatology Biologics register for rheumatoid arthritis. *Rheumatology (Oxford)* 2016;55:1336–7.
6 Watanabe K, Sakai R, Koike R, *et al*. Clinical characteristics and risk factors for Pneumocystis Jirovecii pneumonia in patients with rheumatoid arthritis receiving Adalimumab: a retrospective review and case-control study of 17 patients. *Mod Rheumatol* 2013;23:1085–93.
7 Guillevin L, Cordier JF, Lhote F, *et al*. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. *Arthritis Rheum* 1997;40:2187–98.
8 Stamatiades GA, Ioannou P, Petrikkos G, *et al*. Fungal infections in patients with inflammatory bowel disease: A systematic review. *Mycoses* 2018;61:366–76.
9 Kermani TA, Ytterberg SR, Warrington KJ. Pneumocystis Jiroveci pneumonia in giant cell arteritis: A case series. *Arthritis Care Res (Hoboken)* 2011;63:761–5.
10 Fillatre P, Decaux O, Jouneau S, *et al*. Incidence of Pneumocystis Jiroveci pneumonia among groups at risk in HIV-negative patients. *Am J Med* 2014;127:1242.
11 Hsu H-C, Chang Y-S, Hou T-Y, *et al*. Pneumocystis Jirovecii pneumonia in autoimmune rheumatic diseases: a nationwide population-based study. *Clin Rheumatol* 2021;40:3755–63.
12 Vaquero-Herrero MP, Ragozzino S, Iriart X, *et al*. Candida bloodstream infection in patients with systemic autoimmune diseases. *Med Mal Infect* 2020;50:372–6.
13 Deepak P, Stobaugh DJ, Ehrenpreis ED. Infectious complications of TNF-A inhibitor monotherapy versus combination therapy with immunomodulators in inflammatory bowel disease: analysis of the food and Drug Administration adverse event reporting system. *J Gastrointest Liver Dis JGLD* 2013;22:269–76.
14 Stankovic K, Sève P, Hot A, *et al*. Aspergillosis in systemic diseases treated with steroids and/or immunosuppressive drugs: report of 9 cases and review of the literature. *Rev Med Interne* 2006;27:813–27.
15 Su T, Li H-C, Chen M, *et al*. Invasive pulmonary Aspergillosis in patients with antineutrophil cytoplasmic antibody associated vasculitis. *J Clin Rheumatol* 2009;15:380–2.
16 Girard N, Cottin V, Hot A, *et al*. Opportunistic infections and Sarcoidosis. *Rev Mal Respir* 2004;21(6 Pt 1):1083–90.
17 Liu J, Li M, Liang J-Y, *et al*. Autoimmune diseases in HIV-negative cryptococcal meningitis. *Future Microbiol* 2021;16:1251–9.
18 Lao M, Wang X, Ding M, *et al*. Invasive fungal disease in patients with systemic lupus erythematosus from Southern China: a retrospective study. *Lupus* 2019;28:77–85.
19 Wang LR, Barber CE, Johnson AS, *et al*. Invasive fungal disease in systemic lupus erythematosus: a systematic review of disease characteristics, risk factors, and prognosis. *Semin Arthritis Rheum* 2014;44:325–30.
20 Royer M, Puéchal X. Mucormycosis in systemic autoimmune diseases. *Joint Bone Spine* 2014;81:303–7.
21 Fragoulis GE, Nikiphorou E, Dey M, *et al*. EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2023;82:742–53. 10.1136/ard-2022-223335 Available: https://ard.bmj.com/content/early/2022/11/03/ard-2022-223335
22 Limper AH, Knox KS, Sarosi GA, *et al*. An official American Thoracic society statement: treatment of fungal infections in adult pulmonary and critical care patients. *Am J Respir Crit Care Med* 2011;183:96–128.
23 Terrier B, Darbon R, Durel C-A, *et al*. French recommendations for the management of systemic necrotizing Vasculitides (Polyarteritis Nodosa and ANCA-associated Vasculitides). *Orphanet J Rare Dis* 2020;15(Suppl 2):351.
24 Bretagne S, Sitbon K, Desnos-Ollivier M, *et al*. Active surveillance program to increase awareness on invasive fungal diseases: the French RESSIF network (2012 to 2018). *mBio* 2022;13:e00920-22.
25 De Pauw B, Walsh TJ, Donnelly JP, *et al*. 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;46:1813–21.
26 Donnelly JP, Chen SC, Kauffman CA, *et al*. Revision and update of the consensus definitions of invasive fungal disease from the

European Organization for research and treatment of cancer and the Mycoses study group education and research consortium. *Clin Infect Dis* 2020;71:1367–76.
27 World Bank open data. World Bank Open Data. Available: https://data.worldbank.org [Accessed 19 Jul 2023].
28 Kullberg BJ, Arendrup MC. Invasive Candidiasis. *N Engl J Med* 2015;373:1445–56.
29 Standaert-Vitse A, Sendid B, Joossens M, *et al*. Candida albicans Colonization and ASCA in familial Crohn's disease. *Am J Gastroenterol* 2009;104:1745–53.
30 Takeuchi T, Tatsuki Y, Nogami Y, *et al*. Postmarketing surveillance of the safety profile of Infliximab in 5000 Japanese patients with rheumatoid arthritis. *Ann Rheum Dis* 2008;67:189–94.
31 Koike T, Harigai M, Inokuma S, *et al*. Postmarketing surveillance of the safety and effectiveness of Etanercept in Japan. *J Rheumatol* 2009;36:898–906.
32 Arnaud L, Fagot J-P, Mathian A, *et al*. Prevalence and incidence of systemic lupus erythematosus in France: a 2010 nation-wide population-based study. *Autoimmun Rev* 2014;13:1082–9.
33 Saraux A, Guillemin F, Guggenbuhl P, *et al*. Prevalence of Spondyloarthropathies in France: 2001. *Ann Rheum Dis* 2005;64:1431–5.
34 Anumolu N, Henry K, Sattui SE, *et al*. Is there a role for Pneumocystis Jiroveci pneumonia prophylaxis in giant cell arteritis or Polymyalgia Rheumatica? *Semin Arthritis Rheum* 2023;58:152154.
35 Yukawa K, Nagamoto Y, Watanabe H, *et al*. Risk factors for Pneumocystis Jirovecii pneumonia in patients with rheumatoid arthritis and a prophylactic indication of Trimethoprim/Sulfamethoxazole. *J Clin Rheumatol* 2018;24:355–60.
36 Ogawa J, Harigai M, Nagasaka K, *et al*. Prediction of and prophylaxis against Pneumocystis pneumonia in patients with connective tissue diseases undergoing Medium- or high-dose corticosteroid therapy. *Mod Rheumatol* 2005;15:91–6.
37 Sonomoto K, Tanaka H, Nguyen TM, *et al*. Prophylaxis against Pneumocystis pneumonia in rheumatoid arthritis patients treated with B/tsDMARDs: insights from 3787 cases in the FIRST Registry. *Rheumatology (Oxford)* 2022;61:1831–40.
38 Tanaka M, Sakai R, Koike R, *et al*. Pneumocystis Jirovecii pneumonia associated with Etanercept treatment in patients with rheumatoid arthritis: a retrospective review of 15 cases and analysis of risk factors. *Mod Rheumatol* 2012;22:849–58.
39 Kadoya A, Okada J, Iikuni Y, *et al*. Risk factors for Pneumocystis carinii pneumonia in patients with polymyositis/dermatomyositis or systemic lupus erythematosus. *J Rheumatol* 1996;23:1186–8.
40 Tadros S, Teichtahl AJ, Ciciriello S, *et al*. Pneumocystis Jirovecii pneumonia in systemic autoimmune rheumatic disease: A case-control study. *Semin Arthritis Rheum* 2017;46:804–9.
41 Baulier G, Issa N, Gabriel F, *et al*. Guidelines for prophylaxis of Pneumocystis pneumonia cannot rely solely on Cd4-cell count in autoimmune and inflammatory diseases. *Clin Exp Rheumatol* 2018;36:490–3.
42 Biver E, Beague V, Verloop D, *et al*. Low and stable prevalence of rheumatoid arthritis in northern France. *Joint Bone Spine* 2009;76:497–500.
43 Bourré-Tessier J, Haraoui B. Methotrexate drug interactions in the treatment of rheumatoid arthritis: a systematic review. *J Rheumatol* 2010;37:1416–21.
44 Yamazaki H, Nanki T, Miyasaka N, *et al*. Methotrexate and Trimethoprim-Sulfamethoxazole for Pneumocystis pneumonia prophylaxis. *J Rheumatol* 2011;38:777.
45 Kwon OC, Lee JS, Kim Y-G, *et al*. Safety of the concomitant use of methotrexate and a prophylactic dose of Trimethoprim-Sulfamethoxazole. *Clin Rheumatol* 2018;37:3215–20.
46 Koike R, Takeuchi T, Eguchi K, *et al*. Update on the Japanese guidelines for the use of Infliximab and Etanercept in rheumatoid arthritis. *Mod Rheumatol* 2007;17:451–8.
47 Hayter SM, Cook MC. Updated assessment of the prevalence, spectrum and case definition of autoimmune disease. *Autoimmun Rev* 2012;11:754–65.