# Infections in myelodysplastic syndromes

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## ABSTRACT

Myelodysplastic syndromes are associated with a risk of severe infections. While neutropenia is likely to be the main predisposing factor, several other immune defects have been reported, including impaired neutrophil function, B-, T- and NK-cell defects and the possible consequences of iron overload due to red blood cell transfusions. The advanced age of most patients, their frequent comorbidities, and the fact that drugs such as hypomethylating agents and lenalidomide, which are effective in myelodysplastic syndromes but can transiently worsen neutropenia, may increase the risk of infection and their severity in this context. The majority of infections in myelodysplastic syndromes are bacterial, while the incidence of fungal infections is not well known and viral infections seem to be rare. No prophylactic measures against infections have demonstrated efficacy in myelodysplastic syndromes. However, pending more data, we propose here some recommendations for the management of patients with myelodysplastic syndromes. In the future, an important contribution can be made by prospective trials testing the efficacy of prophylactic and therapeutic approaches to infection in these patients, especially in the context of the new drugs available for myelodysplastic syndromes.

Key words: myelodysplastic syndromes, infection, bacterial, prophylaxis, therapy.

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## Introduction

Myelodysplastic syndromes (MDS) are clonal disorders of hematopoietic stem cells and are mostly observed in elderly patients. They are characterized by ineffective hematopoiesis resulting in blood cytopenias and by a high risk of progression to acute myeloid leukemia (AML).[1] MDS may be triggered by previous chemotherapy (especially using alkylating agents), radiotherapy or by exposure to benzene derivatives, but they are mainly age-related. The frequency of MDS is approximately $4\times10^3$ per 100,000, being the third hematologic malignancy after non-Hodgkin's lymphoma and multiple myeloma. Up to the last decade, due to the lack of effective therapies and to the advanced age of many MDS patients, supportive care was the only therapeutic option proposed. Prognosis of MDS is routinely assessed by an international prognostic scoring system (IPSS), based on the number of blood cytopenias, the percentage of marrow blasts, and on karyotype.[2] This system distinguishes between 4 groups of patients with MDS: low-, intermediate-1, intermediate-2, and high-risk MDS. Patients with low- and intermediate-1 IPSS risk are often grouped into the category of "lower risk MDS", and typically show a relatively low risk of progression to AML and prolonged survival. Patients with intermediate-2 and high IPSS risk are generally grouped as "higher risk MDS", and often progress to AML and have a short survival.

Treatment of patients with lower risk MDS mainly aims at correcting cytopenias, especially anemia (which is generally the predominant or only cytopenia), using erythropoiesis-stimulating agents or, in the case of patients with lower risk MDS and chromosome 5q deletion (del 5q), lenalidomide. In patients with higher risk MDS, treatments aimed at modifying the disease are generally proposed, especially the hypomethylating agents azacitidine or decitabine which have recently been shown to improve survival in this category of patients.[3,4] Less often, chemotherapy may also be proposed for these patients. Allogeneic hematopoietic stem cell transplant (HCT) remains the only curative approach for MDS, but is restricted to relatively younger patients (generally under 65 years of age) with an HLA-identical donor.[5]

Infection has long been recognized as a cause of morbidity and mortality in MDS, and has been attributed mainly to quantitative and qualitative defects of neutrophils.[6-8] Until recently, and before the era of hypomethylating agents, in the absence of effective therapies, the long duration of the disease and the advanced age of the patients did not encourage the design of strategies aimed at reducing infectious risk in MDS. More effective treatments able to correct cytopenias, and especially neutropenia, have recently become available, although there is often a transient worsening of these complications. This has proved to be an incentive to review published data on infections in MDS, with the aim of proposing therapeutic strategies adapted to deal with these and making recommendations for the design of future prospective trials.

### Morbidity and mortality due to infection in myelodysplastic syndromes

Relatively few precise data are available on the incidence

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and respective bacterial, fungal, and viral causes of infection in MDS. Most of these data are retrospective. Some are compromised by inconsistencies in the definition of the infectious events or, although taken from therapeutic trials, may be biased by patient eligibility criteria. In a recent US retrospective series of 273 untreated low- or intermediate-1 risk MDS patients who died in the period from 1980 to 2004, infection was the primary cause of death, accounting for 38% of the total, followed by AML transformation (15%) and hemorrhage (13%).[9] Pneumonia was the most common infection, responsible for 40% of infectious deaths. Infection, mostly of a bacterial origin, was microbiologically documented in 30% of the cases of pneumonia in these MDS patients. As this study covered three decades, it was possible to show a significant decrease in the incidence of infectious deaths over time, likely attributable to improved supportive care. Another US survey of the Medicare population (an insurance covering more than 97% of all US citizens aged 65 years or over) indicated that, in a population of 1.3 million people over the age of 65 years followed between the years 2003 and 2005, patients with MDS had a higher prevalence of infections than the non-MDS Medicare population (22.5% *vs*. 6.1%; $P<0.001$). The difference was most pronounced in patients with MDS who had received transfusions, but there was also a clear difference for patients with MDS with various comorbidities, including diabetes, dyspnea, and hepatic diseases.[10] This suggests that concomitant occurrence of multiple comorbidities, including those cases in which iron overload may be one of the causal factors, could contribute to infection in MDS.

Since hypomethylating agents have become a reference treatment in MDS, we have examined infectious morbidity and mortality in the main published prospective or observational studies using these agents (Table 1). The highly variable rate of infection of the patients studied, ranging from 2.7%[14] to 57%,[16] is probably largely accounted for by the variable proportion of patients with higher risk MDS, who are more prone to infection than patients with lower risk MDS. Again, most of these infections were accounted for by pneumonia, and were mostly considered to be of a bacterial origin, with a significant proportion of them occurring during neutropenic phases (i.e. febrile neutropenia).

Similar variability was seen when considering infection as a cause of death, varying from 2%[12] to 32%.[19] This was probably due to the selection of patients in prospective trials in the former study, whereas the latter study was made up of patients in compassionate-use programs, many of whom would have been excluded from prospective trials.

## Neutropenia, altered neutrophil functions and other spontaneous immune disorders predisposing to infections in myelodysplastic syndromes

Neutropenia (spontaneous or transiently worsened by treatment) likely represents the major reason for increased risk of infection in MDS. However, qualitative neutrophil defects, other less well-known immune disorders and, in some situations, iron overload could also contribute to the risk of infection (Figure 1).

### Neutropenia

Neutropenia occurs in nearly 50% of newly diagnosed patients with MDS, including 70-80% of higher-risk MDS patients, and 15-20% of lower-risk MDS patients. In advanced MDS, neutropenia is part of a more general process of bone marrow failure combining impaired differentiation, apoptosis resistance, and leukemic proliferation.[20,21] In lower risk MDS, it appears to result mainly, like other cytopenias, from accelerated apoptosis of hematopoietic progenitor cells at all stages of maturation.[22-24] Mechanisms underlying this increased apoptosis include activation of cell-death receptors and direct activation of mitochondrial apoptosis. While these apoptotic mechanisms have mainly been illustrated for the erythroid lineage,[25-29] few studies have focused on the accelerated neutrophil apoptosis which may explain neutropenia in early-stage MDS.[30,31]

Immune mechanisms may also be operative in some patients through a T-cell mediated inhibition of hematopoiesis or of autologous granulocytes. This T-cell mediated mechanism is probably associated with the observed increase in levels of plasma TNF-alpha and IFN-gamma, and is potentially reversible through administration of immunosuppressive treatment.[32-35]

However, while neutropenia is considered to be the main cause of infection in MDS, absolute neutrophil counts (ANC) were not found to relate to survival rates following infectious episodes, at least in one historical series of MDS patients in different risk categories, suggesting that other defects may also be important.[6]

### Functional neutrophil impairment

Functional neutrophil defects, often associated with morphological abnormalities of neutrophils,[36] include a marked reduction in phagocytosis and production of oxygen intermediates,[37] and a decrease in bactericidal and fungicidal activities,[38] production of superoxide anions,[39] and expression of CD11b, L-selectin, LFA1, and CD18 leading to defective granulocyte locomotion.[40-42] MDS patients also have deficiencies in the contents of neutrophil granules, including quantitative and/or functional anomalies of myeloperoxidase, lactoferrin and antibiotic proteases such as elastase and cathepsin G,[43-46] deficiencies in granule membrane glycoproteins,[44] and matrix metalloproteinase dysfunction.[47-49] Impaired activity of granule proteases in neutrophils, which can induce tissue injury through an inflammatory-mediated process, is potentially implicated in the increased susceptibility to infections even in the absence of neutropenia.[50-52] However, these defects have still not been well defined in clinical studies.

### Other spontaneous immune disorders potentially predisposing to infection independently of neutrophil impairment

#### *B-cell and antibody production impairment*

The impact of B-cell impairment in MDS on infectious risk has not been well defined. Absolute numbers of peripheral B cells were found to be reduced in patients with MDS compared to controls.[53] Autoreactive B cells with or without detectable serum autoantibodies were observed.[54] Furthermore, hypergammaglobulinemia was found in 39% and hypogammaglobulinemia in 8% of patients with MDS.[54,55] Increased apoptosis of medullary B cells has also been described.[56]

#### *T-cell impairment*

Most patients with MDS have lymphocytopenia, mainly due to a decrease in T-helper lymphocyte counts.[53,57] The balance between $CD4^+$ $T_H1$ cells and $T_H2$ cells was found to be altered in patients with MDS, with a decrease in the number of $T_H1$ cells and a decreased $T_H1$:$T_H2$ ratio.[58,59] An

increased proportion of $CD8^+$ T cells, mainly of cytotoxic $CD8^+CD28^-$ T cells, was observed.[60] Whether such inbalances affect the risk of infections is unknown.

Anomalies of regulatory T (Treg) cells have also been described in patients with MDS, such as a decreased number of Treg cells in high-risk MDS, and impaired Treg function, despite a normal absolute count in low-risk MDS.[61] The number of $CD4^+$ T cells producing IL17 ($T_H17$ cells) is higher in low-risk MDS compared to high-risk MDS, and inversely correlates with the number of Treg cells. The secretion of IFN gamma by the effector T cells is inhibited by Tregs, without modification of the secre-

**Table 1.** Incidence of infectious complications, and of infectious deaths in the larger prospective or observational trials using hypomethylating agents in myelodysplastic syndromes.

| Reference | Study design | Hypomethylating agent | N. patients treated with hypomethylating agents | Median n. cycles (range) | Overall response rate (%) of hypomethylating agent group(s) | Rate of infectious complications | Death from infections (%) in the hypomethylating agent group |
|---|---|---|---|---|---|---|---|
| Silverman LR JCO 2002[11] | Prospective, randomized Azacitidine *vs.* supportive care | Azacitidine 75 mg/m²/d, SCx7d, every 28 days | 99 | | 60% | # 20% | Not available |
| Silverman LR JCO 2006[12] | Sum of 3 prospective trials, including Silverman *et al.* 2002[11] | " | 268 | | 36-48% | 0.64 infection per pt/year in Aza *vs.* 0.95 in supportive care | 3 patients (2%) of 150 pts at cycles 2, 4 and 68 |
| Fenaux P Lancet Oncol 2009[13] AZA-001 | Prospective, randomized, open, high-risk Azacitidine *vs.* supportive care or LD-AraC or intensive chemotherapy | " | 179 (including 34% of RAEB-t and 47% IPSS high-risk) | 9 (4-15) | Any remission: 29% Any improvement: 49% | Infections treated by IV antibacterials/pt/y: 0.60 *vs.* 0.92 in the control group ($P$=0.0032) | Not available |
| Musto P Cancer 2010[14] | Retrospective, compassionate use of azacitidine in lower risk MDS | Azacitidine SC (different schedules) | 74 (all low or intermediate risk) 51% > 70 years | 7 (1-30) | 45.9% * | Grade 1-2†: 2.7% Grade 3-4: 6.8% | 0 |
| Garcia-Manero G JCO 2011[15] | Phase I, maximum-tolerated dose study | Azacitidine, orally | 41 | 4.5 to 12.5 (variable according to the disease) (1-32) | 35% if previously treated, 73% if previously untreated | Grade 3† febrile neutropenia: 8 (19.5%) | 1/41 (pneumonia plus urinary tract infection) |
| Wijermans P JCO 2000[16] | Prospective, open, phase II, Int I or II or high-risk | Decitabine (45 mg/m²/d for 3 days every 6 weeks) | 66 (including 30% of RAEB-t) | Not available | 66% | Fever, infection and septicemia: 38 patients/66 (57%) and 44 episodes/162 (27%) cycles | 3, all during neutropenia ("shortly after the treatment") |
| Issa JP Blood 2004[17] | Prospective, phase 1, multiple low-dose longer exposure schedules, | 7 different regimens of decitabine | 50 (including only 7 patients with MDS) | Not available | 4/7 in the MDS patients In the whole cohort: 32% | No specific information for the 7 MDS patients of the overall cohort: 26 (52%) patients with a febrile episode (FUO: 8, clinically documented: 18 including 6 bacterial and 1 fungal infections | Not available |
| Kantarjian H[4] Cancer 2006 | Prospective, comparative, decitabine *vs.* best supportive care, IPSS ≥ 0.5 | Decitabine IV (15 mg/m x3/d till 135 mg/m²/course) every 6 weeks | 89 (including 19% RAEB-t) | 3 ( 0-9) | 30% * | Febrile neutropenia Grades 3 or 4: 23/83 (27.7%) Pneumonia: 15/83 (18%) | Not available |
| Kantarjian H[18] Blood 2007 | Prospective comparative study of 3 decitabine regimens in high-risk | Decitabine 20 mg/m²/d IV x 5 days or 20 mg/m²/d SC x 5 days or 10 mg/m²/d IV x10 days every 4 weeks | 95 (including 46% int 2 and 20% high-risk) | 6 (1-18) | 73% | Fever of unknown origin: 23/622 cycles (4%/cycle) 7 (1%) sepsis, 24 (4%/cycle) documented minor infections 20 (3.5%) pneumonia 7 (1%/cycle) fungal infections | Unknown. No death directly attributed to decitabine therapy |

**According to IWG 2006 criteria. †According to the National Cancer Institute Common Toxicity Criteria (Bethesda, MI, USA).*

tion of IL17. The level of several inhibitory factors including IL2-receptor and IL10 are decreased in low-risk MDS.[62]

*NK-cell impairment*

The reduced expression of NK receptors such as NKG2D may contribute to the impairment of cytolytic function of NK cells in patients with MDS[63,64] which persists after administration of activating cytokines such as IL-2.[63] Furthermore, NK cells from patients with MDS show decreased levels of IL-32, which could be associated with the lower cytotoxic potential of NK cells observed in these patients.[65]

## Role of iron overload in the risk of infection

Iron overload is common in MDS, mainly due to chronic red cell transfusions and, to a lesser extent, to increased gut absorption of iron as a consequence of ineffective erythropoiesis.[66,67] Iron overload may increase the risk of infections[68] through at least two mechanisms. First, this may be through a direct effect of free iron on bacterial and fungal growth.[69,70] Some pathogens, such as *Yersinia enterolitica*, *Y. pseudotuberculosis*, or *Legionella pneumophilia*, have such an impaired ability to acquire iron that they may obtain the iron essential for their growth from their host; this would be dangerous mainly in hosts with excess iron loads.[71] Second, excess free iron impairs the natural resistance to infection, through complex mechanisms including inhibition of IFN-gamma, TNF-alpha, IL-12, nitric oxide formation, and impairment of macrophage, neutrophil, and T-cell functions.[68,72,73]

However, there are no data evaluating the incidence of infectious episodes in patients with MDS with iron overload and who did not receive an allogeneic HCT. Likewise, the potential benefit of iron chelation for reducing the risk of infection in MDS patients, although suggested by retrospective studies, has not been demonstrated prospectively. A possible predisposing role of iron overload in infectious risk in MDS has not yet been documented outside the transplant setting.

The role of iron overload on the risk of infection has been more clearly demonstrated following allogeneic HCT, which remains the only curative treatment in MDS patients, even though it can only be performed in approximately 15% of cases. In a retrospective study of 190 recipients of myeloablative allogeneic HCT,[74] elevated pre-transplant ferritin blood levels were associated with an increased incidence of bacteremia (60% *vs.* 44%; $P$=0.042). A prospective study in the early phase of allogeneic HCT also showed that non-transferrin-bound iron (NTBI) facilitates the growth of *Staphylococcus epidermidis*, and that the administration of plasma apotransferrin, by decreasing NTBI, can restore the inhibitory effect of patient's serum on this bacterial growth.[75] Given that myeloablative chemotherapy may rapidly increase the serum levels of NTBI,[76] chemotherapy could increase the risk of bacterial infection within the first few days of administration through its effect on iron metabolism, independently of a secondary decrease in ANC.[67]

Iron overload has also been associated with the risk of invasive fungal infections after allogeneic HCT.[77-80] Finally, increasing infectious risk may be one of the mechanisms whereby iron overload negatively impacts on the prognosis of allogeneic HCT in patients with MDS.[74,81,82]

Whether iron chelation could decrease the risk of infection in MDS has not been demonstrated. Deferasirox and deferiprone decrease the levels of labile plasma iron (LPI), making these drugs possible candidates for dealing with this.[83] On the other hand, deferoxamine acts as a siderophore to promote the growth of mucormycosis.[84] Cases of mucormycosis have been reported in MDS patients and some, but not all, of these patients are known to have been treated with deferoxamine.[85-87]

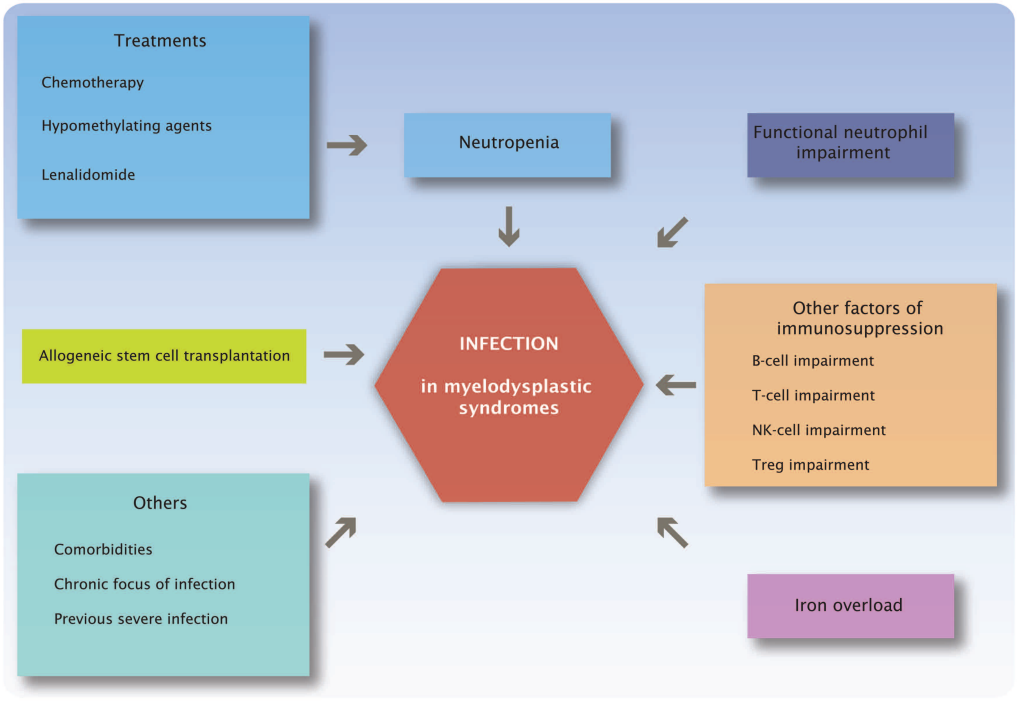


**Figure 1.** Main risk factors of infection in myelodysplastic syndromes.

### Role of therapy in infectious susceptibility of myelodysplastic syndrome patients

In addition to the risk of infection posed by MDS itself, therapy may increase that risk, at least transiently until a hematologic response is achieved. High-dose chemotherapy is still administered to patients with higher risk MDS, especially in cases of transformation in AML, or in order to reduce the tumor load before allogeneic HCT. Hypomethylating agents and lenalidomide are being increasingly administered in specific conditions of MDS. The extensive experience with such drugs allows the merits of their use to be discussed separately for MDS patients in different risk categories. Allogeneic HCT represents a very specific condition in which the infectious risk is well-known and mostly anticipated.[88,89] We review below whether MDS patients who are transplanted have additional risk factors for infection, when compared to other candidates for HCT, which may call for a specific approach.

#### High-dose chemotherapy

Due to the availability of hypomethylating agents, high-dose chemotherapy is used less now than it was ten years ago. When patients with advanced MDS were treated with high-dose chemotherapy, they were often analyzed together with *de novo* AML patients receiving the same regimen, with regards to chemotherapy[90,91] or anti-infective drug trials.[92-95] The infectious risk associated with chemotherapy-induced neutropenia in advanced MDS and *de novo* AML could not, therefore, be compared. However, the incidence of infectious events in advanced MDS patients treated with high-dose chemotherapy is probably comparable to that in AML patients of a similar age treated with the same regimens and experiencing comparable or longer duration of deep neutropenia.[15]

#### Hypomethylating agents

Several large trials performed in patients with high-risk MDS show that hypomethylating agents improve hematologic status[4,13] and, in the case of azacitidine, overall survival.[13] However, the effects of hypomethylating agents on the risk of infection seem poorly documented and heterogeneous. These agents usually worsen pre-existing cytopenias, including neutropenia, with nadir values of ANC occurring usually during the second to third weeks of each cycle.[12,96] On the other hand, azacitidine has been shown to decrease the rate of infections when compared to supportive care or low-dose cytosine-arabinoside (LD-AraC).[12,13,97] This is probably due to the fact that, in responders, neutropenia is less severe or resolved beginning with the third or fourth cycle of azacytidine, whereas neutropenia persists in patients receiving supportive care. In addition, (LD-AraC) appears to be more myelosuppressive than azacitidine.[97] On the other hand, in a randomized trial comparing decitabine and best supportive care, grade 3-4 febrile neutropenia was observed more frequently with decitabine.[4] In a recent retrospective study of 82 high-risk MDS patients and 16 AML patients treated with azacitidine, multivariate analysis showed that the occurrence of infections during azacitidine therapy, but not neutropenia or age, was significantly associated with transfusion dependency prior to the first cycle and to platelet counts of less than $20\times10^9$/L prior to each cycle.[98]

#### Lenalidomide

Lenalidomide has been approved in the US and several other countries for the treatment of anemia in patients associating lower-risk MDS and del 5q.[99] It also has some activity in high-risk patients with del 5q[100] as well as in patients with lower-risk MDS with karyotypes other than del 5q.[101] Grade 3-4 neutropenia is, along with thrombocytopenia, a major side-effect of lenalidomide, particularly in lower-risk MDS with del 5q where it was seen in 55%[99] to 75%[102] of patients. Induction of profound neutropenia (along with thrombocytopenia) was even found to be a favorable prognostic factor of subsequent erythroid response in the pivotal MDS 003 trial.[99] Although febrile neutropenia was reported in only 1%[102] to 4%[99] of the patients, death associated with neutropenia occurred in 3 of the 146 patients included in the MDS 003 trial, and 2 of the 95 patients included in a French compassionate-use program of lenalidomide in lower-risk MDS with del 5q.[103] Further use of lenalidomide may have improved the management of the risk of severe neutropenia and may have prevented deaths associated with neutropenia in del 5q low-risk MDS patients; a recent study showed that such patients had an overall poor prognosis.[102]

In uncommon indications of lenalidomide, such as high-risk patients with del 5q,[100] or low-risk patients without del 5q,[101] grade 3-4 neutropenia varied from 28%[101] to 79% in patients with a baseline ANC count of less than $1.0\times10^9$/L.[100] In high-risk patients, the worsening of baseline neutropenia by lenalidomide therapy may be a main side effect of the drug, leading to septic deaths.[100]

#### Allogeneic stem cell transplantation

Infection following allogeneic HCT to treat MDS is a well-recognized cause of death in MDS, accounting for 53% of overall mortality in a series of 109 patients.[104] Like in acute leukemia patients, this risk was increased by previous infections and use of antibacterials leading to colonization and antibacterial resistance. However, available literature data do not indicate whether patients with MDS are at higher risk of severe infection than allogeneic HCT recipients transplanted for other diseases, and whether this justifies specific measures being taken in MDS patients. However, MDS patients are on average among the oldest patients referred for HCT, and this may explain a higher risk of post-HCT infection, especially of fungal origin, when compared to other patients with different underlying diseases.[105,106] In addition, as mentioned above, iron overload increases the risk of both bacterial[74,75] and fungal[77-80] infections after HCT, and this may play a role in MDS patients who often experience iron overload during RBC transfusions. Finally, in a retrospective cohort of 291 consecutive patients transplanted for MDS, pre-transplant neutropenia (ANC<$1.5\times10^9$/L) was associated with an increased infection-related mortality at three years post transplant (26% *vs.* 12.3%) mainly due to a more frequent occurrence of Gram positive bacterial and fungal infections.[107] Therefore, MDS patients may be at particularly high risk of infections after allogeneic HCT, possibly justifying reinforced surveillance and prophylactic programs in this patient population.

### Are specific infections observed in myelodysplastic syndromes?

Infection has not been a primary end point in prospective studies in MDS, and no detailed epidemiological data on infections in large cohorts of MDS patients were found. However, recent studies raise the possibility that specific infections are observed. We review the evidence for some

of these, including common and uncommon bacterial infections, fungal diseases, as well as viral infections. Given that the impact of allogeneic HCT usually overwhelms that of the underlying disease on subsequent infectious complications, we will only consider infections occurring in patients with MDS outside the HCT setting.

### *Common bacteria*

In the rare studies which looked at the bacterial causes of infections in MDS, the bacteria implicated were similar to those usually identified in febrile neutropenia in general, i.e. enterobacteriae and coagulase negative staphylococci.[108]

Several infections that are unusual because of their localization,[109,110] the responsible pathogen,[109-118] or transfusion-related infections[14,116] were likely reported because of the rare occurrence of the clinical presentation rather than because of a specifically high prevalence in MDS.

Overall, these data suggest that, in the case of febrile neutropenia in patients with MDS, the type of first-line antibacterial therapy should be chosen on the basis of local epidemiological data and clinical presentation[118] rather than on any specific consideration of the underlying disease.

### *Uncommon bacteria*

Mycobacterial infections, including both tuberculosis and non-tuberculosis mycobacteria, have been reported in MDS patients over the last three decades,[119-123] possibly with an increased incidence of extra-pulmonary involvement.[120] Some patients had marrow involvement in the setting of disseminated infection.[121-123] A large survey from China of 508 patients with MDS found 22 (4.3%) with tuberculosis.[124] As most of these reports come from Asia, where the prevalence of mycobacterial infections is higher than in other continents, it is difficult to assess the respective roles of the natural exposure to mycobacteria in the community and of the underlying disease. However, such infections may be difficult to diagnose, and the clinician should be aware of their possible presence in the case of unexplained fever, pneumonia or lymphadenopathy, especially in geographical areas where tuberculosis is reappearing.

### *Invasive fungal infections*

No published prospective data on the incidence of invasive fungal infections (IFI) in MDS is available. In the larger and more recent prospective therapeutic trials in MDS, the incidence of IFI was not mentioned.[4,11-14,16,18,19,125] Dayyani *et al.* found that, among 273 deaths in lower-risk MDS, 23% were due to pneumonia of fungal origin, but no information was given on the fungal pathogen documented in these infections, or on the overall incidence of IFI in this low-risk MDS population.[9]

Large series of IFI usually include MDS as one of the diseases predisposing to these infections. In the report from the Italian IFI registry, covering ten years (1988-1997) in 14 centers, 391 patients with mold infections were identified; 12 of them had MDS (8 with aspergillus, 2 with mucormycosis, and 2 with unidentified filamentous fungi).[126] Four of them had recently received steroids. These corresponded to 1.3% of the MDS cases seen by the centers during the observation period, i.e. a much lower incidence than that observed in AML.[127] However, the study was performed before the era of hypomethylating agents.

While *Aspergillus* pneumonia is an expected complication of prolonged neutropenia, few cases have been reported in patients with MDS. Similarly, several cases of zygomycosis have been reported in MDS. Although the rarity of those infections may have encouraged reports being made.[85-87,128-138] A relationship with the iron overload often seen in MDS cannot be ruled out, as iron overload is a known risk factor for zygomycosis infection (see above). In some cases, zygomycosis was observed at diagnosis of MDS.[137,138] A significant number of patients had additional co-factors for zygomycosis, including diabetes,[137,138] obstructive bronchial pneumonia,[137] and treatment with deferoxamine.[85,87] In some cases, the clinical presentation was atypical,[139] with unusual features like spinal cord[131,135,140] or coronary artery obstruction.[141] In a recent, large European series of zygomycosis infections occurring between 2005 and 2007, MDS was the underlying disorder in only 6 of the 230 (2.6%) cases and in 6 of the 102 (6%) hematologic malignancies.[139]

Other unusual IFI have been reported, such as fusariosis,[142] *Trichosporon beigelii* infection.[143] However, these occurred in the setting of acute transformation treated with intensive chemotherapy. Cryptococcal infection has also been reported with unusual presentations in MDS.[144,145]

*Pneumocystis jirovecii* pneumonia appears to be very uncommon in MDS patients. In two large series of *P. jirovecii* pneumonia in non-HIV patients, MDS was the underlying disease in 3 of 55 (5.4%)[146] and 3 of 82 (4%)[147] of the reported cases, respectively.

Overall, IFI is an expected complication in MDS patients, but it is likely that the risk varies greatly according to the severity of the underlying disease. No recent prospective data are available on the true incidence of, and risk factors for, IFI in MDS.

### *Viral infections*

Severe viral infections rarely complicate the course of non-transplanted patients with MDS. In the series studied by Dayyani *et al.*,[9] viruses were found in only 5% of the cases of lethal pneumonia. Recent large prospective trials do not mention viral infections as being a major complication of MDS[4,12,13,125] However, this complication may be underestimated due to the lack of routine screening.

Parvovirus B19[148-152] and HHV-6 infection,[153] both in children and in adults, have been reported as mimicking MDS blood and marrow features, and these syndromes spontaneously disappeared in 1-2 months.

In HIV infection, marrow features of myelodysplasia have been reported in up to 69% of the patients, without evidence of any relationship between these features and HIV therapies.[33]

## Comments on the current practices for prevention and management of infectious complications in myelodysplastic syndromes

As infection has rarely been an end point in therapeutic trials in MDS, it is impossible to propose evidence-based guidelines for the prevention and treatment of infection in these patients. However, a few recommendations can be made.

### *Prevention*

#### *Growth factors*

Different studies have shown that GM-CSF[154,155] (currently not available in Europe) and G-CSF[156-158] at the conventional doses used after chemotherapy were found to improve neutropenia in 30-70% of neutropenic MDS, with better results in patients with no excess blasts and normal karyotype. Doses as low as 0.1 μg/kg/d of G-CSF[159] and 0.3

μg/kg/d of GM-CSF[160] have been evaluated and may yield slightly lower response rates. Interestingly, with conventional doses, a rapid increase in ANC may occur, probably due to mature neutrophil demargination.[161] In contrast, response to low-dose GM-CSF was delayed.[160]

G-CSF induced a slight myeloid differentiating activity of MDS marrow cells that was greater than that induced by GM-CSF.[162] G- or GM-CSF may also restore, *in vitro* and *in vivo*, several functions impaired in MDS neutrophils, such as chemotaxis and phagocytosis.[159] Both may increase the myeloperoxidase granule content[163] as the surface expression of CD11b molecules on both monocytes and granulocytes.[163,164] On the other hand, the increase in ANC observed with GM-CSF treatment did not always correlate with improvement in neutrophil bactericidal functions.[163] The lower number of GM-CSF receptors present on neutrophils could contribute to the observed impairment of response to GM-CSF.[161]

Two prospective randomized studies, one using GM-CSF[165] and one using G-CSF,[166] were performed around two decades ago in neutropenic MDS patients. The study, using G-CSF doses ranging from 0.5 to 10 μg/kg/d in high-risk patients, did not show any difference in the rate of infections or in overall survival between the 2 treatment arms.[166] However, the overall survival of the subgroup of refractory anemia with an excess of blasts had a shorter survival in the G-CSF group when compared to the controls. This study was never published as a full paper. In the study with GM-CSF, the dose of 3 μg/kg/d of GM-CSF was compared to supportive care and was shown to decrease the rate of infections from 33% in the supportive care group to 15% in the treated group. However, no benefit in survival or in risk of AML transformation was observed.[165]

G and GM-CSF have also been tested after chemotherapy in higher-risk MDS, to determine whether they could reduce the impact of neutropenia. One prospective trial compared LD-AraC either alone or combined with either Gm-CSF or IL-3.[167] Surprisingly, the study showed that infection rates were higher in the GM-CSF or IL3-containing arms. In a trial from the HOVON group, G-CSF was compared to no G-CSF following chemotherapy with daunomycin and cytosine-arabinoside in patients with high-risk MDS.[168] Despite a significant reduction in the duration of neutropenia (from 35 to 23 days), there was no significant effect on the infection rate or on overall survival. Due to the lack of precise data on the use of growth factors during studies examining hypomethylating agents, it is not possible to draw any recommendation for the use of G- or GM-CSF under those conditions[4,12-14,125]

In patients with low-risk MDS and del 5q who receive lenalidomide, neutropenia will generally occur and is often profound, as mentioned above. In order to avoid potentially fatal infections (as seen in the first trials with this agent), a group of experts has recommended adding G-CSF whenever ANC drops below $1.0\times10^9$/L.[169] This approach could also avoid the dose reductions that appear to be associated with lower cytogenetic responses to lenalidomide, as shown by a combined analysis of the MDS 003 and MDS 004 trials in lower-risk MDS with del 5q. On the other hand, it still has to be clearly demonstrated that the use of G-CSF, in this context, can help maintain a higher dose of lenalidomide, especially given that this agent also causes thrombocytopenia.

Therefore, no clear recommendation can be made for the use of G- or GM-CSF as routine infection prophylaxis in MDS patients with neutropenia who are not receiving myelosuppressive treatment.[154,170,171] Likewise, in patients receiving myelosuppressive treatment, no indication for G- or GM-CSF has been clearly established, especially in higher-risk patients in whom these agents could potentially increase the risk of AML progression.

*Antibacterial prophylaxis*

Whether antibacterial prophylaxis may benefit patients with MDS receiving myelosuppressive treatment (mainly hypomethylating agents or chemotherapy) has not been established. A recent retrospective study suggested some benefit from prophylactic antibiotics in decreasing the incidence of febrile episodes in MDS patients treated with decitabine.[108] However, the conclusions drawn from that study should be interpreted with caution since the administration of antibacterial drugs was left to the discretion of the physicians, three different antibacterials were used, and many of the infections did not occur in the setting of neutropenia. The risk-benefit analysis of prophylactic antibacterials should be considered carefully in the context of both increasing bacterial resistance and the risk of a decrease in the availability of new antibacterials over the next decade.[172,173] Prospective randomized trials will be important in resolving this issue and may also provide data on the actual risk of selecting resistant bacteria.

*Antifungal prophylaxis*

As for IFI, prospective controlled data are only available for patients with MDS receiving intensive AML chemotherapy. In this setting, posaconazole significantly reduced the risk of proven and probable IFI when compared to itraconazole or fluconazole in a cohort of 602 patients in whom the mean duration of chemotherapy-induced severe neutropenia was 24 days.[93] In that cohort, however, only 14.5% of the patients' MDS transformed into AML, whereas the other patients had *de novo* AML. In addition, most patients with higher-risk MDS now receive hypomethylating agents and whether antifungal prophylaxis is effective in these patients is unknown. If the incidence of IFI in MDS is comparable to that shown before the era of hypomethylating agents (2% in the Italian experience[126]), primary fungal prophylaxis is not a recommended treatment. This is because, unlike in AML or allogeneic HCT recipients, this incidence in MDS patients is lower than the rate that is usually considered to be that justifying primary prophylaxis (typically at least 5%).[174] Furthermore, MDS patients may have prolonged neutropenia, requiring prolonged prophylactic triazoles, a situation which has been associated with the risk of acquired resistance to those drugs.[175,176] Thus, antifungal prophylaxis with triazoles cannot currently be recommended for MDS patients receiving hypomethylating agents outside controlled trials.

*Iron chelation*

Repairing organ damage, especially in liver and heart, due to iron overload has been the main goal of iron chelation, and little attention has been paid to another potential benefit, i.e. reducing the risk of infection.[177] Whether iron chelation can reduce the risk of infection is still not known. Iron chelation is currently recommended before transplant in iron overloaded patients who are candidates for HCT, including patients with MDS.[74,81] The mechanisms of its beneficial effects in this situation remain largely unknown, but may include reducing the risk of infec-

tion. A small randomized trial assessing the addition of deferasirox to liposomal amphotericin B in the treatment of mucormycosis unfortunately failed to show any benefit from iron chelation.[178]

### Treatment of infectious episodes

Patients with MDS should be educated about neutropenia and the risk of infection. The risk of infection may not change much over time in patients with supportive care only or may worsen for variable periods in patients receiving hypomethylating agents, chemotherapy or lenalidomide. Neutropenic episodes associated with use of lenalidomide are particularly important to monitor, as they occur in patients who were generally not neutropenic at baseline, and induced-neutropenia may be profound. In cases of fever, patients should immediately undergo tests, including blood cultures, and urgently require broad-spectrum empirical antibacterials.[118]

Cases of febrile neutropenia, given the usually more advanced age of these patients, should be admitted to hospital to avoid severe complications. The choice of the antibacterials should be driven by clinical presentation, local epidemiology and severity of the infection.[118] The general practitioner should also be keenly aware of the risks of infection.

### Treatment recommendations according to type of myelodysplastic syndrome therapy and individual risk

Prophylactic measures should be considered in the context of specific clinical situations. In patients who only receive supportive care, it is generally accepted that neutropenia per se does not warrant the administration of prophylactic anti-infectives. The main reason is that the duration of neutropenia would necessitate continuous use of antibacterials or antifungals for months or years. This would likely lead to an unacceptable risk of induced resistance, well-illustrated in the case of long-term treatments with quinolones[179,180] and antifungal triazoles,[175,176] and also a risk of drug-induced adverse effects.

More than half the patients receiving lenalidomide develop grade 3-4 neutropenia during the first course of therapy, and ANC counts of patients receiving this drug should, therefore, be regularly monitored. There are, however, no data to support the routine administration of prophylactic antibacterials or antifungals. Since neutropenia is a limiting side-effect of lenalidomide,[99] treatment adjustment is critical, and a group of experts recommended administration of G-CSF in patients with ANC counts of less than $1.0\times10^9$/L at baseline or during treatment.[169]

In patients receiving hypomethylating agents, neutropenia mainly occurs during the first one or two treatment courses, and mostly in patients who are neutropenic at baseline.[181] However, in the absence of data, there are no established indications for primary or secondary prophylactic anti-infectives or for the use of G-CSF. The administration of G-CSF may additionally be a concern for patients with a significant proportion of blasts in the marrow at baseline, and should probably be restricted to neutropenic patients with overt and severe infection.[182] Recent data from Israel suggest that transfusion dependency and platelet counts less than $20\times10^9$/L prior to each cycle could be an indication of an increased risk of infection during azacitidine therapy.[98]

Two categories of patients deserve specific consideration: those with severe comorbidities known to increase their risk of infection, i.e. chronic obstructive bronchitis or any chronic focus of infection which may reactivate during neutropenia, and those who developed a previous severe infection during a prior course of treatment. Antibacterial prophylaxis should be seriously considered in these patients, especially with the use of quinolones. However, the duration of prophylaxis when administered should be as short as possible, covering only the nadir time of the risk. Consensus guidelines for antibacterial and growth factor prophylaxis in MDS urgently require large, prospective trials addressing their benefits regarding infection prevention, infection-related mortality, overall survival, and assessing their cost-efficacy.

## Conclusion

Patients with MDS mainly develop common bacterial infections, especially when they are profoundly neutropenic. However, the large variety of other infections reported in these patients suggests that, in addition to neutropenia, other mechanisms may contribute to immune suppression, at least in some patients. In those rare patients with MDS who still receive intensive AML-type chemotherapy, measures to prevent and treat infection are similar to those recommended in AML patients who receive intensive therapy. While demethylating agents now provide a real benefit to many of them, solid epidemiological data and controlled studies of infectious complications are urgently needed in order to develop optimal strategies for preventing severe infection in these patients.

## Authorship and Disclosures

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