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Review Article

Invasive Fungal Infections in Patients with Chronic Lymphoproliferative Disorders in the Era of Target Drugs

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Abstract. This review summarizes the more recent evidence about epidemiology and risk factors for invasive fungal infections (IFI) in patients affected by Chronic Lymphocytic Leukemia (CLL), indolent Non Hodgkin Lymphoma (iNHL) and Multiple Myeloma (MM).
Despite advances in the prognosis and treatment of hematological malignancies in recent years, susceptibility to infection remains a significant challenge to patient care. A large amount of data regarding patients with acute leukemia has been published while little information is available on the incidence of IFI in chronic lymphoproliferative disorders (CLD).
New drugs are now available for treatment of lymphoproliferative disorders which may cause suppression of humoral immunity, cellular immunity, and deficiency of white blood cells, increasing the risk for infections which remain the leading cause of mortality in these patients.

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Introduction. Infections are the leading cause of death in patients with CLL and MM, and effective strategies for managing infections remain a crucial aspect of disease management.

Secondary immunodeficiency develops in patients with hematological malignancies as a result of disruption to the immune system from an early stage and even patients who do not require treatment for their malignancy have been shown to be at greater risk of serious infections than the general population.[1,2]

Data published about mycoses in CLD are scanty. Fungal infections in CLL patients range between 0.5 to 18%[3-14] according to treatment received and to selected populations. The majority of studies are retrospective, inclusion criteria heterogeneous and they often included also possible IFI.[9,15] Noteworthy, the incidence of IFI in CLL appears to increase over the years.

Prolonged neutropenia, age, prior IFI, lymphocytopenia or lymphocyte dysfunction, the stage and state of the underlying malignancy (relapsed or progressive disease), corticosteroid use and presence of Graft-Versus-Host Disease (as expected in transplanted patients), were factors more often associated to a higher risk of IFI in these patients.

Interestingly, CLLs with an unfavorable prognostic profile were more often affected by IFI. In particular CD38 expression, genetic analysis (p53, ATM or 12+) and IgvH mutation status represented biological risk factors for IFI.[4,14] Visentin et al. in 2017 demonstrated that at time of IFI, patients had lower levels of IG as compared with those subjects who experienced bacterial

infections or did not have any infections, even if the number of patients analyzed is small.

In the last years, new drugs for the treating CLL have been introduced in clinical practice (e.g., ibrutinib, idelalisib, venetoclax). Recent studies, all retrospective, suggest that patients with lymphoid malignancies receiving ibrutinib are at risk for a variety of serious infections, including IFI, even if they are often pretreated patients.[11,13,16,17] These data are not yet sufficient to give strong recommendations for prophylaxis, but as the indications for ibrutinib use continue to expand, this highlights the need for further studies to define those most likely to benefit from close clinical monitoring for infectious complications and from targeted prophylaxis strategies.

Pathogenesis of Opportunistic Infections in CLL. Patients with CLL are at increased risk for infections because of their compromised immune function. The pathogenesis of infections in CLL is multifactorial, and the major risk factors in these patients are immune defects related to the primary disease and the consequences of therapy.[1]

Disease-related defects include hypogammaglobulinemia, which occurs in virtually all patients with CLL and correlates with disease duration and stage.[18,19] Even with therapeutic response, there is little improvement in the underlying defect.

Another disease related defect is connected to the innate immunity. Quantitative and qualitative neutrophil and monocyte defects are found in CLL patients. Although the absolute number of neutrophils is normal or slightly decreased in untreated patients, defects in phagocytic and bactericidal activity, have been demonstrated.[18]

Decreased levels of components of complement (e.g., properdin) are documented in patients with CLL. Defects in complement activation and binding and reduced expression of complement receptors on CLL B cells have been also reported.[18]

Major infections are reported to occur at least once in >50% of CLL patients contributing to 30% - 50% of deaths.[20-22]

Most data about infections in CLL patients are reported from clinical trials or retrospective analyses at referral centers, not necessarily representative of the overall CLL population.[21]

There are limited data on infections in treatment-naive CLL patients who are at increased risk mainly for bacterial infections caused by common pathogens such as Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa.

Epidemiology of Fungal Infections in CLL. Limited information is available on the epidemiology of IFI in CLL.[3,5,9,10,12]

The overall incidence of IFI is reported from 1,3% to 7,8%. Nevertheless, the estimated mortality is extremely high (up to 80%).[5]

Invasive aspergillosis is the most frequent IFI observed. Risk factors are mainly related to disease status (highest risk in relapsed/refractory disease), a number of previous chemotherapy regimens and Ig levels.[12] Whereas bacterial infections predominate during neutropenia, invasive fungal infections start to develop as neutropenia persists.

Invasive mold infections, due primarily to aspergillus species, are the most frequent cause of serious, often life-threatening infections in patients with neutropenia that persists for more than two weeks.[23] Other risk factors include impaired cellular immunity, prolonged corticosteroid administration, allogeneic stem cell transplantation and advanced age.[6]

Treatment Related Infections. Therapy related immunosuppression has a further impact on immune function in CLL patients, and the infectious complications have evolved in relation to the specific agents.

Alkylators. Chlorambucil has been used for many years as standard therapy for CLL patients. As for treatment-naive patients, the majority of infections are bacterial of mucosal origin and when they occur this is related to neutropenia. Fungal and viral infections are infrequent.

Cyclophosphamide is rarely used as a single agent and is commonly part of combination therapy (see below).

Bendamustine. It is an alkylating agent able to induce a high number of remissions in CLL and more effective than chlorambucil when compared in clinical trials.[24]

Infections during bendamustine treatment may be related to neutropenia and are prevalently bacterial. In untreated patients, when

bendamustine was combined with rituximab, infections were the leading cause of non-hematological toxicity (12 grade 3; three grade 4, mainly febrile neutropenias and pneumonia not otherwise specified) with a total incidence of 7.7%.[25] In the setting of refractory/relapsed patients, no opportunistic infections were reported.[26]

Fludarabine. Purine analogs determine quantitative and qualitative T cell abnormalities giving rise to a wider spectrum of infections compared to reported with alkylating agents.

Fungal infections as *Nocardia, Candida, Aspergillus, Cryptococcus, Pneumocystis* have been reported.[21,27]

The addition of glucocoticoids increases the risk of the opportunistic infections and should be avoided.

Pneumocystis prophylaxis in patients receiving single fludarabine agent is suggested by some experts and guidelines, usually until CD4 count is >200 cells/microL (NCCN Guidelines Insights: Non-Hodgkin's Lymphomas, Version 3.2016.)

Other authors have suggested Pneumocystis Jiroveci Pneumonia (PJP) prophylaxis only when fludarabine is used in combination with other alkylating agents as cyclophosphamide or bendamustine.[21]

Also for patients treated with combinations of fludarabine and rituximab (FR), the PJP prophylaxis is recommended alongside with antivirals.

The fludarabine-cyclophosphamide-rituximab (FCR) combination has been used as salvage therapy for relapsed or refractory CLL patients with antiviral and anti PJP prophylaxis. In this setting major infections occurred in 16% of cases[28] while in naive treatment patients where 3%.[29] A small number of opportunistic infections occurred (PJP, Aspergillus, Candida glabrata).

Anti-CD20 monoclonal antibodies. Rituximab has been used as a single agent in CLL but is more commonly used as part of combination therapy (FR). With this combination, the rate of severe infections is reported up to 20%, mainly of viral origin.[30]

Rituximab has been associated with hepatitis B reactivation and multifocal leukoencephalopathy (PML).

Ofatumumab and Obinutuzumab have an infection profile similar to Rituximab.[28,1]

Most of the infections occurring with obinutuzumab in combination with chlorambucil were of bacterial origin, and opportunistic infections were uncommon.[31]

Alemtuzumab. Although nowadays seldom used for CLL treatment, this anti CD-52 antibody is associated with profound defects in cell-mediated immunity. Reductions in B, T and NK cells occur early in treatment and persist for up to 9 months after discontinuation of therapy.

Alemtuzumab has been associated with a wide range of infections, including bacterial, viral, fungal and protozoal, although CMV reactivation/disease is the most significant infectious complication particularly in previously treated patients.[32]

When used in combination regimens, anti PJP and anti-viral prophylaxis is suggested by experts[33] and guidelines (Prevention and Treatment of Cancer-Related Infections, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology.).

Idelalisib. Idelalisib is a reversible inhibitor of phosphatidylinositol 3-kinase (PI3K) which is a cytoplasmic tyrosine kinase involved in various signaling pathways, most importantly activating the AKT/mTOR pathway. The delta isoform is ubiquitously expressed in leukocytes.

Inhibition of PI3Kdelta induces disruption of interactions between malignant B cells and the microenvironment.

In a trial of idelalisib in combination with rituximab for relapsed CLL, pneumonia occurred in 6% of patients and PJP in 3% (grade 1 or 2 toxicity).[34]

In 2016, an increase in serious adverse events and fatalities was reported from different clinical trials of idelalisib used in combination with other agents. In particular, an increase in cases of PJP and CMV infections was observed.

The overall incidence of PJP was 2.5% in patients on idelalisib ± co-therapy vs 0.2% in patients receiving only anti-CD20 antibody alone or bendamustine and rituximab (relative risk = 12.5). A correlation between CD4 count (<200 cells/mcL) and the increased risk of PJP was not observed.[35]

The manufacturer of idelalisib suggested that PJP prophylaxis should be considered for patients receiving Idelalisib.

Currently, patients treated with idelalisib (with or without rituximab) are considered at high risk of PJP and prophylaxis is recommended at least through active treatment.[36] TMP/SMX is the drug of choice because of its activity against other pathogens like nocardia, toxoplasma, and listeria.

Ibrutinib. PJP and other fungal infections have been reported in small case series and case reports on ibrutinib treated patients.[37,38] In particular, invasive aspergillosis (IA) and cryptococcosis have been described.[39,40]

Recent combination study in patients with primary central nervous system lymphoma reported IA in 39% (7/18) of all patients.[41] Earlier single agent study reported aspergillosis in 5-11% of patients[42,43] suggesting that the combination therapy may account for the observed differences.

In a recently published retrospective survey, an alarming 40% of cerebral localizations of IA has been reported in patients, mainly with CLL, treated with ibrutinib.[17]

How ibrutinib may decrease antifungal immunity remains to be clarified. The molecular target of the drug, the Bruton tyrosine kinase (BTK), is present in normal lymphocytes and can be involved in the exertion of deleterious off-target effects also on the T cell-macrophage axis.

The rate of fungal infections raises concern over the role of BTK and Interleukin-2-inducible kinase (ITK) inhibition and their clinical relevance in antifungal immunity.

BTK is an indispensable component of the B-cell receptor signaling pathway through which it mediates B-cell growth, adhesion and survival.[44] BTK is also found in neutrophils, monocytes and macrophages where it mediates pathways involving innate and adaptive immunity.[44]

Interleukin-2-inducible kinase (ITK), found in T cells, has significant homology with BTK and is irreversibly inhibited by ibrutinib.[45] ITK functions downstream of the T-cell receptor playing a central role in inflammatory responses and T-cell maturation. In the absence of ITK, CD4+ T cells fail to differentiate into Th2 effector cells effectively and are unable to mount a protective response to pathogens.[45]

ITK inhibition by ibrutinib may contribute to the opportunistic infections seen with the use of this drug: a definitive answer to this question would require a carefully designed trial comparing ibrutinib to more specific inhibitors of BTK such as acalabrutinib.

Another relevant issue is related to the important pharmacokinetic interactions between ibrutinib and other drugs metabolized by CYP3A4 (e.g., 2nd generation triazoles like voriconazole and posaconazole). The ibrutinib dose should be reduced to 140 mg (a quarter of maximal prescribed dose) when coadministered with moderate CYP3A4 inhibitors so that exposures remain within observed ranges at therapeutic doses.[46] New triazoles (e.g., isavuconazole, ravuconazole) will be probably increasingly used in this setting for their more favourable toxicity profile and pharmacokinetic characteristics.

However, ibrutinib also allows for partial reconstitution of humoral immunity (in particular serum IgA levels), and the infection rate in patients with CLL is reported to decrease with time.[8]

Lenalidomide. Lenalidomide is an immunomodulatory agent used in monotherapy or in combination with anti CD20 monoclonals or steroids. There is no clear evidence of specific immune dysfunction capable of increasing the risk of opportunistic infections in patients treated with lenalidomide.

Anti PJP and antiviral prophylaxis is suggested only for patients receiving lenalidomide in combination with fludarabine and rituximab.

Venetoclax. Venetoclax is a B cell leukemia/lymphoma-2 (BCL-2) inhibitor used as a single agent or in combination with anti CD20 monoclonals for pretreated patients with CLL and unfavourable citogenetics (17p deletion). Most trials were conducted in patients with relapsed and refractory disease. In a recently published phase II trial, Grade 3 or 4 adverse events (AEs) were primarily hematologic. The infection rate was 81% for AEs of any grade. Forty patients (25%) had grade ≥ 3 infection (four cases were fatal: RSV, *Klebsiella* sepsis, septic shock, and pneumonia). Seven patients had opportunistic infections, with three grade 3 or 4 events (2 PJP and 1 herpes zoster).[47] Antiviral, antifungal and anti PJP prophylaxis is therefore suggested on a case-by-case basis in settings of prior opportunistic

infections or immune defects related to previous treatment.

Epidemiology of Fungal Infections in Indolent NHL (iNHL). All together 17% of IFI in haematological diseases occur in patients affected by NHL.[23]

In iNHL the incidence of IFI is reported from 0.5% to 4%.[3,5,7-11,23,48-53]

Most of the reports concern the epidemiology of IFI in all subtypes of lymphomas, and few data are available about the incidence of IFI in patients with indolent lymphomas that mainly include Follicular lymphomas (FL), mantle cell lymphomas (MCL) and Waldenstrom macroglobulinemia (WM). Moreover, most of them are retrospective and monocentric regarding a limited number of patients. In **Table 1** incidence of mold infection in NHL and iNHL.

The rate of IFI in aggressive lymphomas (aNHL) is higher (2.3-4.3%) compared to the incidence in iNHL (1.7-2%).[9,10] This is likely related to the more aggressive treatment delivered to these patients.[9,10]

According to recent recommendations,[4] lymphomas are allocated in the low risk category, whereas relapsed/refractory Diffuse Large B Cell Lymphomas (DLBCL) and patients undergoing autologous/allogeneic stem cell transplantation (HSCT) belong to the intermediate risk category.

Although transplanted patients are considered at increased risk of IFI, two different studies have shown that the incidence of IFI is comparable in NHL patients undergoing autologous transplantation (1.9%) or not (1.7%).[7,50]

The lung was most frequently involved (88.5%) while other sites of infection were paranasal sinuses, the central nervous system (CNS) and

Table 1. Incidence of mould infections and risk factors in NHL.

Authors and Notes	Moulds in NHL (%)	Moulds in iNHL (%)	Risk factors
Tisi 2017	2.3	2	neutropenia, steroid and transplant. For iNHL in particular relapse/refractory disease and salvage treatment
Teng 2015	4.3	1.7	
Nosari 2014	3.2		prognostic factors: neutropenia and age
SEIFEM 2004	0.9		
Takaoka 2014 NHL in salvage therapy	2.3		refractory disease, >2 lines of therapy, N<500/mmc
Sun 2015	1.26		
Kurosawa 2012	0.3		
Stanzani 2013 HSCT excluded	1.5		prolonged neutropenia, lymphopenia or impairment of the lymphocite compartment in HSCT, previous history of IMD and non remission disease.
Herbrecht 2012	0.8		advanced age, steroid and treatment with monoclonal antibody or purine analogs
Jantunen 2004 only autologous HSCT patients	1.9		
Dimopoulos 2017 WM in ibrutinib		3.2	
Wang 2015 MCL in ibrutinib		2.7	
Varughese 2018 Patients in ibrutinib	3		
Montagna 2012	1.4		
Pagano 2017			prolonged neutropenia, disease in advanced lines of therapy and previous IFI
Pagano 2011			steroid, treatment with monoclonal antibody or purine analogs. Steroid and disseminated IFI are prognostic factors for the outcome of infection
Gil L 2009 CLD in HSCT			previous treatment with Rituximab and purine analogs
Vazques 2017			neutropenia, advanced disease, treatment with anti-CD 52, steroid and hospital near areas under costruction.
Chamilos 2018 ibrutinib			steroid, exposure to spores and number of previous lines of therapy
Fleming 2014 iNHL			previous treatment with purine analogs

abdomen.[54]

Invasive aspergillosis is the most frequent IFI observed (90%), followed by Mucor and Fusarium infection.[5,51] The attributable mortality rate for mold infections seems to be lower in chronic lymphoproliferative disorders (CLD) (16%), compared to what reported in acute myeloid leukemia (AML) (27%).[3,55]

Compared to AML patients, who recover their immunologic competence as soon as disease remission is achieved, the immune system of patients with CLD remains blunted for a long period, probably due to treatments with purine analogs or monoclonal antibodies.[3,56]

The incidence of IFI in NHL is also related to age. An Italian study showed that in pediatric patients with NHL no one had developed mold infections.[52]

There is a rising trend of IFIs in patients with CLD: from the reported 1.6% in 2004[5] to the 4.3% in 2014.[3] This could be related to the introduction of new drugs potentially leading to a greater immune deficiency causing a modification on infectious epidemiology.[4]

Risk Factors for IFI in iNHL. Several studies highlighted the presence of risk factors for IFIs in patients with NHL. The most important are related to disease status (higher risk in relapse/refractory and advance stage disease) and type of treatment (higher risk for steroid administration, intensive chemotherapy with prolonged neutropenia, monoclonal antibody and purine analogs).[10,57-59]

These data were recently confirmed by a Delphi-like analysis in haematological patients published by Vazquez et al.[60] which showed that most experts agree that these are the most relevant risk factors.

Stanzani M et al. developed a score for IFI in patients with hematological malignancies and identified four main risk factors: prolonged neutropenia, lymphopenia or impairment of the lymphocyte compartment in allogenic HSCT patient, previous history of IFI and non remission disease. The score can discriminate patients who have a low or high probability of developing IFI within 90 days of hospitalization. A limitation of this study is related to the presence of some confounding factors such as the different use of antifungal prophylaxis and the underestimation of factors such as GVHD and steroid administration for which it would be necessary to make a special study on patients undergoing allogeneic transplantation.[7]

A similar score was proposed by Takaoka et al. for patients with lymphomas in rescue therapy and identified as main risk factors the refractory disease, more than two lines of therapy and neutropenia inducing treatments (**Table 2**). On this basis, high risk patients have an IFI incidence of 9% and low risk patients an incidence of 0.19%.[48]

In **Table 1**, the main risk factors for mold infection in NHL patients.

IFI Prevention in iNHL. Patients with iNHL are considered to be at low risk for IFI, and therefore there is no consensus for biomarkers monitoring (GM or BDG assays) or need for prophylaxis.[4] Nevertheless, their use at presentation is variable and depends largely on treating physician's opinion.[3]

These patients can move into the intermediate risk category for the following factors: relapse-refractory disease, use of high dose chemotherapy, steroid and therapy with T cell damaging agents, stem cell transplantation.[61]

Therefore prophylaxis is not indicated for iNHL who receive standard chemotherapy[57] and there is no indication also for patients undergoing autologous transplantation with the exception of

Table 2. Risk scores in iNHL.

Stanzani et al. 2013	**Takaoka et al. 2014**
• Prolonged neutropenia (4p) • Lymphocytopenia or functional lymphocytopenia in allogeneic HSCT patients (2p) • Prior history of IMD (4p) • Active disease (3p)	• Primary refractory disease No (0 p) Yes (1 p) • Previous treatment lines One (0 p) Two (1 p) Three or more (2 p) • Neutrophils number (/μL) > 501 (0 p) 0-500 (1 p)
• Low risk category (<6 p) • High risk category (≥6 p)	• Low risk category (0-2 p) • High risk category (>2 p)

conditioning regimens that can cause mucositis. If needed, the recommended drug is fluconazole.[36]

New Treatments. Recently, new drugs have been introduced for treatment of iNHL. They act blocking the B cell receptor signal transduction system (BCR) at different levels. So far, there have been several reports of IFI in patients treated with these molecules so that the Infectious Diseases Working Party of the German Society for Haematology and Medical Oncology pointed out that BTK, bcl2 and PI3K inhibitors result in an increased incidence of severe mold infection but it is still unclear if prophylaxis is indicated or not.[62]

This new scenario requires revision of the epidemiology and specific risk factors for IFIs also among patients with CLD.

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections in Compromised Hosts (ESGICH) investigated the potential infectious risks related to the new molecules highlighting that the drugs related to the increased IFI incidence are BTK inhibitors, followed by PI3K inhibitors while, at the moment, the bcl2 inhibitors do not seem to be related to this type of infections. Anyway, antifungal prophylaxis is not indicated in any group.[63]

Some groups have attempted to identify risk factors for IFIs in this new subset of patients. For ibrutinib, simultaneous treatment with steroids, exposure to spores and previous lines of therapy have been identified as increasing the risk for IFI.[38]

A recent report has shown how IA during ibrutinib treatment occurred with a median of three months after starting the drug and moreover, unlike what seen with standard treatments, about 40% of infections are localized to the CNS.[17]

The most common risk factors for IFIs in NHL (neutropenia, lymphopenia, and treatment with purine analogs) are no more valid for patients treated with ibrutinib, and the incidence of IFI is similar in first or advanced line of therapy (4%), showing that the drug itself can increase the risk of IFI regardless of previous treatments.[11] An increased rate of IFI is also reported in patients treated with ibrutinib for other diseases (e.g., 2.7% in MCL, 3.2% in WM).[53,64]

Epidemiology of Fungal Infections in MM. The overall incidence of IFI in MM ranges from 0.5% to 12.3% and the incidence of mold infections from 0,3% to 3,3% (**Table 3**). In the Italian multicentric retrospective study SEIFEM-2004, the overall incidence of IFI in MM was 0.5% (7 cases in 1616 patients), and molds accounted for more than a half of the infections (4 of the 7 cases). The causative agent was aspergillus in all cases.[5] IFI occurred mostly during disease progression or following the second or third autograft, underlining the relevance of the defining a high risk category that could benefit from active mold prophylaxis.[65,66]

Two French studies[67,68] indicate chronic lymphoproliferative disorders as a new high risk group for invasive aspergillosis (IA) following acute leukemia and allogeneic stem cell transplant (HSCT). Liu et al. showed that the incidence of IFI was 3.8% per chemotherapy course. Most of the infections were possible IFI according to EORTC criteria.[69] Sun et al. in 2015 in a multicentric study, reported three cases of IFI in 395 patients with MM enrolled. The incidence of proven/probable cases was 0.68%.[15]

Risk Factors in MM. In the majority of studies, MM is considered a low risk disease although only a few of them have evaluated the impact of newly available drugs as well as the extensive use of autologous stem cell transplant (ASCT). Immunomodulatory drugs and proteasome inhibitors are less myelosuppressive than the conventional chemotherapy which now tends to be used only in refractory or progressive disease. This could explain why most of the IFI occurred during disease progression or treatment of refractory disease.

Neutropenia is the risk factor reported in the majority of the studies and seems to be related to

Table 3. Incidence of IFI and mould infections in MM.

Study	IFI (%)	Mold infection (%)
Teh, 2015	9/372 (2.4)	3/372 (0.8)
Nosari, 2014	2/300 (0.7)	2/300 (0.7)
Pagano, 2006	7/1616 (0.5)	4/1616 (0.3)
Lortholary, 2000	-	11/338 (3.3) IA
Kurosawa, 2012	3/375 (0.8)	3/375 (0.8)
Huang, 2009	44/357 (12.3)	-

IA: Invasive Aspergillosis.

its duration and severity.[49] Teh et al. reported, as main risk factors, neutropenia less than 0.5 x 10^9/L for ten days or more, corticosteroid therapy (>= 0.5 mg/kg/day of prednisolone equivalent over four weeks) and T cell suppressive chemotherapy before the diagnosis of IFI.[65]

In multivariate analysis, only the number (3 or more) of lines of therapy was independently related with an increased risk of developing IFI, whereas the use of bortezomib retained significance only in univariate analysis.[65]

Together with a high dosage of glucocorticoids and intensive chemotherapy, other risk factors such as the use of bortezomib, thalidomide, lenalidomide or transplant procedures (HSCT) were reported as significant risk factors.[70]

The use of broad- spectrum antibiotics, diabetes, dialysis and the use of fludarabine are also reported to increase the risk of IFI significantly.[66]

The presence of central vein catheterization, the use of broad spectrum antibiotics for > 7 days, hepatic dysfunction, decreased serum albumin and antifungal prophylaxis did not emerge as significant risk factors. Only a prior history of IFI was confirmed to predict the onset of a new IFI significantly.[69]

In **Table 4** main risk factors for IFI in MM patients.

IFI Prevention in MM. Patients with MM are generally considered at low risk for IFI, and so far there is no consensus for antifungal prophylaxis. Nevertheless, several studies tried to identify subgroups that are likely to benefit from it. The most common prophylactic agents are triazoles in many centers.

The Hema e-chart study underlined that the type of antifungal prophylaxis was correlated with the number of IFI diagnosed because the galactomannan test (GM) was positive in a significantly lower proportion of proven/probable mould infections when active mould prophylaxis, like itraconazole or posaconazole, was used. This could be due to the reduced sensitivity of the GM test during prophylaxis, that could lead to underscoring IA as possible infections with subsequent insufficient antifungal treatment.[56]

In the study by Liu et al. the incidence of IFI was higher in patients who received antifungal prophylaxis probably because these patients had more risk factors at baseline and were considered as having a much higher risk to develop IFI. The mortality rate for patients with probable or possible IFI was 11,7%.[69] In **Table 5**, data about the mortality rate in different studies are reported.

The parameters associated with an increased risk of death were older age, a diagnosis based on positive culture together with two positive GM detections in serum samples, the presence of pleural effusion or CNS involvement, while an initial antifungal treatment including voriconazole was associated with a decreased risk of death.[68]

Conclusions. CLDs are rather common haematological malignancies, nevertheless, the real incidence of fungal infections in these patients is largely unknown. The majority of published data are case reports or monocentric studies, and therefore the landscape is quite heterogeneous.

In CLL the incidence of IFI is reported up to 7,8%.[5] Risk factors are mainly related to disease

Table 4. Risk factors for IFI in MM.

Study	Risk Factors
Teh, 2015	Neutropenia, Corticosteroid therapy, T cell suppressive chemotherapy
Kurosawa, 2012	Neutropenia, GvHD and immunosuppression
Nucci, 2009	High dose glucocorticoid therapy, intensive chemotherapy, use of bortezomib, thalidomide, lenalidomide, HSCT
Liu, 2016	Prior history of IFI, deep vein catheterization, use of broad spectrum antibiotics for > 7 days, hepatic dysfunction, decreased serum albumin and antifungal prophylaxis
Huang, 2009	Use of broad- spectrum antibiotics, diabetes, dialysis and the use of fludarabine, persistent agranulocytosis

Table 5. Mortality rates for IFI in MM.

Study	Mortality rate
Liu, 2016	11.7%
Kurosawa, 2012	36.8% (30.4% for IA) pooled data
Pagano, 2006	75%
Cornet, 2002	53% (IA)
Lortholary, 2000	58% (IA)
Nosari, 2014	16% pooled data
Nosari, 2013	17.3% pooled data

status, with the highest risk in relapsed/refractory disease, some previous chemotherapy regimens and immunoglobulin levels.[12] Depending on treatment administered, the risk is different: IFIs are mainly associated with the use of monoclonal anti-CD20 antibodies, purine analogs and BTK inhibitors.[30,38]

In NHL the overall incidence of IFI is reported up to 4% although in aggressive lymphomas the rate is higher (2.3-4.3%) compared to what observed in iNHL (1.7-2%).[10] Risk factors are related either to disease status (higher risk in relapse/refractory and advance stage disease) or to the modality of treatment (steroid use, intensive chemotherapy with prolonged neutropenia, monoclonal antibody and purine analogs).[58]

Patients with iNHL are considered to be at low risk for IFI, and therefore there is no consensus for biomarkers monitoring (GM or BDG assays) or need for prophylaxis.[4] An increased rate of IFI is also reported in patients treated with ibrutinib (2.7% in MCL, 3.2% in WM).[53,64]

In MM the incidence of IFI is reported from 0.5% to 12.3% with a mortality rate for probable or possible IFI of 11,7%.[69] IFI occurred mostly during disease progression or following the second or third autograft, underlining the relevance of the definition of a high risk category that could benefit from prophylaxis.[65,66] The main risk factors are prolonged neutropenia, steroid therapy, and T cell suppressive chemotherapy before the diagnosis of IFI.[65] Immunomodulatory drugs and proteasome inhibitors are less myelosuppressive compared to conventional chemotherapy which now is mainly used in refractory or progressive disease, and this could explain why most of the IFI occurred during treatment of advanced or refractory cases.

The epidemiology of fungal infections in CLD is changing over time, and this mutation is apparently related to the new treatments recently introduced into clinical practice. The new “target drugs” not only act on neoplastic cells but also on the healthy counterpart, interacting with the normal functioning of the immune system. This could lead to an increase in the risk of infections including IFI. Longer follow-up and larger studies are warranted to define better the risk in CLD patients treated with the new molecules, to identify those who could benefit from adequate prophylaxis.

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