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Fungal infections in patients with inflammatory bowel disease: A systematic review

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Summary

Background—Despite reports of fungal infections in patients with inflammatory bowel disease (IBD), their clinical and microbiological characteristics remain unknown.

Objectives—The aim of this systematic review was to examine all available evidence regarding fungal infections in patients with IBD.

Methods—Systematic search of PubMed (through 27 May 2017) for studies providing data on clinical, microbiological, treatment and outcome data of fungal infections in patients with IBD. The primary study outcome was to record the most common fungal species in patients with IBD. Secondary outcomes were classified into 3 categories: (i) characteristics of fungal infections; (ii) data on IBD and (iii) treatment and outcomes of fungal infections in patients with IBD.

Results—Fourteen studies with data on 1524 patients were included in final analysis. The most common fungal infections in patients with IBD were caused by *Candida* species (903 infections); the most commonly reported site of *Candida* infection was the gastrointestinal tract. Available evidence shows that most fungal infections occur within 12 months of IBD treatment and within 6 months when anti-TNFα agents are used.

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CONFLICT OF INTERESTS

All authors declare no conflict of interest.

ETHICAL APPROVAL

Not required.

Conclusions—This systematic review thoroughly describes fungal infections in patients with IBD and provides important information for the early detection and management of these infections.

Keywords

Crohn's; fungal infection; inflammatory bowel disease; opportunistic; systematic review; ulcerative colitis

1 | INTRODUCTION

Patients with inflammatory bowel disease (IBD) are at increased risk of infectious complications caused by bacteria, viruses, fungi and parasites. These pathogens may be common or opportunistic, ie microorganisms with limited pathogenic capacity under ordinary circumstances, but are able to cause serious disease under specific circumstances.^{1–3} Various factors have been associated with an increased risk of infection in these patients, including immunosuppressive and immunomodulatory therapy, severity of disease activity, comorbidity, narcotic analgesic treatment, surgery, malnutrition, leucopenia and older age.^{2–6} In particular, the evolution of treatment of IBD, that has introduced the use of anti-tumour necrosis factor α (anti-TNF α) agents, has led to an increased risk of infections in IBD.^{3,6}

TNF- α inhibitors inhibit TNF- α , a central mediator in immunity with important roles in inflammatory cell migration and maturation, granuloma formation and production of inflammatory cytokines.^{7,8} TNF- α inhibition increases susceptibility to invasive fungal infection by defects in cellular immune response due to reduced interferon- γ production, decreased expression of pattern recognition receptors like Toll-like receptors and leucocyte apoptosis.^{9–12} Even though their mechanism of immunosuppression greatly varies, it involves alteration in intracellular signalling, inhibition of cytokine production and reduced leucocyte adhesion and migration.^{13–15} Lastly, glucocorticoids also increase the risk for fungal disease, through reduction in production of pro-inflammatory cytokines, neutrophil adhesion and chemotaxis, macrophage activation and other mechanisms.^{16,17}

Fungal infections are a recognised cause of morbidity and poor outcomes in certain populations, such as in patients with haematologic and solid organ malignancy, and critically ill patients.^{18,19} Despite reports of fungal infections in patients with IBD, their clinical and microbiological characteristics have not been extensively described, and their significance in clinical practice and patient outcomes remain unknown. For this reason, the aim of this systematic review was to examine all available evidence in the literature regarding fungal infections in patients with IBD, focusing on the most common fungal causes of infection in IBD and their characteristics,

2 | METHODS

2.1 | Data search

This review has adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²⁰ Eligible studies were identified through search of Pubmed

MEDLINE from inception with the following combination of text-words: (Inflammatory Bowel Disease*[tw] OR Crohn*[tw] OR Ulcerative Colitis[tw] OR colitis[tw] OR ileocolitis[tw] OR IBD[tw]) AND (fung*[tw] OR opportunistic[tw] OR infect*[tw]). Day of last search was 27th May 2017.

2.2 | Study selection

Studies that met the following criteria were included in analysis: (i) published in English; (ii) reported clinical data, laboratory data, infection treatment and/or outcomes and (iii) included patients with IBD who were diagnosed with a fungal infection. Studies with any of the following were excluded from analysis: case reports and case series with fewer than 4 patients (most of them were individual case reports); cases of fungal infections of the skin; experimental studies in animals; secondary research papers (eg reviews); editorials, perspectives and papers not reporting results of primary research; papers irrelevant to fungal infections in patients with IBD; papers not in English. Two investigators (PI, GS) independently reviewed the titles and abstracts of the citations for potentially relevant articles using Abstrackr²¹; the full-text publications of potentially relevant articles were retrieved and rescreened by the same 2 investigators. Disagreements were resolved by consensus with a third investigator (CT). Reference lists of included studies were searched for relevant articles.

2.3 | Outcomes of interest

The primary study outcome was to record the most common fungal species in patients with IBD. Secondary outcomes were classified into 3 categories: (i) characteristics of fungal infections; (ii) data on IBD and (iii) treatment and outcomes of fungal infections in patients with IBD.

2.4 | Data extraction and definitions

Data from each eligible study were independently extracted by 2 investigators (PI, GS). Extracted data included study type, year of publication and country; patient demographics (age, gender); IBD-related data (years of disease prior to infection, treatment of IBD, duration of treatment); infection-related data and microbiology (criteria or mode of diagnosis of fungal infection, predisposing factors for fungal infection, infection site, presence of complications, isolated fungal strains) and treatment (administered for the fungal infection) and outcomes (ie death). When applicable, invasive fungal infections were defined according to the revised 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 definitions.²² Recorded complications were any clinical deterioration or organ dysfunction that were considered by the authors to be related to the fungal infection. Relation of death to the index infection was reported according to the study authors. The quality of the evidence of the outcomes of included studies was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE).²³

3 | RESULTS

3.1 | Literature search

For this systematic review, we screened 15 184 non-duplicate citations from PubMed. After review of the titles and abstracts, 358 articles were retrieved for full-text review. We excluded 344 studies from our review: in 122 studies the microbiological cause of infection was not specified, 98 studies involved fewer than 4 cases, 58 studies had no fungal infections, 21 studies had no infections, 19 studies did not have primary research, 17 studies had no separate data on fungal infections, 6 studies did not have IBD patients, 2 studies did not involve humans and 1 study was on skin infections. No additional studies were found through hand-screening of the references of included studies. Finally, 14 studies^{4,5,24–35} met our inclusion criteria. Additional information was kindly provided by the corresponding authors of 3 studies.^{24,29,34} The review process is presented graphically in Figure 1.

3.2 | Study characteristics

The 14 included studies involved 1524 patients in total. Table 1 summarises the characteristics of included studies. Nine studies were conducted in North America,^{4,5,24–28,30,33} 3 studies were performed in Asia^{29,31,32} and 2 studies were conducted in Europe.^{34,35} Eight studies involved both adult and paediatric patients,^{5,24,25,27,30–32,35} 4 studies involved only adults^{4,28,29,33} and 2 studies involved exclusively paediatric patients.^{26,34} Age of patients ranged from 6 to 69.5 years. The majority of included studies were observational studies and case series; as a result the overall quality of the evidence that contributed to our systematic review was rated as low to very low.²³

3.3 | Microbiology and characteristics of fungal infections

Clinical characteristics of included patients with IBD and fungal infections are presented in Table 2. All studies provided data on the microbiology of infections. Most fungal infections were caused by *Candida* species (903 infections, of which *C. albicans* were reported in 41, and *C. tropicalis* and *C. glabrata* in 1 case each, whereas the remaining were not reported),^{4,5,27–35} followed by *Histoplasma capsulatum* (140 infections),^{5,24,26,28,30,33} *Pneumocystis jirovecii* (19 infections),^{4,25,33} and *Cryptococcus neoformans* (1 infection).⁵ In 462 infections,^{28,30} fungal species were not reported. Table 3 classifies infection site per pathogen. According to the EORTC/MSG definitions which were applicable in 3 studies,^{5,24,26} 34 cases were classified as proven mycosis and 4 cases were classified as probable; in the remaining cases, either clinical and/or mycological criteria were not applicable, or information was insufficient (Table 4).

Risk factor analysis for opportunistic or fungal infections was performed in 8 studies,^{4,5,28,29,32–35} whereas 6 studies^{5,24,26,28,30,33} involving 1454 patients reported risk factors or predisposing conditions for fungal infections in IBD. The predominant condition associated with fungal infection in IBD was use of anti-TNF α agents, which was reported in all studies.^{5,24,26,28,30,33} In detail, predisposing conditions or risk factors included: use of anti-TNF α with or without additional immunomodulators or corticosteroids in 760 cases (including 197 cases of *Candida* infection and 113 cases of Histoplasmosis)²⁸; use of anti-TNF α in 641 cases of *Candida* infection and 13 cases of histoplasmosis³³; use of corticosteroids in 26

cases of *Candida* infection⁵; use of 6-mercaptopurine or azathioprine in addition to anti-TNF α agents in 5 cases of histoplasmosis²⁶; use of prednisone, methotrexate and/or azathioprine in addition to anti-TNF α agents in 4 cases of histoplasmosis²⁴; use of infliximab in 3 cases of histoplasmosis⁵; presence of central vascular line in 2 cases of candidaemia.³⁰ In addition, one study focused on patients with IBD and postoperative *Candida* infection³⁴ and 2 studies included IBD patients with spontaneous intra-abdominal *Candida* abscess.^{31,32}

Complications were present in 8 of 22 infections where data were provided.^{4,24,26,27,34} These included (more than one complications occurred in some patients): need for intensive care support (4 infections),²⁴ sepsis (3 infections),^{4,34} disseminated intravascular coagulation (2 infections),²⁴ surgical wound infection (2 infections)³⁴ and abscess formation (1 infection).³⁴

3.4 | Data on IBD

Sixty-eight patients suffered from Crohn's disease and 5 patients suffered from ulcerative colitis; in 4 studies (1451 patients),^{5,28,29,33} the type of IBD was not defined. Duration of disease prior to infection, reported in 2 studies,^{26,34} was 6 months to 10 years (average, 33 months). In patients with available data, treatment for IBD included anti-TNF α agents in 837/1491 patients (infliximab in 52 patients, adalimumab in 5 patients, not defined in 780 patients),^{4,5,24–28,30,33,35} systematic corticosteroids (243/793 patients)^{4,5,24,26,28,35} and disease-modifying anti-rheumatic drugs (DMARDs, 296/793 patients).^{4,5,24,26,28,35} Based on data from 6 studies,^{4,24–26,29,30} fungal infections occurred within 5 days–12 months of initiation of treatment for IBD; in 4 of these studies where infliximab was administered, fungal infections occurred within 5–180 days.^{4,24–26}

3.5 | Treatment and outcomes

Data on treatment of fungal infections were available in 6 studies (24 patients).^{24,26,29,29,32,34} Antifungal treatment included amphotericin B (8 patients)^{24,26,34} and triazoles (8 patients),^{26,34} whereas in one study,²⁹ no treatment was administered in 3 patients. Surgical intervention (either surgery or abscess drainage) was reported in 10 infections.^{31,32,34} Death related to the infection, according to the study authors, was reported in 104 out of 816 patients with available information on mortality.^{4,5,24,26–28,34,35} Of note, nearly all recorded deaths (103 patients) were recorded in one study.²⁸

4 | DISCUSSION

The present systematic review provides important information on fungal infections in patients with IBD. Our findings show that *Candida* species are the predominant pathogens in fungal infections in patients with IBD, the most frequent sites of infection are the respiratory and gastrointestinal tract, and fungal infections occur early during treatment of IBD (especially with anti-TNF α agents). Despite study heterogeneity, our observations offer useful information for the management of patients with IBD, who are often characterised by comorbidity and considerable disability.^{1,36}

Certain observations are worth noting on the microbiology of fungal infections. Although *Candida* was the predominant pathogen and candidaemia is considered the most frequent form of *Candida* infection,¹⁶ bloodstream infections were uncommon compared to other infection sites. Indeed, fungal infections most commonly affected the respiratory and gastrointestinal tract, whereas bloodstream infections represented fewer than 10% of infections in studies with available data. The fact that IBD lead to gastrointestinal mucosal injury, thus facilitating pathogen penetration, lends support to the higher frequency of gastrointestinal tract infections in these patients. It should be stated though, that in one study with a high number of *Candida* infections, the sites of *Candida* infections were not specified.³³ *Histoplasma capsulatum* was the second most common fungus and was isolated exclusively in studies performed in the USA, where histoplasmosis is endemic. Therefore, local epidemiology remains an important consideration during management of infections in patients with IBD. Management of these infections in IBD patients is not different from other populations, whereas antifungal prophylaxis is currently recommended only for *P. jirovecii* in patients receiving certain combinations that include immunomodulators.^{3,37}

A worthwhile remark is that no cases of invasive mould disease were included in this study. One reason is the fact that we excluded studies with few reported cases, consequently excluding numerous case reports. Another reasonable explanation is that the major risk factors for development of invasive aspergillosis are neutropenia and prolonged corticosteroid treatment, which are not the typical features of immunosuppression used in patients with IBD.³⁸ This is also shown in our study, where the majority of invasive fungal infections occurred within a short period of time after initiation of immunosuppression. Another explanation could be associated with the pathophysiology of invasive fungal disease by *Candida* and moulds. *Candida* is thought to be able to invade the damaged epithelial barrier of the gut and cause invasive disease, which is quite reasonable in the case of IBD, especially with concurrent immunosuppression.¹⁶ On the other hand, invasive mould disease requires penetration of the alveolar epithelium, with no clear evidence suggesting a defective alveolar epithelium in patients with IBD.³⁸

Currently available evidence does not allow for safe conclusions on infection severity and mortality. Although we observed considerable mortality rates (>10%), the majority of reported deaths were from one study,²⁸ whereas exclusion of this study from analysis leaves a much lower reported death rate of 1 out of 56 patients with available outcome data. In addition, the burden of disease caused by fungal infections is difficult to define, as data on the presence or not of complications was available in a total of 22 patients from 5 studies. However, despite current lack of credible data on patient outcomes, it is known that invasive fungal infections carry significant morbidity and mortality and thus, early presumptive antifungal treatment can be of benefit in patients treated for IBD who develop a systematic infection.^{8,16}

Fungal infections occurred within 12 months of treatment for IBD, indicating that immune-modifying treatment has an important association with these infections in IBD. In addition, the fact that most of these studies reported treatment with infliximab within 6 months of infection onset,^{4,24–26} raises the issue of early suspicion of fungal infection in patients with recent initiation of anti-TNFα agents. In line with our findings, a recent meta-analysis of

randomised controlled trials showed a much higher relative risk for opportunistic infections in trials with short therapy duration (<8 weeks) compared to trials with longer therapy duration (>8 weeks).³⁹ Furthermore, a previous review demonstrated that most fungal infections occurred a median of 55 days (IQR, 15–140 days) after initiation of treatment with infliximab.⁸ Concern over the risk of infection with the increasing use of biological therapies in IBD has led to several recent meta-analyses on this subject, which demonstrated an increased risk of infections and opportunistic infections in patients treated with biological agents.^{6,40} Corroborating with the above, we further found that prior or current use of anti-TNFα agents was a universal finding in all studies that performed risk factor analysis or explored predisposing factors for fungal infections in patients in IBD.^{5,24,26,28,30,33} There are certain limitations in our systematic review that should be acknowledged. First, significant heterogeneity between studies, especially as regards to design and outcomes, precludes concrete assumptions in several aspects, such as individual predisposing factors per site of fungal infection, infection severity, treatment and outcomes. Second, despite the notable number of included patients, a large proportion was derived from 2 studies, but only few data from these studies could be used in our review. Future studies should provide a more detailed description of risk factors, clinical characteristics, pathogen distribution and treatment of fungal infections in IBD. In addition, it is necessary to report duration of IBD treatment prior to infection, as well as details of treatment for IBD prior to infection (including type of treatment), to elucidate the association between specific agents and fungal infections.

In conclusion, the present systematic review outlines the clinical and microbiological profile of fungal infections in patients with IBD, with significant clinical implications. Published evidence shows that fungal pathogens, mainly *Candida* species, should be suspected in infections that occur early during treatment for IBD, especially when TNFα inhibitors are administered.

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FIGURE 1.
PRISMA flow diagram

TABLE 1

Study characteristics

Study, year published, Country	Study description	Study age group	Number of patients (CD, UC, total)	Age range (y)	Gender male, n (%)
Lee et al, 2002, USA ^{24a}	Retrospective (Database surveillance)	Children & adults	4 CD 0 UC 4 total	11–42 (median 28.5)	4 (100%)
Kaur et al, 2007, USA ²⁵	Retrospective (Database surveillance)	Children & adults	14 CD 2 UC 16 total	NR	NR
Toruner et al, 2008, Ireland ^{5a}	Retrospective case-control	Children & adults	CD ND UC ND 29 total	NR	NR
Doison et al, 2011, USA ²⁶	Retrospective case series	Children	5 CD 0 UC 5 total	13–21 (median 14)	2 (40%)
Panaccione et al, 2011, USA ²⁷	Prospective interventional single-arm trial	Adults	4 CD 0 UC 4 total	NR	NR
Lichtenstein et al, 2012, USA ⁴	Prospective observational registry	Adults	5 CD 0 UC 5 total	26.4–69.5 (mean 46.2)	NR
Deepak et al, 2013, USA ²⁸	Retrospective (Database surveillance)	Adults	CD ND UC ND total 760	NR	NR
Naganuma et al, 2013, Japan ²⁹	Prospective case-control	Adults	CD ND UC ND 6 total	NR	NR
Seminario et al, 2013, USA ³⁰	Retrospective cohort	Children & adults	21 CD 0 UC 21 total	NR	NR
Park et al, 2014, South Korea ³¹	Retrospective cohort	Children & adults	4 CD 0 UC 4 total	NR	NR
Li et al, 2015, China ³²	Retrospective cohort	Children & adults	5 CD 0 UC 5 total	NR	NR
McAuliffe et al, 2015, USA ³³	Retrospective cohort	Adults	CD ND UC ND 656 total	NR	NR
Penninck et al, 2016, France ^{34a}	Retrospective cohort	Children	3 CD 1 UC 4 total	6–17 (median 13)	3 (75%)

Study, year published, Country	Study description	Study age group	Number of patients (CD, UC, total)	Age range (y)	Gender male, n (%)
Vögelin et al, 2016, Switzerland ^{35a}	Retrospective cohort	Children & adults	3 CD 2 UC 5 total	34–56 (mean 43.4)	1 (20%)

CD, Crohn’s disease; ND, not defined; NR, Not reported; UC, Ulcerative colitis.

^aMore than 1 site of infection reported in some patients.

TABLE 2

Clinical characteristics and outcomes

Study, year published	Total number of patients	Type of immunosuppressive treatment, n (%)	Criteria used for infection diagnosis	Site of fungal infections, n (%)	Microbiology of infections	Type of antifungal treatment, n (%)	Infection outcomes, n (%)
Lee et al, 2002 ²⁴	4	Corticosteroids or DMARDs 4 (100%) Anti-TNFa (infliximab) 4 (100%)	Tissue biopsy	Lower respiratory tract 4 (100%) Secondary bloodstream 3 (75%) Secondary upper respiratory 1 (sinusitis) (25%) Secondary liver 1 (25%)	<i>Histoplasma</i> 4 (100%)	Amphotericin B 4 (100%) formulation NR Itraconazole (maintenance) 1 (25%)	Clinical cure 4 (100%) ^a Mortality 0 (0%)
Kaur et al, 2007 ²⁵	16	Corticosteroids NR DMARDs NR Anti-TNFa (infliximab) 16 (100%)	NR	Lower respiratory tract 16 (100%)	<i>Pneumocystis jirovecii</i> 16 (100%)	NR	NR
Toruner et al, 2008 ⁵	29 ^b	Corticosteroids 11/14 (78.6%) ^b DMARDs 1/14 (7.1%) ^b Anti-TNFa (infliximab) 2/14 (14.3%) ^b	Causative microorganism was identified (either by microbiologic or pathologic diagnosis), or there was a pathognomonic clinical picture	Oesophagus & blood & perianal 26 (89.7%) Lung 3 (10.3%)	<i>Candida</i> species 26 (89.7%) <i>Histoplasma capsulatum</i> 2 (6.9%) <i>Cryptococcus neoformans</i> 1 (3.4%)	NR	Mortality 0 (0%)
Dotson et al, 2011 ²⁶	5	DMARDs 5 (100%) (6-MP 4 80% MTX 1 [20%]) Anti-TNFa 5 (100%) (infliximab 4, adalimumab 1)	Complement-fixation assay or culture from bronchoscopy specimen or positive <i>Histoplasma</i> antigen test (urine, blood)	Lower respiratory tract 5 (100%)	<i>Histoplasma capsulatum</i> 5 (100%)	Itraconazole 5 (100%) Amphotericin B (induction) formulation NR 2 (40%)	Clinical cure 5 (100%) Mortality 0 (0%)
Panaccione et al, 2011 ²⁷	4	Corticosteroids NR DMARDs NR Anti-TNFa (adalimumab) 4 (100%)	NR	Oral 4 (100%)	<i>Candida</i> species 4 (100%)	NR	Mortality 0 (0%)
Lichtenstein et al, 2012 ⁴	5	Corticosteroids 2 (40%) DMARDs 2 (40%) Anti-TNFa (infliximab) 4 (80%)	NR	Bloodstream 4 (80%) Lower respiratory tract 1 (20%)	<i>Candida</i> 2 (40%)-unspecified <i>Candida glabrata</i> 1 (20%) <i>Candida tropicalis</i> 1 (20%) <i>Pneumocystis jirovecii</i> 1 (20%)	NR	Mortality 1 (20%)
Deepak et al, 2013 ²⁸	760	Corticosteroids 223 (29.3%) DMARDs 289 (38%)	NR	Respiratory tract 164 (21.6%)	<i>Candida</i> species 197 (25.9%) <i>Histoplasma capsulatum</i> 113 (14.9%)	NR	Mortality 103 (13.6%)

Study, year published	Total number of patients	Type of immunosuppressive treatment, n (%)	Criteria used for infection diagnosis	Site of fungal infections, n (%)	Microbiology of infections	Type of antifungal treatment, n (%)	Infection outcomes, n (%)
Naganuma et al, 2013 ²⁹	6	NR	NR	Gastrointestinal tract 13 (14.9%) Other ND 483 (63.5%)	Other ND 450 (59.2%)	No antifungals 3 (50%)	Clinical cure 3 (50%) ^a
Seminario et al, 2013 ³⁰	21	Corticosteroids NR DMARDs NR Anti-TNFa 21 (100%)	Candidiasis diagnosed with culture. Other fungal infections NR	Oesophagus 4 (19%) Bloodstream 2 (9.5%) Wound ulcer 2 (9.5%) Lower respiratory tract 2 (9.5%) Other ND 10 (47.6%)	<i>Candida</i> (unspecified) 8 (38.1%) <i>Histoplasma capsulatum</i> 3 (14.3%) Other ND 10 (47.6%)	NR	NR
Park et al, 2014 ³¹	4	NR	Microorganism isolated from culture of abscess pus	Intra-abdominal abscess 4 (100%)	<i>Candida</i> species 4 (100%)	Drainage in 4 (100%) Antifungals NR	NR
Li et al, 2015 ³²	5	NR	Confirmation of abscess with imaging and positive culture of drained pus	Intra-abdominal abscesses 5 (100%)	<i>Candida albicans</i> 5 (100%)	Surgery or drainage in 5 (100%) Antifungals NR	NR
McAuliffe et al, 2015 ³³	656	Corticosteroids NR DMARDs NR Anti-TNFa 60 (9.1%)	NR	Respiratory tract 15 Other ND 641	<i>Candida</i> 641 (97.7%) ^c <i>Histoplasma capsulatum</i> 13 (2%) <i>Pneumocystis jirovecii</i> 2 (0.3%)	NR	NR
Penninck et al, 2016 ³⁴	4	NR	NR	Bloodstream 2 (50%) Digestive and surgical site infection 1 (25%) Digestive tract and anal 1 (25%)	<i>Candida albicans</i> 4 (100%)	Liposomal Amphotericin B 2 (50%) Fluconazole 2 (50%) Drainage in 1 (25%)	Clinical cure 4 (100%) ^a Mortality 0 (0%)
Vögelin et al, 2016 ³⁵	5	Corticosteroids NR DMARDs 5 (100%) (AZA 4/5, MTX 2/5, tacrolimus 2/5, 6-MP 1/5) Anti-TNFa 0 1 (20%)	Oral, perianal or vaginal candidiasis was diagnosed by characteristic clinical appearance and response to antifungal therapy. In oesophageal candidiasis, endoscopic and histological confirmation	Oesophagus 2 (40%) Vaginal & perianal 1 (20%) Oral 1 (20%) Oesophagus & oral 1 (20%)	<i>Candida</i> species 6 ^d (100%)	NR	Clinical cure 5 (100%) ^a Mortality 0 (0%)

6-MP, 6-mercaptopurine; AZA, azathioprine DMARDs, disease-modifying anti-rheumatic agents; MTX, methotrexate; ND, not defined; NR, not reported; TNF, tumour necrosis factor.

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- ^aDefined as clinical resolution of the infection.
- ^bData available only for 14/29 patients in this study.
- ^cSites of *Candida* infection not specified.
- ^dTwo *Candida* species were isolated in one infection.

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TABLE 3

Classification of infections per pathogen (n = 1063)

	Gastrointestinal tract	Respiratory tract	Bloodstream	Wound infection	Site not reported
<i>Candida</i> spp.	26 oesophagus, blood, perianal ^{a5} 12 oesophagus ^{27,28,33} 9 intra-abdominal abscess ^{29,30} 4 oral ²⁵ 1 both oesophagus & oral ³³ 1 perianal-vaginal ³³ 1 digestive-anal ³²		6 candidaemia or sepsis ^{b1,28,32}	2 wound ulceration (not otherwise specified) ²⁸ 1 digestive and surgical wound infection ³²	840 infections ^{4,26,31}
<i>Histoplasma capsulatum</i>		129 referred to as histoplasmosis ^{2,6,28,31} 11 lung ^{5,22,24}			
<i>Pneumocystis jirovecii</i>		19 lung ^{4,23,31}			
<i>Cryptococcus neoformans</i>		1 lung ⁵			

^aNo further description provided.^b2 cases were vascular line-associated.³

TABLE 4

Application of the revised European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group definitions

Study, year published	Total number of patients	Host factor	Clinical criteria	Mycological criteria	EORTC/MSG category	Comments
Lee et al, 2002 ²⁴	4	R	R	R	Proven endemic mycosis	
Kaur et al, 2007 ²⁵	16	R	NA	NA	NA	Pneumocystis pneumonia is not included in the criteria
Toruner et al, 2008 ⁵	29	R	R	R	Proven invasive fungal disease	
Dotson et al, 2011 ²⁶	5	R	R	R	4 probable/1 proven endemic mycoses	
Panaccione et al, 2011 ²⁷	4	R	NR	NR	NA	Oral candidiasis is not mentioned in the criteria
Lichtenstein et al, 2012 ⁴	5	R	NR	NR	NA	
Deepak et al, 2013 ²⁸	760	R	NR	NR	NA	
Naganuma et al, 2013 ²⁹	6	R	NA	NA	NA	Oesophageal candidiasis is not mentioned in the criteria
Seminario et al, 2013 ³⁰	21	R	NR	NR	NA	Candidiasis diagnosed with culture. Other fungi NR
Park et al, 2014 ³¹	4	R	NA	NA	NA	Abscesses are not mentioned in the criteria (microorganism was isolated from abscess drainage)
Li et al, 2015 ³²	5	R	NA	NA	NA	Abscesses are not mentioned in the criteria
McAuliffe et al, 2015 ³³	656	R	NR	NR	NA	
Penninck et al, 2016 ³⁴	4	R	NR	NR	NA	
Vögelin et al, 2016 ³⁵	5	R	NA	NA	NA	Gastrointestinal candidiasis is not mentioned in the criteria

NA, not applicable; NR, not reported; R, reported.