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Original Article

Aspergillus fumigatus—a systematic review to inform the World Health Organization priority list of fungal pathogens

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Abstract

Recognizing the growing global burden of fungal infections, the World Health Organization established a process to develop a priority list of fungal pathogens (FPPL). In this systematic review, we aimed to evaluate the epidemiology and impact of invasive infections caused by *Aspergillus fumigatus* to inform the first FPPL. The pre-specified criteria of mortality, inpatient care, complications and sequelae, antifungal susceptibility, risk factors, preventability, annual incidence, global distribution, and emergence were used to search for relevant articles between 1 January 2016 and 10 June 2021. Overall, 49 studies were eligible for inclusion. Azole antifungal susceptibility varied according to geographical regions. Voriconazole susceptibility rates of 22.2% were reported from the Netherlands, whereas in Brazil, Korea, India, China, and the UK, voriconazole susceptibility rates were 76%, 94.7%, 96.9%, 98.6%, and 99.7%, respectively. Cross-resistance was common with 85%, 92.8%, and 100% of voriconazole-resistant *A. fumigatus* isolates also resistant to itraconazole, posaconazole, and isavuconazole, respectively. The incidence of invasive aspergillosis (IA) in patients with acute leukemia was estimated at 5.84/100 patients. Six-week mortality rates in IA cases ranged from 31% to 36%. Azole resistance and hematological malignancy were poor prognostic factors. Twelve-week mortality rates were significantly higher in voriconazole-resistant than in voriconazole-susceptible IA cases (12/22 [54.5%] vs. 27/88 [30.7%]; $P = .035$), and hematology patients with IA had significantly higher mortality rates compared with solid-malignancy cases who had IA (65/217 [30%] vs. 14/78 [18%]; $P = .04$). Carefully designed surveillance studies linking laboratory and clinical data are required to better inform future FPPL.

Key words: *Aspergillus fumigatus*, invasive aspergillosis, invasive fungal disease, mortality, susceptibility, risk factors, incidence, epidemiology.

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Introduction

Aspergillus fumigatus causes a wide spectrum of infection, ranging from allergic and colonization to acute life-threatening invasive infection.[1] Risk factors for invasive aspergillosis (IA) include underlying hematological malignancy, prolonged neutropenia, hematopoietic stem cell transplantation (HSCT), solid-organ transplantation (SOT), severe lung disease, particularly in those admitted to the intensive care unit (ICU), receipt of corticosteroid therapy, and liver cirrhosis.[2–5] Viral infections such as influenza and more recently COVID-19 can be complicated by IA in up to 38% and are associated with a high mortality (>50%).[6–12] *Aspergillus fumigatus* had a number of characteristics that contribute to its predominance as a human fungal pathogen, including its abundance in the environment, small conidial size, melanin in the cell wall allowing it to evade phagocytosis, and its capacity to produce secondary metabolites that exert an immunosuppressive effect on the host.[13]

Whereas the most common site of IA is the lungs, sinonasal, and cerebral IA have also been reported in the immunocompromised.[14] Hematogenous spread can occur to the spleen and kidneys.[15] Rare manifestations of IA include endocarditis, vertebral osteomyelitis, arthritis, or thyroiditis.[16] Cutaneous aspergillosis may rarely occur by hematogenous spread or by direct inoculation.[17] Pulmonary infection is usually treated with antifungal agents alone, whereas extrapulmonary disease often requires adjunctive surgical treatment.[14]

Triazoles antifungal agents are usually used as first-line treatment of IA and along with early diagnosis using non-culture based diagnostic tests have reduced mortality rates to 30%. However, increasing antifungal resistance due to the wide-spread use of azole antifungal agents, particularly in the agricultural sector, threatens this progress.[18,19] A voriconazole resistance rate of 20.2% ($n = 26$) was detected in a Dutch–Belgian cohort of hematology patients with culture-positive proven or probable IA and in those with voriconazole-resistant IA, 12-week mortality was significantly higher (54.4% vs. 30.7%; $P = .035$).[18]

Given its predominance, the ongoing high mortality rates, and levels of azole resistance, *A. fumigatus* is now considered as one of the most important fungal pathogens. The aim of this systematic review is to evaluate *A. fumigatus* against a set of criteria; mortality, inpatient care, complications and sequelae, antifungal susceptibility, preventability, annual incidence, global distribution, and emergence in the 5 years from 1 January 2016 to 10 June 2021. The generated data identified knowledge gaps for *A. fumigatus* informing the fungal priority pathogens list (FFPL) of the World Health Organization (WHO).[20]

Methods

Study design

A systematic review was performed using the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Guidelines.[21]

Inclusion and exclusion criteria

Studies were included if they reported data on: (a) adults and/or pediatric populations; (b) *A. fumigatus*; (c) invasive infection; (d) at least one criterion (mortality, inpatient care, complications/sequelae, antifungal susceptibility, preventability, annual incidence, global distribution, and emergence in the previous 10 years); (e) retrospective or prospective observational studies, randomized controlled trials, and epidemiological or surveillance studies; and (f) were published between 1 January 2016 and 10 June 2021. Studies were excluded if they reported on/were: (a) animals and/or plants only; (b) bacteria, viruses, and/or parasites only; (c) other fungi or criteria; (d) included <30 IA cases or *A. fumigatus* isolates; (e) novel antifungals in pre-clinical studies or early-phase trials or unlicensed antifungals only; (f) *in vitro* resistance mechanisms only; (g) case reports, conference abstracts, or reviews; (h) not in English; and (i) outside the study time-frames.

Search strategy

We conducted a comprehensive search for studies published in English using the PubMed and Web of Science Core Collection databases between 1 January 2016 and 10 June 2021. On PubMed, the search was optimized using medical subject headings (MeSH) and/or keyword terms in the title/abstract for *A. fumigatus* and each criterion. On the Web of Science, MeSH terms are not available, and therefore topic, title, or abstract searches were used. The final searches used can be found in the supplementary materials.

PubMed and related databases are underpinned by a standardized taxonomy database; so, using a species name as a search term retrieves articles with obsolete or updated nomenclature.[22]

Study selection

The final search results from each database were imported into the reference manager, Endnote™, and the online systematic review software, Covidence® (Veritas Health Innovation, Australia), and duplicates were removed. The remaining articles underwent title and abstract screening based on the eligibility criteria, and no reasons were provided for excluding articles at this step. Then, full-text screening was performed to determine eligibility for inclusion and the reasons for excluding any articles recorded. The title/abstract screening and full-text screenings were performed independently by two reviewers (T.M.D. and E.M.) in Covidence®. Any discrepancies were resolved by a third reviewer (J.W.A.). Any additional articles identified from the references of the included articles were added.

Data extraction

Data from the final set of eligible studies were extracted for each relevant criterion by one of the screening reviewers (T.M.D. or E.M.) and were independently checked for accuracy by the other reviewers (H.Y.K. and C.O.M.).

Risk of bias assessment

Risk of bias assessment was independently performed by two reviewers (H.Y.K. and C.O.M.) for the included studies. Risk of bias tool for randomized trials version 2 (ROB 2) and risk of bias tool for non-randomized studies (RoBANS) were used in this assessment.[23,24] For the overall risk, using ROB 2 tool, the studies were rated low, high, or some concerns. Using RoBANS tool, the studies were rated as low, high, or unclear risk.

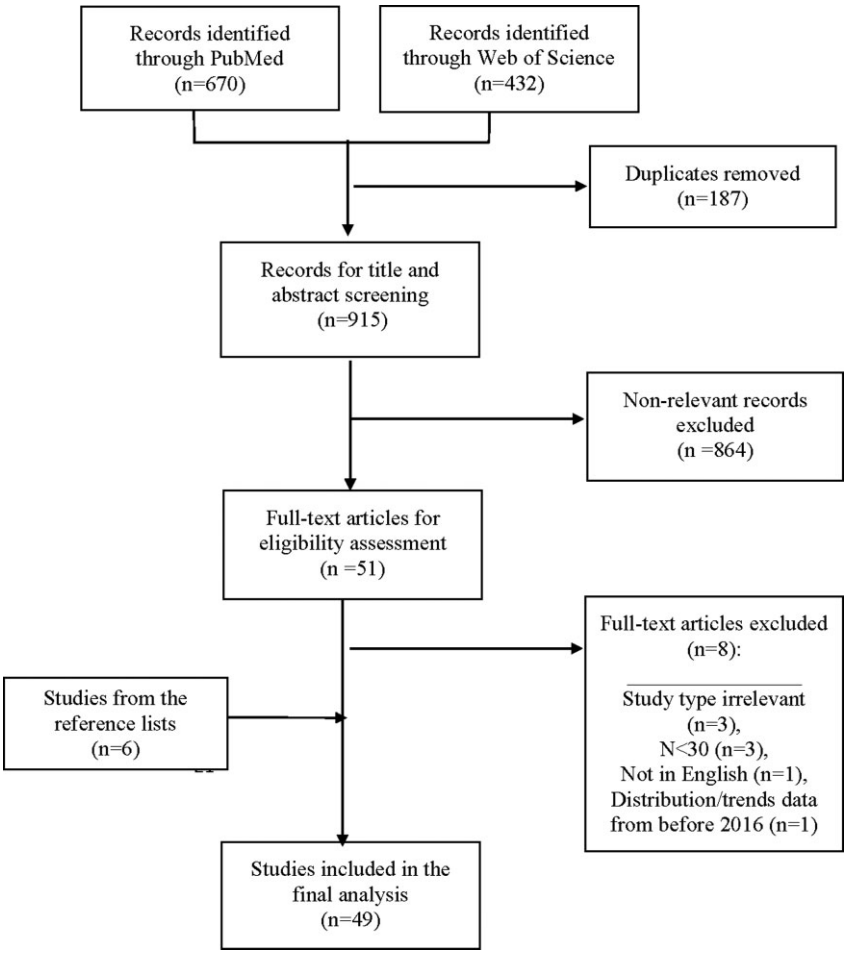

Figure 1. Flow diagram for selection of studies included in the systematic review of *Aspergillus fumigatus* based on: the PRISMA 2020 statement: an updated guideline for reporting systematic reviews.[21]

This systematic review was intended to inform on specific criteria; therefore, we used each criterion as an outcome of the study and assessed if any bias was expected based on the study design, data collection, or analysis in that particular study. With this approach, studies classified as unclear or high overall risk were still considered for analysis.

Data synthesis

The extracted data on the outcome criteria were quantitatively (e.g., proportions [%], mean, median, and range) or qualitatively analyzed depending on the amount and nature of the data.

Results

Study selection

Between 1 January 2011 and 10 June 2021, 670 and 432 articles were identified in PubMed and World of Science Core Collection databases, respectively. After excluding the duplicated and non-relevant articles, 51 articles underwent full-text screening, of which 43 studies were deemed eligible. Six additional articles were identified from the reference lists; resulting in 49 articles for inclusion in the final analysis. A flow diagram outlining the process of study selection is shown in Figure 1.

Risk of bias

The overall risk of bias for each study is presented in Table 1. Of the included studies, 16/49 (32.7%) were classified as low risk of bias in the domains used for classification (i.e., study design, data collection, or data analysis). Twenty-eight studies (57.1%) were classified as unclear risk of bias, mostly due to unclear eligibility criteria or population groups (18/28 [64.3%]) or unclear confirmation/consideration of confounding variables (21/28 [75%]) (Supplementary Table S1). Five studies (10.2%) were considered high-risk of bias, with 80% (4/5) related to confounding (Supplementary Table S1). The details of the risk of bias assessment for each domain can be found in the supplementary material (Supplementary Table S1).

Analysis of the criteria

Mortality

Overall 30-day mortality in a prospective cohort of 1416 azole-naïve immunosuppressed patients suspected of having IA was 13.6%.[25] Four studies (44.4%) reported Day-42/6-week mortality rates. Three studies of patients with mainly hematological malignancies who were diagnosed with proven, probable, or putative (if in ICU)[26] IA reported overall/all-cause mortality rates of between 31% and 36%, and one

Table 1. Overall risk of bias for included studies.

Author	Year	Risk	Reference
Abdolrasouli et al.	2018	Unclear	34
Abdolrasouli et al.	2018	Low	35
Alastruey-Izquierdo et al.	2018	Low	36
Ashu et al.	2018	Unclear	38
Borman et al.	2020	Low	39
Buil et al.	2018	Low	40
Bustamante et al.	2020	Unclear	41
Castanheira et al.	2017	Low	42
Chen et al.	2016	Unclear	43
Cho et al.	2019	Unclear	29
Dabas et al.	2018	Unclear	25
Deng et al.	2017	Unclear	44
Dib et al.	2020	Low	67
Espinel-Ingroff et al.	2018	High	49
Forsythe et al.	2020	High	33
Fukuda et al.	2018	Unclear	110
Guegan et al.	2021	Unclear	111
Heo et al.	2017	Low	27
Jensen et al.	2016	Unclear	37
Koehler et al.	2017	Unclear	50
Lane et al.	2018	High	32
Lass-Flörl et al.	2018	Unclear	51
Lavergne et al.	2019	Low	52
Lee et al.	2020	Low	112
Lestrade et al.	2016	High	68
Lestrade et al.	2018	Low	30
Lestrade et al.	2019	Low	28
Lestrade et al.	2020	Unclear	53
Messer et al.	2020	Unclear	55
Mohammadi et al.	2018	Unclear	56
Nabili et al.	2016	Unclear	57
Nawrot et al.	2018	Unclear	58
Nawrot et al.	2019	Unclear	59
Negri et al.	2017	Unclear	60
Parent-Michaud et al.	2020	Unclear	61
Pfaller et al.	2017	Unclear	45
Pinto et al.	2018	Unclear	46
Prigitano et al.	2017	Low	47
Reichert-Lima et al.	2018	Unclear	48
Resendiz-Sharpe et al.	2019	Low	18
Salmanton-García et al.	2021	Unclear	6
Seufert et al.	2018	Unclear	62
Sui et al.	2018	High	113
Takeda et al.	2021	Low	63
Talbot et al.	2018	Unclear	64
Tsuchido et al.	2019	Low	65
vanPaassen et al.	2016	Low	31
Wu et al.	2020	Unclear	54
Zhang et al.	2017	Unclear	66

study examining COVID-associated pulmonary aspergillosis (CAPA) reported a rate of 47.8% (Table 2).[6,18,27,28] Two studies reported 12-week mortality rates; 50% (93/186) and 41.1% (53/129) in CAPA and non-CAPA cases, respectively.[6,18] One prospective study of hematology patients with culture-positive proven or probable IA reported a 100-day mortality rate of 43% (12/28).[29] IA has long-term negative impacts as 6-month mortality was determined to be significantly higher in hematology patients with IA when compared with hematology patients who never had IA (14/38 [36.1%] vs. 63/362 [17.4%]; $P = .01$).[30] Most studies (3/4; 75%) comparing voriconazole-resistant IA to voriconazole-susceptible IA found that mortality rates were significantly higher in voriconazole-resistant IA cases (Table 2).[18,27,28,31]

Inpatient care and complications and sequelae

Only one (1/49; 2.04%) study reported on the length of hospital stay in those with IA, which ranged from 21 to 532 days (Table 3).[32] No data were reported on the excess length of stay related to the diagnosis and management of IA. A cross-sectional study, using an electronic medical record network that integrated data from 30 US hospitals (>34 million patients), reported that patients on immunosuppressant agents, cancer patients, transplant patients, and patients living with HIV were more likely to be hospitalized if they had a systemic mycosis compared with matched controls who did not have a systemic mycosis (Table 3).[33] No studies reported on the complications and/or sequelae related to IA.

Antifungal susceptibility testing

Forty (81.6%) studies reported on the antifungal drug susceptibility profiles of *A. fumigatus*.[18,25,27–31,34–66] The study methods can be found in Supplementary Table S2. Drug susceptibility to azoles and other antifungal drugs is presented in Tables 4 and 5. Azole susceptibility varied widely between studies, ranging from 9.6% to 100% for the most commonly used azoles (i.e., itraconazole, voriconazole, and posaconazole) across ICU, non-specified, unselected, or mixed patient populations (Table 4 and Supplementary Table S2).[31,45,53,59] Voriconazole susceptibility rates of 22.2% were reported from the Netherlands, whereas in Brazil, Korea, India, China, and the UK, voriconazole susceptibility rates were 76%, 94.7%, 96.9%, 98.6%, and 99.7%, respectively (Table 4 and Supplementary Table S2).[25,29,34,43,48] Out of 27 studies, 7 (25.9%) studies reported itraconazole susceptibility rates of >97.5% for *A. fumigatus* isolates.[34,41,42,45,48,59,61] Similarly, 11/27 (40.7%) and 7/20 (35%) studies reported voriconazole and posaconazole susceptibility rates of >97.5%, respectively.[34,36,41–45,50,52,59,61,66] Lestrade et al. reported high resistance rates of 77.8%–90.4% to itraconazole, voriconazole, posaconazole, and isavuconazole based on 640 *A. fumigatus* isolates collected from patients attending five university medical centers in the Netherlands.[53] Of the voriconazole-resistant isolates ($n = 498$), 423 (85%) were resistant to itraconazole and 462 (92.8%) were resistant to posaconazole.[53] In addition, 413/640 (64.5%) of these isolates were pan-azole resistant, 51 (8%) were resistant to more than one azole, and 27.5% (176/640) were resistant to a single azole.[53] Furthermore, Lestrade et al. reported an increase in azole antifungal resistance rates over the time-frame of the study (7.6% [95% confidence interval [CI]: 5.9%–9.8%] in 2013 to 14.7% [95% CI: 12.3%–17.4%] in 2018).[53]

Only 11 studies reported on isavuconazole susceptibility.[28,40,44,51–55,58,59,62] One study reported high resistant rates (82.1%).[53] The voriconazole and isavuconazole MIC values for *A. fumigatus* isolates were strongly correlated (Spearman's p of .887; $P = .01$).[40] Thus, a high voriconazole minimum inhibitory concentration (MIC) is predictive of a high isavuconazole MIC.[40]

Susceptibility rates to echinocandins were reported as very high even in azole-resistant *A. fumigatus* isolates (100%),[25,28,30,35,42,44,45,55] and the MIC_{90} or minimum effective concentration $(MEC)_{90}$ ranges were low in all but one of eight studies (87.5%) (Table 5).[36,44,45,48,55,57,64,65] High rates of susceptibility to amphotericin B (96.6%–100%) were reported in eight studies (Table 5).[25,28,35,36,42,44,45,55] One study reported high rates of resistance to amphotericin B (57/71

Table 2. Mortality due to invasive aspergillosis.

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients with pathogen (*N*)	Mortality type *n*/*N* (%)
Cho et al.[29]	2019	Prospective cohort study Single center	January 2016–April 2018	Korea	Tertiary	Hematological malignancy patients with IA: (207)	Clinical pathogens: (82) *Aspergillus fumigatus*: (38)	100-day mortality with azole-susceptible clinical pathogens: 12/28 (43%)
Dabas et al.[25]	2018	Prospective cohort study	2012–2016	India	NS	Azole-naïve immunocompromised patients suspected of having IA: (1416)	Diagnosed with proven or probable IA: (706/1416 [49.9%]) Culture positive *Aspergillus fumigatus*: (122/706 [17.3%])	30-day mortality: 192/1416 (13.6%)
Heo et al.[27]	2017	Laboratory-based surveillance Single center	January 1999–December 2015	USA	Tertiary	Hematological malignancy: (107) And/or Autologous HSCT: (12) Allogeneic HSCT: (34)	*Aspergillus fumigatus*: (150)	Day-42 mortality in patients with an azole-susceptible isolate: 30/83 (36%) Day-42 mortality in patients with an azole-resistant isolate: 7/19 (37%) No statistically significant difference: ($P = .95$)
Lane et al.[32]	2018	Retrospective cohort study Single center	2010–2016	USA	Community hospital	Patients with positive fungal culture: (3929) Patients with positive *Aspergillus* cultures: (117/3929 [3%]) Chronic respiratory disease: (27/117 [23.1%]) Diagnosed with IPA: (33/117 [28.2%])	IPA cases cultured *Aspergillus fumigatus:* (26/33 [78.8%])	Overall mortality rate in IPA patients: 9/33 (27.3%) Mortality rate in colonized patients: 8/84 (9.5%) Statistically significant difference: ($P < .026$)
Lestrade et al.[30]	2018	Retrospective cohort study Single center	2006–2012	The Netherlands	University medical center	Patients receiving intensive chemotherapy for treatment of AML or MDS: (182 [42.1%]) Allogeneic HSCT recipients: (250 [57.9%])	*Aspergillus fumigatus*: (47)	Mortality at 180 days in patients with proven or probable IA: 14/38 (36.1%) Significantly higher than in those without IA: 63/362 (17.4%); ($P = .01$)

Table 2. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients with pathogen (*N*)	Mortality type *n*/*N* (%)
Lestrade et al.[28]	2019	Retrospective cohort study Multicenter	January 2011–December 2015	The Netherlands	University medical centers	Patients with a positive *Aspergillus fumigatus* culture: (2266) Patients met the case definition*: (196 [8.6%]) Proven IA: (43/196 [21.9%]) Probable IA: (117/196 [59.7%]) Putative IA: (36 [18.4%])	(196)	Overall mortality; Day 42: 62/196 (32%) Overall mortality; Day 90: 81/196 (42%) Statistically significantly lower mortality rate in voriconazole-susceptible cases compared with voriconazole-resistant cases at Day 42: 44/158 (28%; 95% CI: 21%–35%) vs. 18/37 (49%; 95% CI: 34%–66%); (*P* = .017) Day 90: 58/158 (37%; 95% CI: 30%–45%) vs. 23/37 (62%; 95% CI: 47%–77%); (*P* = .0038)
Resendiz-Sharpe et al.[18]	2019	Retrospective study Multicenter	2012–2017	Belgium The Netherlands	University medical centers	Hematology patients with *Aspergillus fumigatus* culture positive proven or probable IA: (129)	*Aspergillus fumigatus*: (129)	6-week all-cause mortality: 40/129 (31%) 12-week all-cause mortality: 53/129 (41.1%) Non-ICU voriconazole-susceptible cases 12-week mortality statistically significantly lower than in voriconazole-resistant cases: 27/88 (30.7%) vs. 12/22 (54.5%); (*P* = .035)

Table 2. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients with pathogen (*N*)	Mortality type *n*/*N* (%)
Salmanton-García et al.[6]	2021	Retrospective cohort study Multicenter	1 March 2020–31 August 2020	France, Italy, Germany, The Netherlands, Belgium, Spain, UK, Denmark, Ireland, Switzerland, Austria, Pakistan, Mexico, Brazil, Qatar, Argentina, Australia	NS	CAPA: 186	*Aspergillus fumigatus* (122)	Total number of patients who died: 97 (52.2%) *Aspergillus* attributable mortality: 17.2% (32/186) 6-week mortality: 89/186 (47.8%) 12-week mortality: 93/186 (50%) *Aspergillus fumigatus*-specific mortality was unavailable
Van Paassen et al.[31]	2016	Retrospective cohort study Single center	January 2010–December 2013	The Netherlands	Tertiary	ICU patients: 38	*Aspergillus fumigatus* isolates in ICU patients: (38)	90-day mortality, azole-susceptible IA: 23/28 (82%) 90-day mortality a azole-resistant IA: 10/10 (100%)

N, number; *n*/*N*, number that died/number included in study; IA, invasive aspergillosis; NS, not stated; USA, United States of America; HSCT, hematopoietic stem cell transplant; IPA, invasive pulmonary aspergillosis; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; CI, confidence interval; ICU, intensive care unit; UK, United Kingdom; and CAPA, COVID-associated pulmonary aspergillosis.
*Case definition; received antifungal therapy within 30 days of a positive culture, received at least 2 days of antifungal therapy, and could be classified as IA according to the EORTC/MSG or AspICU criteria.

Table 3. Length of inpatient stay associated with invasive aspergillosis.

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients with pathogen (*N*)	Length of stay (days)
Lane et al.[32]	2018	Retrospective cohort study Single center	2010–2016	USA	CH	Patients with positive fungal culture: (3929) Patients with positive *Aspergillus* cultures: (117/3929 [3%]) Chronic respiratory disease: (27/117 [23.1%]) Diagnosed with IPA: (33/117 [28.2%])	IPA cases cultured *Aspergillus fumigatus*: 26/33 (78.8%)	In IPA cases Range: 21–532 days
Forsythe et al.[33]	2020	Cross-sectional study	2012–2017	USA	NS	Patients with: aspergillosis, coccidioidomycosis, histoplasmosis, blastomycosis, para-coccidioidomycosis, sporotrichosis, chromoblastomycosis, phaeohyphomycosis. Patients who are otherwise healthy, aged >65 years, those receiving immunosuppressants, with cancer, post-transplantation, or with HIV infection	SM: (33 230) Aspergillosis using ICD-10-CM codes: (37.7%)	NS Hospitalizations significantly greater in patients with SM and, on immunosuppressant medications (36.9% [$n = 5513$] vs. 17.5% [$n = 4\,166\,383$]) With cancer (50.2% [$n = 3284$] vs. 8.88% [$n = 775\,313$]) Post-transplantation (74.5% [$n = 1099$] vs. 65.1% [$n = 37\,913$]) With HIV infections (39.1% [$n = 532$] vs. 13.3% [$n = 91\,275$])

N, number; USA, United States of America; CH, community hospital; IPA, invasive pulmonary aspergillosis; NS, not stated; SM, systemic mycoses; ICD-10-CM, International Classification of Diseases-Tenth Revision-Clinical Modification; and HIV, human immunodeficiency virus.

Table 4. Susceptibility of *Aspergillus fumigatus* to azole antifungal agents.

Author	Year	MIC determination method	Itraconazole *n/N* (% susceptible)	Voriconazole *n/N* (% susceptible)	Posaconazole *n/N* (% susceptible)	Isavuconazole *n/N* (% susceptible)
Abdolrasouli et al.[34]	2018	CLSI M38-A2 (1998–2011) EUCAST (2015–2017)	1998–2011 1148/1151 (99.7%) 2015–2017 312/318 (98.1%)	1998–2011 1148/1151 (99.7%) 2015–2017 317/318 (99.7%)	1998–2011 717/720 (99.6%) 2015–2017 312/318 (98.1%)	NS
Abdolrasouli et al.[35]	2018	VIPcheck™ EUCAST	145/167 (86.8%)	157/167 (94%)	152/167 (91%)	NS
Alastruey-Izquierdo et al.[36]	2018	EUCAST	257/260 (89.8%) MIC (mg/l) GM: 0.20 MIC_{50}: 0.12 MIC_{90}: 0.5 Range: 0.03–16	258/260 (99.2%) MIC (mg/l) GM: 0.47 MIC_{50}: 0.5 MIC_{90}: 1 Range: 0.12–4	257/260 (89.8%) MIC (mg/l) GM: 0.06 MIC_{50}: 0.06 MIC_{90}; 0.12 Range: 0.015–8	NS
Buil et al.[40]	2018	EUCAST	NS	NS	NS	Phenotypically WT: 254/279 (91%) Phenotypically non-WT: 12/208 (5.8%)
Bustamante et al.[41]	2020	CLSI M38-A2	140/143 (97.9%) MIC_{50}: 0.25 MIC_{90}: 0.5 Range: 0.125 to >16	142/143 (99.3%) MIC_{50}: 0.5 MIC_{90}: 0.5 Range: 0.25–2	141/143 (98.6%) MIC_{50}: 0.06 MIC_{90}: 0.125 Range: 0.003–1	NS
Castanheira et al.[42]	2017	CLSI M38-A2	MIC_{50} or MEC_{50} (μg/ml): 0.5 MIC_{90} or MEC_{90} (μg/ml): 1 WT: 389/391 (99.5%)	MIC_{50} or MEC_{50} (μg/ml): 0.5 MIC_{90} or MEC_{90} (μg/ml): 0.5 WT: 390/391 (99.7%)	NS	NS
Chen et al.[43]	2016	EUCAST	309/217 (97.5%)	142/144 (98.6%)	NS	NS
Cho et al.[29]	2019	CLSI M38-A2	36/38 (94.7%)	36/38 (94.7%)	36/38 (94.7%)	NS
Dabas et al.[25]	2018	CLSI M38-A2 EUCAST	26/32 (81.25%) 26/32 (81.25%)	31/32 (96.87%) 31/32 (96.87%)	31/32 (96.87%) 31/32 (96.87%)	NS
Deng et al.[44]	2017	CLSI M38-A2	152/159 (95.6%) MIC/MEC range: 0.063 to >16	158/159 (99.37%) MIC/MEC range: 0.063–2	154/159 (96.86%) MIC/MEC range: 0.031–1	153/159 (96.2%) MIC/MEC range 0.063–4
Koehler et al.[50]	2017	E-test® EUCAST	75/77 (97.4%)	76/77 (98.7%)	NS	NS
Lass-Flörl et al.[51]	2018	E-test® EUCAST	NS	MIC_{50}: 0.25 MIC_{90}: 1	MIC_{50}: 0.125 MIC_{90}: 0.25	MIC_{50}: 0.5 MIC_{90}: 1
Lavergne et al.[52]	2019	EUCAST	335/355 (94.3%)	336/355 (94.6%)	354/355 (99.7%)	355/355 (100%)
Lestrade et al.[30]	2018	VIPcheck™ EUCAST	24/28 (85.7%)	26/28 (92.8%)	26/28 (92.8%)	NS
Lestrade et al.[28]	2019	VIPcheck™ EUCAST	7 of 37 (18.9%) voriconazole-resistant isolates were sensitive to itraconazole	159 of 196 (81.1%)	5 of 37 (13.5%) voriconazole-resistant isolates were sensitive to posaconazole	0 of 14 (0%) voriconazole-resistant isolates were sensitive to isavuconazole

Table 4. Continued

Author	Year	MIC determination method	Itraconazole *n*/*N* (% susceptible)	Voriconazole *n*/*N* (% susceptible)	Posaconazole *n*/*N* (% susceptible)	Isavuconazole *n*/*N* (% susceptible)
Lestrade et al.[53]	2020	Azole screening agar EUCAST	82/640 (12.8%)	142/640 (22.2%)	62/640 (9.6%)	115/640 (17.9%)
Messer et al.[55]	2020	CLSI M38Ed.3	MIC_{50}: 0.5 MIC_{90}: 1 Range: 0.25 to >8 % WT: 93.7	MIC_{50}: 0.5 MIC_{90}: 0.5 Range: 0.06 to > 8 % WT: 96.4	MIC_{50}: 0.25 MIC_{90}: 0.5 Range: 0.06–4	MIC_{50}: 0.5 MIC_{90}: 2 Range: 0.12 to > 8 % WT: 88.7
Mohammadi et al.[56]	2018	Azole agar screening plate EUCAST	166/172 (96.5%) MIC range: 0.0063 to >16	166/172 (96.5%) MIC range: 0.031–8	167/172 (97.1%)	NS
Nabili et al.[57]	2016	CLSI M38-A2	GM: 0.5196 MIC_{50}: 0.063 to >16 MIC_{90}: 0.5 Range: 0.5 WT: 68/71 (95.8%)	GM: 0.0855 MIC_{50}: 0.031–8 MIC_{90}: 0.25 Range: 0.063 WT: 69/71 (97.2%)	GM: 0.0491 MIC_{50}: 0.008–4 MIC_{90}: 0.25 Range: 0.063 WT: 69/71 (97.2%)	NS
Nawrot et al.[58]	2018	EUCAST	116/121 (95.9%) isolates 104/109 (95.4%) patients	NS	117/121 (96.7%) isolates	120/121 (99.2%)
Nawrot et al.[59]	2019	EUCAST	75/75 (100%) Mean MIC: 0.18 Range: 0.06–0.5	75/75 (100%) Mean MIC: 0.38 Range: 0.03–1	75/75 (100%) Mean MIC: 0.044 Range: 0.015–0.06	75/75 (100%) Range: 0.125–1
Negri et al.[60]	2017	CLSI M38-A2	GM: 0.502 MIC_{50}: 0.5 MIC_{90}: 1 Range: 0.125–1	GM: 0.486 MIC_{50}: 0.5 MIC_{90}: 1 Range: 0.125–2	GM: 0.156 MIC_{50}: 0.125 MIC_{90}: 0.25 Range: 0.125–2	NS
Parent-Michaud et al.[61]	2020	Modified broth microdilution CLSI M38-A2	984/985 (99.9%) MIC: 2	984/985 (99.9%) MIC: 2	984/985 (99.9%) MIC: 1	NS
Pfaller et al.[45]	2017	CLSI M38-A2	MIC_{50}: 0.5 MIC_{90}: 1 Range: 0.25–1 56/56 (100%)	MIC_{50}: 0.25 MIC_{90}: 0.5 Range: 0.12–1 56/56 (100%)	MIC_{50}: 0.25 MIC_{90}: 0.5 Range: 0.06–0.5 6/56 (100%)	NS
Reichert-Lima et al.[48]	2018	CLSI M38-A2	MIC_{50}: 1 MIC_{90}: 1 Range: 0.25–4 165/168 (98.2%)	MIC_{50}: 1 MIC_{90}: 2 Range: 0.25–8 128/168 (76%)	NS	NS
Resendiz-Sharpe et al.[18]	2019	VIPcheck™ EUCAST	NS	103/129 (79.8%)	NS	NS
Seufert et al.[62]	2018	Screening: Azole-containing agar Confirmed: EUCAST 9.3	MIC_{90}: >8 MIC_{50}: >8 Range: 2 to >8	MIC_{90}: 16 MIC_{50}: 8 Range: 0.5 to >16	MIC_{90}: 2 MIC_{50}: 1 Range: 20.5 to >8	MIC_{90}: >16 MIC_{50}: 16 Range: 0.5 to >816
Takeda et al.[63]	2021	CLSI M38Ed.3	112/120 (93.3%)	115/120 (95.8%)	NS	NS

Table 4. Continued

Author	Year	MIC determination method	Itraconazole *n*/*N* (% susceptible)	Voriconazole *n*/*N* (% susceptible)	Posaconazole *n*/*N* (% susceptible)	Isavuconazole *n*/*N* (% susceptible)
Talbot et al.[64]	2018	VIPcheck™ CLSI M38Ed.3	GM: 0.22 MIC/MEC_{90}: 0.50 Range: 0.06 to >16 Isolates from humans with invasive disease	GM: 0.28 MIC/MEC_{90}: 0.5 Range: 0.06–8 Isolates from humans with invasive disease	GM: 0.11 MIC_{90}: 0.50 Range: 0.015–1 Isolates from humans with invasive disease	NS
Tsuchido et al. [65]	2019	CLSI M38Ed.3 (testing) EUCAST (breakpoint determination)	Range: 0.25 to >8 51/55 (92.7%)	Range: 0.5 to >8 48/55 (87.3%)	NS	NS
van Passen et al.[31]	2016	Screening: Azole-containing agar Confirmed: EUCAST	10/38 (73.6%) Range: 16 to >16	10/38 (73.6%) Range: 4 to >16	10/38 (73.6%) Range: 0.5–2	NS
Wu et al.[54]	2020	CLSI M38-A2	203/222 (91.4%)	210/222 (94.6%)	203/222 (91.4%)	203/222 (91.4%)
Zhang et al.[66]	2017	EUCAST	122/126 (96.8%)	125/126 (99.2%)	125/126 (99.2%)	NS

MIC, minimum inhibitory concentration; *n*/*N*, number susceptible *Aspergillus fumigatus* isolates/total number of *Aspergillus fumigatus* isolates tested; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; NS, not stated; GM, geometric mean; MIC_{50}, MIC required to inhibit the growth of 50% of isolates; MIC_{90}, MIC required to inhibit the growth of 90% of isolates; WT, wild type, MEC_{50}, 50% minimum effective concentration; MEC, minimum effective concentration; and MEC_{90}, 90% minimum effective concentration.

[80.3%]) (Table 5).[38] Only one study reported on terbinafine susceptibility with MIC values ranging from 0.25 to 32 mg/l.[36]

Risk factors and preventive measures

Table 6 outlines the risk and prognostic factors in those who develop IA. One study found that invasive pulmonary aspergillosis (IPA) in hematological malignancy patients had very different predisposing factors compared with IPA in solid-organ malignancy patients. Hematological malignancy patients with IPA were more likely to have diabetes mellitus (72/225 [35%] vs. 12/86 [14%]; $P = .001$), received corticosteroids (168/218 [77%] vs. 24/86 [28%]; $P < .0001$), received chemotherapy (104/225 [46%] vs. 24/86 [28%]; $P = .003$), or received immunotherapy 58/225 [26%] vs. 8/86 [9%]; $P = .002$) within 30 days of IPA diagnosis (Table 6).[67] Whereas, those with a solid-organ malignancy and IPA were more likely to have chronic obstructive pulmonary disease (28/86 [33%] vs. 17/225 [8%]; $P < .0001$) or received radiotherapy (41/86 [48%] vs. 31/219 [14%]; $P < .0001$) prior to the IPA diagnosis.[67] In addition, a complete response to the treatment of IPA was less common in hematology patients (87/220 [40%] vs. 45/68 [66%]; $P = .001$), and 12-week IA-attributable mortality was significantly higher in patients with hematological malignancies (65/217 [30%] vs. 14/78 [18%]; $P = .04$) compared with solid-organ malignancy patients, respectively (Table 6).[67]

Risk factors for IPA due to azole-resistant *A. fumigatus* included Asian race (odds ratio [OR] 20.9 [95% CI: 2.5–173.5]; $P = .0048$) and previous azole exposure (OR 4.4 [95% CI: 1.03–18.6]; $P = .046$) (Table 6).[27] One study examined CAPA and reported that 182/186 (97.8%) were admitted to ICU and 98/186 (52.7%) received corticosteroids.[6] Other common underlying conditions patients with CAPA had included chronic cardiovascular disease (94/186 [50.5%]), renal failure (74/186 [39.8%]), diabetes mellitus (64/186 [34.4%]), obesity (47/186 [25.3%]), chronic pulmonary disease (40/186 [21.5%]), or hematologic or oncologic disease (21/186 [11.3%]) (Table 6).[6]

The studies in Supplementary Table S3 delineate the data that have potential for use in developing future preventative interventions. Dib et al. reported that antifungal prophylaxis was administered more often to high-risk hematology patients than to low-risk patients with solid-malignancy (133/225 [59%] vs. 9/86 [10%]; $P < .0001$).[67] Clinical and environmental *A. fumigatus* isolates were shown to be genetically related by Prigitano et al. (Supplementary Table S3).[47] Two (of 49 [4.1%]) studies reported an association between the long-term use of azoles and the subsequent detection of azole-resistant isolates (Supplementary Table S3).[56,62] van Paassen et al. reported that other resistance mechanisms besides CYP51A mutations exist.[31]

Annual incidence

A multicenter survey from the Netherlands reported that the incidence of IA was an average of eight (range 2–30) cases/year (Table 7).[68] The incidence of proven/probable IA was 1.3/1000 patient-days in a prospective cohort of Korean patients with hematological malignancies, and Koehler et al. reported that the incidence of IA was 5.84/100 patients in a German cohort with acute leukemia.[29,50] The incidence of IA in the ICU setting was determined as 15/1000 ICU admissions.[31] Two studies examined the incidence of CAPA. [6,39] Borman et al. reported that the incidence of proven/probable CAPA was 5% in 61 critically ill UK patients who had multiple samples for galactomannan and *Aspergillus* PCR testing, mi-

Table 5. Susceptibility of *Aspergillus fumigatus* to echinocandins and amphotericin B.

Author	Year	MIC determination method	Anidulafungin *n/N* (% susceptible)	Caspofungin *n/N* (% susceptible)	Micafungin *n/N* (% susceptible)	Amphotericin B *n/N* (% susceptible)	Terbinafine *n/N* (% susceptible)
Abdolrasouli et al.[35]	2018	VIPcheck™ EUCAST	100% of azole-resistant isolates were sensitive to anidulafungin: Itraconazole ($n = 22$) Voriconazole ($n = 10$) Posaconazole ($n = 15$)	100% of azole-resistant isolates were sensitive to caspofungin: Itraconazole ($n = 22$) Voriconazole ($n = 10$) Posaconazole ($n = 15$)	100% of azole-resistant isolates were sensitive to micafungin: Itraconazole ($n = 22$) Voriconazole ($n = 10$) Posaconazole ($n = 15$)	100% of azole-resistant isolates were sensitive to amphotericin B Itraconazole ($n = 22$) Voriconazole ($n = 10$) Posaconazole ($n = 15$)	NS
Alastruey-Izquierdo et al.[36]	2018	EUCAST	GM: 0.02 MEC_{50}: 0.015 MEC_{90}: 0.03 Range: 0.007–8	GM: 0.35 MEC_{50}: 0.25 MEC_{90}: 1 Range: 0.004–32	GM: 0.01 MEC_{50}: 0.015 MEC_{90}: 0.03 Range: 0.003–4	GM: 0.36 MIC_{50}: 0.5 MIC_{90}: 0.5 Range: 0.015–1 258/260 (99.23%)	GM: 2.94 MIC_{50}: 4 MIC_{90}: 8 Range: 0.25–32
Ashu et al.[38]	2018	CLSI M38-A2	NS	NS	NS	14/71 (19.7%) Clinical isolates	NS
Castanheira et al.[42]	2017	CLSI M38-A2	MIC_{50} or MEC_{50}: ≤0.008 MIC_{90} or MEC_{90}: 0.03	MIC_{50} or MEC_{50}: 0.015 MIC_{90} or MEC_{90}: 0.03 WT: 100%	MIC_{50} or MEC_{50}: ≤0.008 MIC_{90} or MEC_{90}: 0.015	MIC_{50} or MEC_{50}: 1 MIC_{90} or MEC_{90}: 2 WT: 100%	NS
Dabas et al.[25]	2018	CLSI M38-A2 EUCAST	NS	32/32 (100) WT: 32/32 (100%)	2/32 (100) WT: 32/32 (100%)	31/32 (96.6%) WT: 31/32 (96.87%)	NS
Deng et al.[44]	2017	CLSI M38-A2	MIC/MEC range: ≤0.008–0.063 159/159 (100%)	MIC/MEC range: 0.125–0.5 159/159 (100%)	MIC/MEC range: ≤0.008–0.5 159/159 (100%)	MIC/MEC range: 0.5–2 159/159 (100%)	NS

Table 5. Continued

Author	Year	MIC determination method	Anidulafungin *n*/*N* (% susceptible)	Caspofungin *n*/*N* (% susceptible)	Micafungin *n*/*N* (% susceptible)	Amphotericin B *n*/*N* (% susceptible)	Terbinafine *n*/*N* (% susceptible)
Lass-Flörl et al.[51]	2018	Etest EUCAST	MEC_{50}: 0.25 MEC_{90}: 1	NS	NS	MIC_{50}: 0.5 MIC_{90}: 2	NS
Lestrade et al.[30]	2018	VIPcheck™ EUCAST	Anidulafungin MICs > 0.032 mg/l (the highest MIC being 0.25 mg/l) were found for 16 isolates from 15 patients The two voriconazole-resistant isolates had anidulafungin MICs of 0.063 and 0.125 mg/l, respectively	NS	NS	Two isolates from two patients had amphotericin MICs of 2 mg/l and were also resistant to voriconazole	NS
Lestrade et al.[28]	2019	VIPcheck™ EUCAST	NS	NS	NS	196/196 (100%)	NS
Messer et al.[55]	2020	CLSI M38Ed.3	MIC_{50}: 0.015 MIC_{90}: 0.03 Range: ≤0.008–0.06	MIC_{50}: 0.03 MIC_{90}: 0.03 Range: ≤0.008–0.06 WT: 100%	MIC_{50}: ≤0.008 MIC_{90}: 0.015 Range: ≤0.008–0.03	MIC_{50}: 1 MIC_{90}: 2 Range: 0.25–2 WT: 100%	NS
Nabili et al.[57]	2016	CLSI M38-A2	NS	GM: 0.0622 MIC_{50}: 0.008–0.5 MIC_{90}: 0.125 Range: 0.063	NS	GM: 0.5674 MIC_{50}: 0.125–4 MIC_{90}: 0.5 Range: 0.5	NS

Table 5. Continued

Author	Year	MIC determination method	Anidulafungin *n*/*N* (% susceptible)	Caspofungin *n*/*N* (% susceptible)	Micafungin *n*/*N* (% susceptible)	Amphotericin B *n*/*N* (% susceptible)	Terbinafine *n*/*N* (% susceptible)
Pfaller et al.[45]	2017	CLSI M38-A2	MIC_{50}:≤0.008 MIC_{90}: 0.015 Range: ≤0.008–0.03	MIC_{50}: 0.03 MIC_{90}: 0.03 Range: 0.015–0.06	MIC_{50}: 0.015 MIC_{90}: 0.015 Range: ≤0.008–0.03	MIC_{50}: 2 MIC_{90}: 2 Range: 0.5–2 WT: 56/56 (100%)	NS
Reichert-Lima et al.[48]	2018	CLSI M38-A2	NS	MEC_{50}: 0.25 MEC_{90}: 0.25 Range: 0.06–0.5	MEC_{50}: ≤0.015 MEC_{90}: 0.03 Range: ≤0.015–0.03	MIC_{50}: 1 MIC_{90}: 2 Range: 0.25–8 22/168 (72.6%)	NS
Talbot et al.[64]	2018	VIPcheck™ CLSI M38Ed.3	GM: 0.02 MEC_{90}: 0.03 Range: <0.015–0.06 Isolates from humans with invasive disease	GM: 0.04 MEC_{90}: 0.12 Range: <0.008–0.5 Isolates from humans with invasive disease	GM: 0.01 MEC_{90}: 0.015 Range: <0.008–0.03 Isolates from humans with invasive disease	GM: 1.2 MIC_{90}: 2 Range: 0.25–8 Isolates from humans with invasive disease	NS
Tsuchido et al.[65]	2019	CLSI M38Ed.3 (testing) EUCAST (breakpoint determination)	NS	Range: 0.06–0.25	Range: ≤0.015–0.03	Range: 0.5–2	NS
Wu et al.[54]	2020	CLSI M38-A2	NS	NS	NS	19 azole-resistant isolates: MIC_{50}:0.5 MIC_{90}:1 Range: 0.12–1	NS

MIC, minimum inhibitory concentration; *n*/*N*, number susceptible *Aspergillus fumigatus* isolates/total number of *Aspergillus fumigatus* isolates tested; EUCAST, European Committee on Antimicrobial Susceptibility Testing; NS, not stated; *n*, number; GM, geometric mean; MEC_{50}, 50% minimum effective concentration; MEC_{90}, 90% minimum effective concentration; MIC_{50}, MIC required to inhibit the growth of 50% of isolates; MIC_{90}, MIC required to inhibit the growth of 90% of isolates; CLSI, Clinical and Laboratory Standards Institute; and WT, wild type.

Table 6. Risk factors for and outcomes of invasive aspergillosis.

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients with pathogen (*N*)	Risk factors/outcomes
Dabas et al.[25]	2018	Prospective cohort study	2012–2016	India	NS	Azole-naive ICH suspected of IA	Total: (1416) Diagnosed with proven or probable IA: (706/1416 [49.9%]) Culture positive *Aspergillus fumigatus*: (122/706 [17.3%])	Prognostic factors: Culture positivity: Culture positive vs. culture negative: 44/122 (36.1%) vs. 63/584 (10.8%) Azole resistance: Resistant vs. susceptible: 4/6 (66.7%) vs. 9/26 (34.6%)
Dib et al.[67]	2020	Retrospective cohort study Single center	March 2004–December 2016	USA	Tertiary	Patients >18 years of age with an underlying solid tumor, HM, or HSCT within 1 year of proven or probable IPA diagnosis	*Aspergillus fumigatus* isolates: (142)	Risk factor univariate analysis: Patients with HM were more likely than solid tumor patients to have: Diabetes mellitus: 72/225 (35%) vs. 12/86 (14%); $P = .001$ Received corticosteroids within 30 days of IPA diagnosis: 168/218 (77%) vs. 24/86 (28%); $P < .0001$ Received chemotherapy within 30 days of IPA diagnosis: 104/225 (46%) vs. 24/86 (28%); $P = .003$ Received immunotherapy within 30 days of IPA diagnosis: 58/225 (26%) vs. 8/86 (9%); $P = .002$ Neutropenia at time of IPA diagnosis: 83/223 (37%) vs. 2/86 (2%); $P < .0001$ Patients with solid organ tumors were more likely than patients with hematological malignancies to have: COPD: 28/86 (33%) vs. 17/225 (8%); $P < .0001$ Received radiotherapy prior to IPA diagnosis: 41/86 (48%) vs. 31/219 (14%); $P < .0001$ Response to treatment: Complete or partial response to the treatment of IPA occurred significantly less in patients with an HM as compared with solid tumor patients: 87/220 (40%) vs. 45/68 (66%); $P = .001$ 12-week IPA-attributable mortality significantly higher in patients with HM than in solid tumor patients: 65/217 (30%) vs. 14/78 (18%); $P = .04$

Table 6. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients with pathogen (*N*)	Risk factors/outcomes
Fukuda et al.[110]	2018	Retrospective cohort study Single center	January 2012–December 2014	Japan	Tertiary	Patients who isolated *Aspergillus* species: ($n = 104$)	*Aspergillus fumigatus* isolates: (55) Non-*Aspergillus fumigatus* isolates: (49)	Patients who isolated *Aspergillus fumigatus* were significantly more likely to have chronic respiratory disease that those who isolated a non-*Aspergillus fumigatus* isolate: 36/55 (65%) vs. 22/49 (44.8%); $P = .035$ Lung fibrosis was significantly higher in those who isolated *Aspergillus fumigatus* as compared with those who isolated a non-*Aspergillus fumigatus* isolate: 10/55 (16.4%) vs. 2/49 (4.1%); $P = .025$
Heo et al.[27]	2017	Laboratory-based surveillance Single center	January 1999–December 2015	USA	Tertiary	HM: 107 And/or Autologous HSCT: 12 Allogeneic HSCT: 34	*Aspergillus fumigatus* (150)	Independent risk factors for azole-resistant IPA after adjusting for year of diagnosis: Asian race: (OR 20.9 [95% CI: 2.5–173.5]; $P = .0048$) Previous azole exposure: (OR 4.4 [95% CI: 1.03–18.6]; $P = .046$) Independent prognostic factors for death at 42 days: Neutropenia: (OR 3.4 [95% CI: 1.4–8.3]; $P = .03$) Lymphopenia: (OR 4.9 [95% CI: 1.9–12.9]; $P = .017$) In ICU at diagnosis: (OR 43.6 [95% CI: 5.4–349.8]; $P < .001$) Earlier time period of diagnosis: (1992–2002 vs. 2003–2015) (OR 0.4 [95% CI: 0.2–1.0]; $P = .008$)

Table 6. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients with pathogen (*N*)	Risk factors/outcomes
Lane et al.[32]	2018	Retrospective cohort study Single center	2010–2016	USA	CH	Patients with positive fungal culture: (3929) Patients with positive *Aspergillus* cultures: (117/3929 [3%]) Chronic respiratory disease: (27/117 [23.1%]) Diagnosed with IPA: (33/117 [28.2%])	IPA cases cultured *Aspergillus fumigatus* (26/33 [78.8%])	Patients treated for IPA were significantly more likely to have received high-dose prednisone (>20 mg/day): $P < .004$ Mortality rate was significantly higher in patients with IPA as compared to those with colonization: 9/33 (27.3%) vs. 8/84 (9.5%); $P < .026$
Lestrade et al.[28]	2019	Retrospective cohort study Multicenter	January 2011–December 2015	The Netherlands	University medical centers	Patients with a positive *Aspergillus fumigatus* culture: (2266) Patients met the case definition*: (196 [8.6%]) Proven IA: (43/196 [21.9%]) Probable IA: (117/196 [59.7%]) Putative IA: (36 [18.4%])	(196)	HM was the most frequent underlying disease: 103/196 (53%)
Mohammadi et al.[56]	2018	Laboratory-based surveillance Multicenter	January 2009–November 2014	Iran	Not stated	Transplant patients, patients with granulocytopenia, CLD, COPD, ABPA (172)	Aspergillus *fumigat us* isolates: (172)	Most common underlying diseases: Transplantation: 58 (33.7%) Granulocytopenia: 42 (24.4%) CLD: 31 (18.0%) COPD: 23 (13.4%) ABPA: 18 (10.5%)

Table 6. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients with pathogen (*N*)	Risk factors/outcomes
Parent-Michaud et al.[61]	2020	Other: laboratory surveillance Single center	2000–2013	Canada	Tertiary	Patients at risk of aspergillosis	(807)	Emergence of azole-resistant cryptic *Fumigati* species
Pinto et al.[46]	2018	Laboratory-based surveillance Multicenter	January 2010–March 2016	Portugal	Tertiary	Mixed population ($n = 207$)	Clinical isolates: (227) *Aspergillus fumigatus* isolates (190)	Most common underlying conditions: Hemato-oncological: 48/207 (23.2%) Oncological: 36/207 (17.4%) Lung disease: 33/207(15.9%) SOT: 15/207 (7.2%)
Salmanton-García et al.[6]	2021	Retrospective cohort study Multicenter	1 March 2020–31 August 2020	France, Italy, Germany, The Netherlands, Belgium, Spain, UK, Denmark, Ireland, Switzerland, Austria, Pakistan, Mexico, Brazil, Qatar, Argentina, and Australia	NS	Patients with CAPA: (186)	*Aspergillus fumigatus* isolates: (122)	Admitted to ICU: 26/33 (78.8%) Received corticosteroids: 98/186 (52.7%) Underlying conditions: Chronic cardiovascular disease: 94/186 (50.5%) Renal failure: 74/186 (39.8%) Diabetes mellitus: 64/186 (34.4%) Obesity: 47/186 (25.3%) COPD: 40/186 (21.5%) Hematologic or oncologic disease: 21/186 (11.3%)

N, number; NS, not stated; ICH, immunocompromised host; IA, invasive aspergillosis; USA, United States of America; HM, hematological malignancy; HSCT, hematopoietic stem cell transplant; IPA, invasive pulmonary aspergillosis; COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; ICU, intensive care unit; CH, community hospital; CLD, chronic liver disease; ABPA, allergic bronchopulmonary aspergillosis; SOT, solid organ transplant; UK, United Kingdom; and CAPA, COVID-associated pulmonary aspergillosis.
*Case definition; received antifungal therapy within 30 days of a positive culture, received at least 2 days of antifungal therapy, and could be classified as IA according to the EORTC/MSG or AspICU criteria.

Table 7. Annual incidence of invasive aspergillosis.

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients with pathogen (*N*)	Incidence (annual, other)
Borman et al.[39]	2021	Laboratory-based surveillance Multicenter	11 March–14 July 2020	UK	NS	ICU patients with COVID-19: (719)	*Aspergillus fumigatus* isolates: (46)	Incidence of proven/probable CAPA: 5% Incidence of possible CAPA: 15%
Cho et al.[29]	2019	Prospective cohort study Single center	January 2016–April 2018	Korea	Tertiary	HM patients with IA: (207)	Clinical pathogens: (82) *Aspergillus fumigatus*: (38)	Incidence of proven/probable IA: 1.3 cases/1000 patient-days and 2.6/100 admissions to the Catholic Hematology Hospital, Seoul
Koehler et al.[50]	2017	Prospective cohort study Multicenter	09/2011–12/2013	Germany	Tertiary	All patients with AML or ALL	Total: (3067) IA: (179)	Incidence rate of IA in patients with acute leukemia: 5.84/100 patients
Lane et al.[32]	2018	Retrospective cohort study Single center	2010–2016	USA	CH	Patients with positive fungal culture: (3929) Patients with positive *Aspergillus* cultures: (117/3929 [3%]) Chronic respiratory disease: (27/117 [23.1%]) Diagnosed with IPA: (33/117 [28.2%])	IPA cases cultured *Aspergillus fumigatus* (26/33 [78.8%])	Prevalence of *Aspergillus fumigatus* isolates ascribed to IPA from all sputum cultures: 26/11 164 (0.23%)

Table 7. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients with pathogen (*N*)	Incidence (annual, other)
Lestrade et al.[68]	2016	Multicenter survey	2015	The Netherlands	University medical centers and non-academic teaching hospitals	NS	NS	Overall (probable) IA cases: Range: 2–30/center/year Average: 8/center/year
Salmanton-García et al.[6]	2021	Retrospective cohort study Multicenter	1 March 2020–31 August 2020	France, Italy, Germany, The Netherlands, Belgium, Spain, UK, Denmark, Ireland, Switzerland, Austria, Pakistan, Mexico, Brazil, Qatar, Argentina, and Australia	NS	Patients with CAPA: (186)	*Aspergillus fumigatus* isolates: (122)	Cumulative incidence of CAPA in ICU patient: Range: 1.0%–39.1%. Prevalence of CAPA: COVID-19 patients overall: 131/35 381 (0.4%) COVID-19 patients in ICU: 131/1902 (6.9%) COVID-19 patients on mechanical ventilation: 131/1278 (10.3%)
Van Paassen et al.[31]	2016	Retrospective cohort study Single center	January 2010–December 2013	The Netherlands	Tertiary	ICU patients: (38)	*Aspergillus fumigatus* isolates from ICU patients: (38)	15 IA cases/1000 admissions to ICU

N, number; UK, United Kingdom; NS, not stated; ICU, intensive care unit; CAPA, COVID-associated pulmonary aspergillosis; HM, hematological malignancy; IA, invasive aspergillosis; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; USA, United States of America; CH, Community; and IPA, invasive pulmonary aspergillosis.

croscopy, and culture.[39] Salmanton-Garcia reported that the cumulative incidence of CAPA in patients admitted to ICU ranged between 1.0% and 39.1%.[6]

Global distribution of and trends in IA, 2016–2021

One study reported that CAPA is globally distributed.[6] Most cases were reported from Europe, but cases were also detected in South America, Australia, the Middle East, and Pakistan (Supplementary Table S4).[6] One study reported that the trends in systemic mycoses (including aspergillosis [37.7%]) were stable over the study time-period, 2016–2021 (Supplementary Table S5).[33]

Discussion

This systematic review evaluated the epidemiology, susceptibility, and outcomes of invasive fungal disease (IFD) due to *A. fumigatus*. Even with one of the most common fungi, the data are limited with only 32.7% of the included studies classified as high quality with a low risk of bias. Despite this, it is evident that *A. fumigatus* is a critically important fungus, associated with persistently medium to high antifungal resistance and mortality rates.

The data derived from the present systematic review were used along with the data from the systemic reviews of 18 other fungal pathogens (Supplementary Table S6) to develop the WHO fungal priority pathogen list.[69] This involved a level being assigned to each of the pre-selected criteria (i.e., mortality, inpatient care, complications and sequelae, antifungal susceptibility, risk factors, preventability, annual incidence, global distribution, and emergence) using the data generated from each of the systematic reviews.[69] For example, using the data from Table 2 of the present study, a medium level (30%–70%) was assigned to invasive *A. fumigatus* infection mortality rates.[69] Then a discrete choice experiment (DCE) was performed to determine the importance weight of each pre-specified criterion.[69–71] The allocated level for each criterion for each pathogen from the systematic reviews was then multiplied by the importance weight for each criterion from the DCE to create the research and development (R&D) rank.[69] Following this, a best–worst scaling survey was performed to determine the weight of each pathogen according to perceived public health importance.[69] Finally, the R&D rank and the public health rank were combined according to their relative weight to formulate the final FPPL.[69] The final FPPL, developed using the data from the systematic reviews (including the present one), will be used in the future to identify preventative strategies to reduce the burden of IFD.

Mortality rates varied widely dependent on type of mortality being measured (e.g., overall, attributable), time-point of measurement (e.g., 30-day, 6-week), and the patient population (e.g., patients with a hematological malignancy, post-transplant, in ICU) (Table 2). This makes it very difficult to compare rates across particular patient groups and regions (e.g., low-middle-income countries [LMICs] vs. high-income countries [HICs]) and importantly, to examine trends over-time. Most randomized controlled trials, particularly recently, have used 6- and 12-week all-cause mortality; thus, these metrics are recommended to be used to report mortality due to IA in all future studies[72,73] Two studies reported on attributable mortality.[6,67] It can be very difficult to determine the extent to which IA has contributed to any patient's death. However, it is an important metric as it is reflective of the burden of disease. A few definitions exist that variously include outcomes such as autopsy evidence of active IA, or if no autopsy has been performed, the patient had stable or progressive IA at the time of death or had a partial response to antifungal therapy but died as a result of an event involving any of the sites of the original proven or probable IA or died directly from antifungal drug toxicity.[67,74] Using these, a consensus definition should be developed and used in all future studies. This will allow for a determination of the burden of disease across regions, different patient groups, and over time. Importantly, it will also assist with determining the relative efficacy of different antifungal therapies.

Similar to other filamentous fungi, *A. fumigatus* is angioinvasive, which may result in complications such as erosion of pulmonary blood vessels causing hemoptysis or areas of necrotic tissue requiring surgery.[75] Other reasons for surgical interventions include inadequate penetration of tissues by antifungal therapy (e.g., eyes) and the prevention of dissemination (e.g., sinuses).[14] Such surgical interventions may result in impaired respiratory capacity, visual loss, and facial disfigurement, which can lead to stigmatization, loss of work, and poverty, particularly in LMICs.[76] IA may also cause delays in administering further courses of chemotherapy, limiting overall cancer survival.[77] This systematic review did not identify any studies examining IFD-attributable excess costs and length of stay. However, a 2011 study reported these as a median of AU$30 957 (95% CI: AU$2368–AU$59 546; $P = .034$) and a median of 8 days (95% CI: 1.8–14 days; $P = .012$).[78] While other factors may contribute to the excess costs and increased length of hospital stay (e.g., underlying disease), it is evident that IA has a significant impact. Thus, it is clear that future cohort studies should systematically collect data on complications/sequelae, excess costs, and increased hospital lengths of stay. The importance of this is to give an accurate assessment of the global burden of IA and its public health importance. This will then allow for the development of novel and effective interventions and optimization of currently available preventative strategies.

The issue of *A. fumigatus* antifungal resistance has gained prominence over the last 20 years. The first large-scale systematic study was performed by van der Linden et al. in 2015; examining rates of azole antifungal resistance in centers, globally.[79] The overall prevalence was 3.2%; however, in some centers, rates of up to 26.1% were reported.[79] This systematic review has demonstrated ongoing variability in resistance rates (9.6%–100%) for itraconazole, voriconazole, and posaconazole (Table 4).[31,45,53,59] The critical importance of azole antifungal resistance is the increased mortality rates it confers (Table 2).[28] Concerningly, azole resistance rates have increased over time, even within the time-frame of the systematic review (from 7.6% [95% CI: 5.9%–9.8%] in 2013 to 14.7% [95% CI: 12.3%–17.4%] in 2018.[53] Cross-resistance is common even with the recently introduced isavuconazole (all isolates that were voriconazole-resistant were also isavuconazole-resistant).[53]

There are two main ways by which azole antifungal resistance arises. One is related to long-term treatment or prophylaxis with an azole antifungal agent, which can result in single point mutations (G54, G138, P216, M220, and G448) in the 14-α-lanosterol demethylase gene (*Cyp*51A).[80] The other route is from the environment. Azole fungicides

are commonly used in agriculture, and selective pressure can result in changes to the promoter region of *Cyp*51A followed by (or not) a point mutation in the gene (TR_{34}/L98H, TR46/Y121F/T289A, and TR53).[81,82] Other less common non-*Cyp*51A mutations have been identified: *Cdr*1B, *Hmg*1, and *Hap*E (Supplementary Table S3).[83–85]

The yield of *Aspergillus* culture is low. In addition, susceptibility testing takes several days. As survival is dependent on appropriate antifungal therapy, faster methods of detecting azole resistance are required. Several in-house molecular-based assays have been developed to detect azole resistance directly from clinical specimens.[86–88] Denning et al. reported high rates of TR_{34}/L98H mutations (n = 27/29 [L98H, of which 16 had also had a TR_{34} mutation]).[87] Zhao et al.[88] added a new molecular beacon (G448) to the nested PCR of Denning et al.[87] Of the 94 bronchoalveolar lavage (BAL) samples, 71 were pan-*Aspergillus* positive, and of these, 61 (86%) amplified the *Cyp51A* gene. Four samples that were *Cyp51A* negative were culture positive for *A. flavus*. The high rates of TR_{34}/L98H mutations seen by Denning et al. were not detected by Zhao et al.[87,88] This is likely due to differences between the studies in design, patient population, and type of *A. fumigatus* infection. Commercial assays offer the advantage of standardization, use in multicenter studies, and comparison across different studies. Two commercial assays are available for the detection of *Aspergillus* azole resistance, namely, AsperGenius (PathNostics, Maastricht, the Netherlands) and MycoGenie (Ademtech, Pessac, France). The AsperGenius has been examined in BAL, serum, and plasma samples, and the MycoGenie has been examined in respiratory samples. In summary, these studies have shown that the commercially available assays are more sensitive than culture, have similar utility as VIPcheck, can differentiate between wild type (WT) and resistant *A. fumigatus* even in culture-negative BAL samples, can detect mixed WT and resistant *A. fumigatus* infection, and the detection of resistance is associated with treatment failure.[89–96] The yield from BAL is greater than from serum (70%–100% vs. 33%–57%),[89,90,95,97] making BAL the optimal sample. Several sequence-based methods exist and have the advantage of being able to detect other *Cyp51A* mutations.[98–101] Currently, most such assays can be accessed in specialized or reference laboratories if azole-resistant *A. fumigatus* infection is suspected.

Given the serious consequences of increasing azole antifungal resistance in *A. fumigatus* a number of interventions have been recommended including adopting a One Health approach to reduce the use of azole antifungal pesticides in agriculture, active and comprehensive antifungal stewardship including the systematic use of therapeutic drug monitoring, the further development of rapid tests to detect azole resistance early,[31] the development and use of antifungal treatment algorithms, ongoing epidemiological surveillance of *A. fumigatus* isolates to determine rates and trends in resistance overtime, and further research into the mechanisms of azole antifungal resistance (Supplementary Table S3). Furthermore, molecular methods need to be made available in regional laboratories and LMICs.

The risk factors identified in this systematic review were those that have been traditionally identified and included patients with hematological malignancy or solid-organ malignancy, granulocytopenia/neutropenia, SOT, and chronic lung disease (Table 6). In recent years, several new targeted therapies for hematological malignancies have been developed for use in clinical practice, and they have subsequently been identified as new risk factors for IA. For example, Bruton's kinase (BTK) inhibitors, which are used in the treatment of chronic lymphocytic leukemia, Waldenström's macroglobulinemia, mantle-cell lymphoma, and marginal cell lymphoma, alone or in combination. After registration, several studies reported high rates of IA occurring in patients on ibrutinib.[102,103] A disproportionate number of these IA cases were localized to the brain (40%), and most occurred in the first 6 months post-commencement of ibrutinib (85%).[103] Associated mortality rates were very high (52.9%).[103] Other factors such as prior chemotherapy, neutropenia, and corticosteroid therapy may have contributed to the risk of IA in the setting of BTK inhibitor use. However, a pharyngeal aspiration experiment in 26 BTK knock-out and 20 WT mice showed that BTK inhibitors had an independent effect with 27% of the BTK knock-out and none of the WT mice dying after *A. fumigatus* infection.[104] This highlights the critical need for careful and ongoing clinical surveillance for IA cases when new immunomodulating treatments are being examined in clinical trials and introduced into clinical practice. This is so we can develop effective preventative strategies and avoid unnecessary mortality.

We identified one study that reported on the epidemiology and outcomes of CAPA.[6] Many of the risk factors were non-traditional and included ICU admission and chronic diseases such as cardiovascular disease, renal failure, obesity, liver disease, and pulmonary diseases.[6] The non-traditional risk factors may have delayed the diagnosis contributing to the apparent higher mortality rates seen in CAPA cases (47.8% vs. 31%–36%) (Table 2).[6,18,27,28] Other risk factors that have been identified include corticosteroid and immunomodulatory therapies, leukopenia, and malignancy.[105,106] Moreover, cases were reported globally, indicating the extent of the threat.[6] The European Confederation of Medical Mycology in collaboration with the International Society for Human and Animal Mycology developed criteria for diagnosis that will help with determining the correct prevalence and burden of CAPA and allow for comparison of mortality rates between regions and over time.[107] Antifungal prophylaxis has been studied in high-risk COVID-19 patients. A decrease in the incidence of CAPA without a reduction in overall mortality has been detected in two studies to date.[108,109] The results of a study examining isavuconazole are awaited. First-line treatment is with voriconazole or isavuconazole, with liposomal amphotericin B as an alternative in azole-resistant cases.[107] Further research is required, including the development of novel diagnostic tests and new algorithms for prophylaxis, diagnosis, and treatment of CAPA.

This systematic review has several limitations. The inclusion/exclusion criteria, including the timeframe of 5 years, may have resulted in the failure to include important studies and may have affected the findings of this systematic review. The lack of inclusion of conference abstracts and studies that were not in English may also have biased the findings, including the determination of the global resistance patterns, morbidity, and the true burden of disease. This study confined itself to acute invasive disease; thus, the epidemiology, burden, and outcomes of other *A. fumigatus* infections such as chronic cavitary pulmonary aspergillosis remain to be delineated.

Aspergillus fumigatus poses an emerging threat to human health and is associated with persistently medium to high

antifungal resistance and mortality rates. However, several knowledge gaps exist, particularly related to the complications and sequelae of IA and its excess costs and hospital lengths of stay. Carefully designed epidemiological studies using internationally accepted definitions and collecting detailed laboratory findings linked with clinical data are required to generate more accurate results on the morbidity outcomes, global distribution of infection, annual incidence, trends in mortality, and resistance patterns.

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Supplementary material

Supplementary material is available at *Medical Mycology* online.

Declaration of interest

Dr. David Denning and his family hold Founder shares in F2G Ltd, a University of Manchester spin-out antifungal discovery company. All the other authors have no conflicts of interest to declare.

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