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Review

# Infection control in patients with myelodysplastic syndromes who are candidates for active treatment: Expert panel consensus-based recommendations

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ABSTRACT

The improvement in supportive care and the introduction of new therapeutic agents, including lenalidomide and hypomethylating agents, in myelodysplastic syndromes have improved patients' outcomes; however, at the same time, the frequency and epidemiology of infections have changed. Therefore, the great strides in the indications and use of new treatment strategies for myelodysplastic syndromes need a parallel progress in the best approach to prophylaxis and supportive therapy for infections. Based on the recognition that the above issues represent an unmet clinical need in myelodysplastic syndromes, an Italian expert panel performed a review of the literature and composed a framework of the best recommendations for optimal infection control in patient candidates to receive active treatment for myelodysplastic syndromes. In this consensus document we report the outcomes of that review and of the consensus meetings held during 2017. The issues tackled in the project dealt with: information to be collected from candidates for active treatment for myelodysplastic syndromes; how to monitor the risk of infection; antimicrobial prophylaxis; the role of iron chelation and antiviral/antibacterial vaccinations. For each of these issues, practice recommendations are provided.

## 1. Introduction

Myelodysplastic syndromes (MDS) are a group of clonal myeloid malignancies with variable clinical presentation and disease prognosis. In lower-risk MDS, erythropoiesis-stimulating agents and lenalidomide are the recommended treatments, whereas hypomethylating agents (HMAs) are considered the standard of care in higher-risk MDS patients for whom allogeneic stem cell transplant is not feasible [1–3]. Out of the HMAs azacitidine, decitabine and, very recently, guanecitabine actually azacitidine is the most widely used in higher-risk MDS patients. Infections historically represent a major complication in MDS patients; however, their frequency and spectrum in the different subgroups of MDS patients receiving current treatment approaches has not been specifically investigated and infection-control strategies, in particular anti-infective prevention for high-risk disease, have not been standardized [4–7]. Hence, the great strides in the treatment of MDS patients need parallel progress in the best approach to prophylaxis and supportive treatment for infections.

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Based on these considerations, a panel of Italian experts in the management of MDS patients took part in a project aimed at providing useful recommendations for the risk stratification and prevention of infectious complications in MDS patient candidates for active treatment.

## 2. Methods

The expert panel included 12 hematologists selected because of their expertise in research and clinical practice of MDS. An Advisory Committee chaired by four clinicians (CG, RL, MTV, VS) with expertise in clinical epidemiology ensured the proper methodology of the process. The goal of the project was to develop recommendations for infection-control strategies in patients with MDS who were candidates for active treatment other than acute myeloid leukemia (AML)-like chemotherapy and allogeneic hematopoietic stem cell transplant. The areas of major concern in the infection-control strategy in MDS patients were selected by generating clinical key questions using the criterion of clinical relevance, i.e., impact on the management of patients and risk of inappropriateness, through a Delphi process [8]. The Delphi method is a structured, interactive communication technique which relies on a panel of experts The experts answer questionnaires in two or more rounds. After each round, a facilitator provides a summary of the experts' forecasts from the previous round as well as the reasons they provided for their judgments. Thus, experts are encouraged to revise their earlier answers in light of the replies of other members of their panel. It is believed that during this process the range of the answers will decrease and the group will converge towards the "correct" answer. The Advisory Committee examined the current state of knowledge regarding infection-control strategies in patient candidates for active treatment of MDS, identified key questions and drafted statements to address these questions. A systematic review of the literature on the epidemiology of infections in MDS populations was performed using the PubMed database, limiting the choice to English-language articles. Articles that included large single center or multicenter series of MDS patients, as well as review articles and position papers by other expert groups, were considered. During the first meeting in February 2017, the key questions proposed by the Advisory Committee were discussed and approved by the expert panel, and one or more panelists were given the task of producing recommendations for a specific key question based on literature analysis and their own experience. Each panelist scored their agreement with the statements made by the other panelists and provided suggestions for rephrasing. The ensuing comments were centrally combined for a subsequent round of electronic consultation; agreement on the statements and approval of the full body of recommendations were definitively reached during a second meeting in December 2017. The overall goal of the meetings was to reach a definite consensus over question-specific statements for which there was disagreement during the first-round postal phase. We used the nominal group technique [9] – a group process involving problem identification, solution generation, and decision making - through which participants were first asked to comment in round-robin fashion on their preliminary votes and then to propose a new vote. First, every member of the group gave their view of the solution, with a short explanation. Then, duplicate solutions were eliminated from the list of all solutions, and the members proceeded to rank the solutions, 1st, 2nd, 3rd, 4th, and so on. If an 80% consensus on the statement was not achieved, the choices were discussed and a further vote taken. If an 80% consensus was still not attained, the issue was declared unresolved and no further attempt was made. A facilitator (CG) encouraged the sharing and discussion of reasons for the choices made by each group member, thereby identifying common ground, and a plurality of ideas and approaches. Recommendations specifically considered the current MDS treatment strategies, which require proper stratification according to the International Prognostic Scoring System (IPSS) or the IPSS-Revised (IPSS-R) [2,3].

## 3. Epidemiology of infections in patients with MDS receiving current therapy

In patients with MDS, infectious complications have a highly variable incidence according to MDS subtype, patient characteristics and treatment [4,5].

Considering the MDS intrinsic immune impairment, several patients have an infection at the onset of the disease before starting any treatment. Although the observation of an infection in MDS patients at the onset of the disease is common in the clinical practice, specific prospective epidemiological studies are scarce in this phase and most of the recent data in MDS populations are derived from retrospective studies in patients at different phases of the disease or from Phase II–III clinical trials performed to test new therapeutic agents for MDS; therefore, endpoints are different from incidence of infectious complications. Moreover, to date, the infectious risk in MDS and the real impact of these complications on the survival of MDS patients are still unclear [4]. In a recent report from the Dusseldorf registry, examining cause of death in a large cohort of 3792 patients with MDS, 2877 patients (75.9 %) had deceased at the time of analysis. From 1665 patients with a clearly documented cause of death, 449 (27%) died as a result of an infection [10].

Table 1 shows the most recent prospective Phase II and III clinical trials testing new drugs in MDS and reporting information on infectious adverse events [11–21]. Table 2 shows the results of retrospective observational studies focused on infectious complications in MDS patients [5,7,22–26]. As detailed, infectious complications have a variable, but not negligible, incidence, especially in clinical trials enrolling higher-risk MDS patients (including IPSS-R intermediate to very high), in which the rate of grade $\geq 3$ infections reaches 58% of treated cases [13]. Conversely, in studies involving lower-risk MDS patients, infections and febrile neutropenia of grade $\geq 3$ are less frequent, ranging from 2% to 21% of treated cases [5,17–19].

The effect of HMA therapy in worsening cytopenia and in increasing the risk of infection in MDS is still poorly documented. In fact, in early studies in patients with higher- and lower-risk MDS (CALBG 8421, 8921, 9221 trials) receiving azacitidine, there was no increase in the infection rate during azacitidine therapy compared with the “best supportive care” cohort [27]. However, more recent “real-world” studies have suggested an increase in infectious events in higher-risk MDS patients treated with HMAs, especially during the early (first 2–3) cycles of therapy, before achieving a response, when the drug-induced cytopenia is associated with active-phase MDS [4,25,26]. In addition, clinical trials clearly show that the percentage of infectious events is high, not only in the therapeutic arm but also in the control group, emphasizing that there is an inherent risk of infection in MDS, regardless of the therapeutic approach, due to both neutropenia and the altered function of neutrophils [11–14,19–21]. When detailed, most reported infections in MDS occur in the presence of neutropenia and are prevalently of bacterial origin, with subsequent pneumonia, bacteremia and/or sepsis [4,28,29].

## 4. Infectious risk assessment and monitoring

### *4.1. Which MDS patients eligible for active treatment are at higher risk of infection, and what information and tests are recommended to identify/stratify the risk of infection?*

#### *4.1.1. Preliminary considerations*

Although infections may occur and cause death independently of specific risk factors [10,28–35], baseline neutropenia, present in > 50% of higher-risk IPSS/IPSS-R and 15–20% of lower-risk MDS, is likely the main predisposing factor in these patients [4,6,29,35]. Furthermore, several other functional defects of granulocytes, as well as various types of B-, T-, natural killer and regulatory T-cell abnormalities, have been reported to also impair the response to infectious

**Table 1**
Rate of grade 3 or higher infections from Phase II and III clinical trials in MDS patients treated according to the current strategies.

| Author, year (reference) | Type of study | Study treatment | Number and type of patients on study; mean age, years (range) | Type of grade ≥3 infections |
|---|---|---|---|---|
| Fenaux P, [11] | Phase III randomized | AZA (1:1) *vs.* BSC | 359 IR and HR MDS; 69 (38–88) | Febrile neutropenia: AZA 12.6%; BSC 6.9%. Pneumonia: AZA 10.3%; BSC 7.8% |
| Kantarjian H, [12] | Phase III randomized | DEC (1:1) *vs.* BSC | 170 IR and HR MDS; 70 (30–85) | Febrile neutropenia: DEC 23%; BSC 4%. Pneumonia: DEC 15%; BSC 9%. Overall infections: DEC 57%; BSC 52% |
| Lübbert M, [13] | Phase III randomized | DEC (1:1) *vs.* BSC | 233 IR and HR MDS; 70 (60–90) | Febrile neutropenia: DEC 25.4%; BSC 7.1%. Overall infections: DEC 57.9%; BSC 50% |
| Garcia-Manero G, [14] | Phase III randomized | Rigosertib (2:1) *vs.* BSC | 299 HR MDS (after failure of hypomethylating drugs); 74 (69–79) | Overall infections: rigosertib 12%; BSC 4% |
| Sekeres MA, [15] | Phase III randomized | AZA *vs.* AZA+LENA *vs.* AZA + vorinostat | 277 HR MDS and CMML; 70 (28–93) | Overall infections: AZA alone 8%; AZA+LENA 16%; AZA + vorinostat 11% |
| Garcia-Manero G, [16] | Phase II randomized | AZA (1:1) *vs.* AZA + pracinostat | 102 IR-2 and HR MDS; 70 (26–90) | Febrile neutropenia (any grade): AZA 20%; AZA + pracinostat 33% Pneumonia (any grade): AZA 16%; AZA + pracinostat 18% |
| List A, [17] | Phase II | LENA | 148 LR and IR MDS with 5q-; 71 (37–95) | Febrile neutropenia: 2% Pneumonia: 3% |
| Fenaux P, [18] | Phase III randomized | LENA 10 mg or 5 mg (2:1) *vs.* placebo | 205 LR and IR MDS not 5q-; 69 (36–86) | Febrile neutropenia: LENA 10 mg 1%; LENA 5 mg 3% Infections: LENA 10 mg 12%; LENA 5 mg 9% |
| Santini V, [19] | Phase III randomized | LENA (2:1) *vs.* placebo | 239 LR and IR MDS not 5q-; 71 (43–87) | Infections: LENA 14.4%; placebo 3.8% |
| Platzbecker U, [20] | Phase I/II randomized | Eltrombopag (2:1) *vs.* placebo | 98 HR MDS; 73 (29–88) | Febrile neutropenia: eltrombopag 7%; placebo 21% Pneumonia: eltrombopag 16%; placebo 17% Sepsis: eltrombopag 13%; placebo 18% |
| Oliva EN, [21] | Phase II randomized | Eltrombopag (2:1) *vs.* placebo | 90 LR and IR MDS; 71 (29–91) | Febrile neutropenia: eltrombopag 7%; placebo 21% Pneumonia: eltrombopag 16%; placebo 21% Overall infections: eltrombopag 5%; placebo 9% |

AZA: azacitidine; CMML: chronic myelomonocytic leukemia; DEC: decitabine; LENA: lenalidomide; MDS: myelodysplastic syndromes; HR: high risk; IR: intermediate risk; LR: low risk; BSC: best supportive care.

microorganisms in the absence of neutropenia in patients with MDS [4,31]. The true contribution of such abnormalities to the development of infections in MDS, however, has not been specifically investigated in the clinical setting.

Frailty, chronic infections or previous severe infectious episodes, environmental (home, hospital), and patients' (airways) bacterial or fungal colonizations, iron overload (IO), bone marrow reserve (cytopenias) and biological status of the disease (number of blasts and genetic characteristics), have all been variably associated with an increased risk of infections and with their severity [4–6,29,34,36–38].

Importantly, specific drugs and treatments currently employed in MDS, which have demonstrated efficacy in selected subtypes, can also transiently worsen or determine severe neutropenia and immunosuppression, thus possibly playing an additional relevant role in the development of infections. In this setting, no evidence of an increased risk of infection (in particular life-threatening pneumonia and sepsis) has been reported in two prospective, randomized trials comparing azacitidine to best supportive care [11,27]. However, azacitidine induced sustained neutropenia (grade 3–4) in up to 91% of these patients, including those who had baseline grade 0–2 and shifted to grade 3–4 neutropenia on therapy (84%). Of interest, the infection rate in azacitidine-treated patients was significantly lower than in those receiving low-dose cytarabine or intensive chemotherapy, resulting in a 34% reduction in the rate of infection [11].

In a retrospective study of 184 patients treated with azacitidine, the most relevant prognostic factors for infections in a multivariate analysis were low platelet counts ($< 20 \times 10$ [9]/L), poor risk cytogenetics and low hemoglobin levels ($< 10$ g/dL) [26]. In this study, absolute neutrophil counts before each azacitidine cycle and marrow blast percentage (but not age, transfusion dependency, azacitidine dose or serum creatinine) were also found to be risk factors in the univariate analysis, but they did not maintain their prognostic relevance in the multivariate model. Two studies reported a higher risk of infectious complications in patients treated with azacitidine 75 mg/m$^2$ for 7 days, than in those receiving 5 days of therapy either in the first cycle [39] or during the entire treatment [40]. Notably, the rate of infectious events tended to decline with sequential azacitidine cycles (in particular after the first three cycles) [7,23,25,26,41,42]. This is probably due to the progressive resolution of neutropenia in responders.

In another retrospective study, febrile episodes appeared to be more frequent if intensive chemotherapy had been employed before azacitidine, compared with when azacitidine was used frontline [25]. In this study, there was no relationship between neutrophil counts lower than $0.5 \times 10$ [9]/L and probability of infectious complications; however, severe neutropenia was associated with a higher incidence of proven/probable invasive fungal diseases (IFDs) in MDS patients receiving azacitidine [24].

Response to azacitidine impacts on the probability of infections, with a significantly lower prevalence of these complications in patients who achieved at least a hematologic response, compared with those with progressive or stable disease [23]. In this study, older age was associated with a not significant higher rate of infections, whereas comorbidities or IPSS-R had no influence. Conversely, a very high IPSS-R has recently been identified as an independent risk factor for infections in azacitidine-treated patients, with a relevant attributable mortality [7].

In another real-world Italian experience in 184 MDS patients treated with azacitidine, higher platelet levels were the only factor associated with an increased incidence of febrile events, whereas age, months from diagnosis, hemoglobin, white blood cell and neutrophil counts, bone marrow blasts, MDS comorbidity index, body mass index, IPSS and IPSS-R, azacitidine dose, and response were not [41]. Of note, at the time of the events, disease remission had not been achieved in most cases (only 11% of events occurred in responsive patients); a high risk of death due to pneumonia and bowel infection was also observed. An infectious event was the attributable cause of death mainly in patients

**Table 2**
Most recent retrospective epidemiological studies on infections in MDS patients treated according to the current strategies.

| Reference | Study | Study endpoint | Patients on study | Infection complications |
|---|---|---|---|---|
| Ali AM, [22] | Observational retrospective study | Infections during DEC 10 day/cycle treatment | 85 pts AML (68%) and MDS 282 cycles | Incidence of infections: 96.3% in MDS and 77.5% in AML Microbiological documented infections in 44.8% Prevalence of bacterial infections (bacteremia and pneumonia) Viral infections 3.7%, fungal infections 1.2% |
| Schuck A, [23] | Observational retrospective study | Impact of infections during AZA treatment | 77 pts MDS 614 AZA cycles | 81/614 AZA cycles (13%) with one or more infections Higher infections in the first 3 cycles Higher infections in non-responders *vs.* responders ($P = 0.002$) Bacterial infections 88%, viral infections 5%, fungal infections 7% of infections |
| Trubiano JA, [7] | Observational retrospective study | Incidence, etiology and timing of infections following AZA therapy for MDS | 68 pts AML and MDS 884 AZA cycles | Infections in 25% of AZA cycles Higher infections in very high IPSS-R and in the first two AZA cycles Prevalence of bacterial infections Febrile neutropenia in 5.3% of AZA cycles, bacteremia 2%, invasive aspergillosis 0.3% |
| Pomares H, [24] | Observational retrospective study | Invasive fungal infections in AML/MDS treated with AZA | 121 pts AML (29%) and MDS 948 AZA cycles | Patients with febrile neutropenia 37% Fungal infections 1.6% (4.1% in pts with severe neutropenia) |
| Falantes JF, [25] | Observational retrospective study | Patterns of infection in MDS and AML treated with AZA as salvage therapy | 64 pts AML (33%) and MDS 523 AZA cycles | Patients with infections 31/64 (48%); infections in 14% of AZA courses Higher risk of infections and risk of fungal infections during the first 3 treatment cycles Pneumonia was the most common infection (35%) |
| Sullivan LR, [5] | Case control study | Epidemiology and risk factors for infections requiring hospitalization in MDS | 497 pts MDS | Incidence of IC 21% (103/497 pts); total of IC episodes 201 Prevalence of bacterial infections, 82% (bacteremia and pneumonia) of IC viral infections 8%, fungal infections 10% of IC Risk factors for IC: HR MDS, neutropenia, comorbidities |
| Merkel D, [26] | Observational, retrospective-multicenter, study | Incidence and predisposing risk factors for infections in AZA-treated pts | 184 pts AML (15%) and MDS 928 AZA cycles | 153/928 AZA cycles (16.5%) with one or more IC 75% of IC required hospitalization and 19.6% of IC were fatal Higher incidence in the first two cycles (26% and 23%) Poor cytogenetics, low PLT count and neutrophil count below $0.5 \times 10^9$/L recorded before first AZA cycle identified "prone to infections" patients (52.7% *vs.* 33.9%; 56.1% *vs.* 35%; 53.1% *vs.* 35.6%, respectively; $P < 0.05$ for all comparisons). |

AML: acute myeloid leukemia; AZA: azacitidine; DEC: decitabine; HR: high risk; IC: infection complication; IPSS-R: International Prognostic Scoring System-Revised; LENA: lenalidomide; MDS: myelodysplastic syndromes PLT: platelet.

with progressive or stable disease.

IFDs have been reported at rates varying between 4% and 12% in MDS patients undergoing HMA therapy [26,39,43,44]. The rate was significantly higher in those who had received previous intensive chemotherapy, up to about 25% [25]. Similar to other infections, the risk of IFD was highest during the first three treatment cycles.

Pulmonary infections are associated with poor prognosis in MDS patients treated with azacitidine [41,44]. Given the different etiologies, interstitial pneumonia associated with azacitidine should be differentiated from other lung infections [45].

Specific data on the risk of infections associated with decitabine treatment in MDS are limited. Overall, decitabine appears to increase myelotoxicity compared with azacitidine. In particular, one comparative, retrospective study found that patients who had received decitabine experienced more frequent episodes of grade 3 or 4 cytopenia and infection than those receiving azacitidine; this was particularly frequent in elderly patients [43]. In a retrospective study of 85 AML and MDS patients treated in a prospective clinical study using 10-day cycles of decitabine, culture results were available for 163 infection-related complications that occurred in 70 patients. Infection-related deaths occurred only in Gram-negative events (13%); infection-related complications occurred during any cycle of therapy, and the incidence did not decrease during later cycles [22]. A recent meta-analysis has indicated that the rate of infections in decitabine-treated patients did not decrease when reducing the decitabine dose [46].

In prospective and retrospective, real-life studies, lenalidomide induced grade 3–4 neutropenia in most (about three-quarters) of treated patients (55% in a Phase II study), mainly during the first 8 weeks of treatment [17,18,47]. As a consequence, infections were frequently observed in these patients, although < 15% were of a higher grade (febrile neutropenia 1–3%). Similar results have been reported in higher-risk patients with complex karyotypes including del5q [48], whereas in lower-risk MDS without del5q, severe neutropenia and infections seem to be less frequent [49]. Development of neutropenia is significantly associated with treatment response only in del5q MDS, suggesting specificity of the cytotoxic action of lenalidomide [15]. Septic deaths associated with neutropenia in lenalidomide-treated MDS patients have been reported, particularly in patients who present with worsening neutropenia under treatment [47]. Interestingly, del5q has been recently associated with interstitial lung disease, the etiology of which may include recurrent infections [50].

The risk of infections in advanced MDS receiving intensive chemotherapy may not be different from that of AML patients of similar age, treated with the same regimens and experiencing comparable duration of neutropenia, although this is not supported by dedicated studies. For these patients, hospitalization and use of central venous catheters might represent additional risk factors [36].

Overall, immunosuppressive therapies have been associated with an increased risk of infection in MDS [34], although the specific role of antithymocyte globulin and/or cyclosporine has not been clearly reported in patients eligible for these treatments (i.e., with hypoplastic MDS) [51].

Recommendations for infectious risk management should be generally tailored on the basis of treatment aims, although a well-defined infection risk-based algorithm aiming at selecting specific treatments for specific patients has not yet been developed. This is mainly due to: (i) the inconsistency/heterogeneity of data so far reported in the literature; (ii) the currently still limited therapeutic armamentarium of MDS, which has well-established targets that do not allow significant alternative options in the therapeutic approach based on infectious risk. The association of the patient and disease variables with the risk of infections according to the above studies has been summarized in Table 3. The results of the various studies were conflicting so it was not possible to elaborate recommendations as the result of a meta-analysis of available data but rather as an expert opinion based both on the personal experience and the subjective interpretation of the literature data.

#### 4.1.2. Recommendations

The panel considered the following conditions at higher risk of infection, requiring careful evaluation and monitoring:

- Patients with baseline severe and prolonged cytopenia (ANC < 500/cmm for more than 1 month) and Iron Overload secondary to packed red blood cell transfusions (sees next paragraph on iron overload).
- Presence of single or combined relevant comorbidities (chronic liver, heart and renal organ failures, chronic obstructive pulmonary diseases, diabetes, other malignancies and autoimmune disorders).
- Chronic infections and previous severe infectious episodes (i.e. infections which required hospitalization and/or parenteral antimicrobial therapy).
- Recent hospitalization.

The following anamnestic, clinical, laboratory, instrumental and environmental data were considered useful in this setting:

- Accurate personal and medical history and concomitant medications (particularly steroids and other agents inducing cytopenia and/or immunosuppression), secondary MDS, duration of MDS.
- Environmental and occupational exposure as significant risk factors for IFD.
- Baseline laboratory assessments, including depth and duration of neutropenia, the presence of Iron Overload, immunoglobulin levels and viral profiles (particularly hepatitis B virus [HBV] and hepatitis C virus [HCV]).
- Instrumental work-up: chest X-ray or computed tomography, particularly in patients with prior pulmonary infections. Although chest X-ray is a radiological method that is easy to perform and represents a standard in the diagnosis of pulmonary infections, especially in the outpatient setting, computed tomography could be preferred as a more sensitive and specific method, especially in neutropenic patients.
- Local infectious epidemiology in hospitalized patients.

### 4.2. What schedule of clinical and laboratory assessments and follow-up management should be applied (outside of acute infectious episodes) to evaluate the risk of infection in patients with MDS?

#### 4.2.1. Preliminary considerations

There are no specific guidelines on the pre-treatment and on-treatment infectious screening in MDS patients. Therefore, the recommendations on clinical and laboratory parameters that should be considered in order to predict the infectious risk in these patients generally derive from those used in other cancer and high-risk populations. We shall focus our recommendations on the pre-treatment screening and management of HBV infection, HCV infection, tuberculosis (TB), multidrug-resistant (MDR) bacteria and fungi [52–55].

Reactivation of HBV infection in hematologic patients undergoing immunosuppressive or antineoplastic treatment occurs in approximately 20–50% of surface antigen of HBV (HBsAg)-positive (chronic HBV infection) patients and < 1–10% in HBsAg-negative/hepatitis B core antibody (anti-HBc)-positive (resolved HBV infection) patients. However, most of the literature refers to patients with lymphoproliferative diseases or acute leukemia, whereas there is no information pertaining to the incidence of HBV infection and the risk of HBV reactivation in patients with MDS. In particular, clinical trials in patients treated with lenalidomide or HMAs did not report HBV reactivations as adverse events [7,11–21,29]. Consequently, recommendations given for other low-risk populations may be used as reference [52,53]. It should also be considered that the evolving nature of MDS and subsequent treatments may change the antiviral strategy over time in each

**Table 3**
Risk factors of infectious complications in MDS patients: summary of available literature data.

| Risk factors | Comments |
|---|---|
| Age | In most of studies there was no clear association between age and infectious risk [23,26,41]. |
| Comorbidities | Comorbidities had variable and no clear influence in the rate of infections [23,41]. |
| Neutrophil count | Absolute neutrophil counts before each azacitidine cycle were found to be risk factors in the univariate analysis [26]. In another study there was no relationship between neutrophil counts lower than $0.5 \times 10^9$/L and probability of infectious complications [25]. Severe neutropenia was associated with a higher incidence of proven/probable invasive fungal diseases (IFDs) in MDS patients receiving azacitidine [24]. |
| Hemoglobin levels | Low hemoglobin levels (< 10 g/dL) was predictive of the risk of infection during the first two cycles of therapy at multivariate analysis [26]. This correlation was not observed in another study [41]. |
| Platelet counts | Low platelet counts ($< 20 \times 10^9$/L) was predictive of the risk of infection during the first two cycles of azacitidine therapy at multivariate analysis in a study [26], conversely in another real-world experience in MDS patients treated with azacitidine, higher platelet level was the only factor associated with an increased incidence of febrile events [41]. |
| Blast percentage, cytogenetic risk and International Prognostic Scoring System Revised (IPSS-R) | Marrow blast percentage before each azacitidine cycle was found to be risk factor in the univariate analysis, but not in the multivariate model [26]. Poor cytogenetics was predictive of the risk of infection during the first two cycles of therapy at multivariate analysis [26]. A very high IPSS-R has been identified as an independent risk factor for infections in azacitidine-treated patients, with a relevant attributable mortality, in a study [4], while IPSS or IPSS-R had no influence in the rate of infections in another experience [23]. |
| Hypomethylating agents treatment | *Response*: response to azacitidine impacted on the probability of infections in one study [23], while no correlation was observed in another experience [41].<br>*Dosage*: a higher risk of infectious complications was observed in patients treated with azacitidine 75 mg/m$^2$ for 7 days, than in those receiving 5 days of therapy [39,40]. This association was not observed in other experiences [23,26] The rate of infections in decitabine-treated patients did not decrease when reducing the decitabine dose [46].<br>*Cycles*: the rate of infectious events was higher in the first 3 azacitidine cycles and tended to decline with sequential cycles [7,23,25,26,41,42]. |

patient. In all patients about to receive treatment for a malignant disease, HBV screening is recommended for planning a prophylaxis strategy or the laboratory monitoring of seroreversion and/or viremic rebound, and the subsequent introduction of pre-emptive therapy [52,53].

Increases in liver enzyme activity are common in HCV RNA-positive patients receiving chemotherapy, but such increases are usually mild to moderate. Some studies have suggested that chemotherapy does not increase the risk of clinically significant hepatotoxicity in HCV RNA-positive patients with hematologic malignancies [52].

Targeted screening and treatment of latent TB infection (LTBI) is an important strategy for groups at high risk of developing active TB. A recent meta-analysis showed that patients with hematologic cancer have a nine-fold higher rate of developing active TB compared with those without cancer and would benefit from targeted latent TB screening and therapy [55]. However, no data are specifically available for patients with MDS.

During the outpatient management of MDS patients, colonization by MDR Gram-negative bacteria and subsequent infection are uncommon. Conversely, in patients with severe neutropenia, infections by MDR bacteria may be significant, particularly in hospitals with high prevalence of such pathogens. In these cases, knowledge of colonization patterns may be required to define infection-control measures and tailored antibiotic therapy [56,57]. Actually infections and colonization by MDR gram positive bacteria [i.e. methicillin resistant Staphylococcus aureus (MRSA) and vancomycin resistant Enterococci (VRE)] do not seem to represent challenging problems in hematologic patients.

The role of fungal colonization and antigen monitoring in the overall management of IFDs in patients with hematologic malignancies is a debated issue. It could be taken into consideration in high-risk conditions, but it does not seem to be cost-effective in populations at moderate to low risk of IFDs, such as those affected by MDS.

#### *4.2.2. Recommendations*

The following HBV and HCV screening is recommended in all patients at the diagnosis of MDS:

- HBV and HCV
  - o HBsAg, anti-HBc, anti-HBsAg, HBV DNA if HBsAg or anti-HBc detected, anti-HCV and HCV RNA if anti-HCV-positive.
- Tuberculosis
  - o We recommend screening with interferon-γ-release assays (IGRAs) or tuberculin skin testing (TST) or combined TST-IGRA testing to detect LTBI in all patients regardless of the MDS treatment strategy in high TB prevalence regions [58].
  - o In low TB prevalence regions [58], screening is recommended in patients with a suspected history of TB infection, in those who come from high TB prevalence regions and in those who have other conditions that are associated with an increased risk of TB infection.
- MDR bacteria
  - o We do not recommend monitoring colonization by MDR bacteria during outpatient management.
  - o Conversely, in hospitalized patients colonization screening with rectal swab culture is recommended to detect colonization by MDR Gram-negative bacteria in hospitals with high prevalence. When a patient with colonization or infection by such microorganism is detected, all patients in the ward should be monitored regardless of the underlying disease or condition. Colonization screening should be performed at hospital admission and weekly if other cases of colonization or infection are present in the ward.
  - o Patients colonized by certain MDR Gram-negative bacteria (i.e., carbapenem-resistant enterobacteria, MDR *Pseudomonas aeruginosa*) may require precautions for contact infections and tailored antibiotic therapy in the event of febrile neutropenia or deep infections.
- Fungi
  - o Surveillance cultures for colonization by fungi (either yeasts or molds) are not recommended in any MDS treatment phase.
  - o Surveillance screening of fungal antigens (galactomannan, beta-D-glucan) is not recommended.

## 5. Prevention of infections

### 5.1. In which MDS patients and when is prophylaxis with antibacterial and/or antifungal and/or antiviral drugs recommended according to treatment?

#### 5.1.1. Preliminary considerations

There are no data on antimicrobial prophylaxis specifically in MDS populations with the exception of those treated with AML-like chemotherapy or allogeneic stem cell transplant. In particular, to our knowledge, no study of antibacterial, antifungal or antiviral prophylaxis has been published to date. For these reasons, recent guidelines and experts do not recommend the use of primary antibacterial, antifungal or antiviral prophylaxis, nor the use of granulocyte-colony stimulating factor (G-CSF) in MDS patients receiving active treatment, including HMAs [3,4,41,59,60].

Recent studies focusing the infection risk in patients receiving HMA treatments showed an increased infectious risk during the first 2-3 cycles before achieving a response, when the drug-induced cytopenia is associated with active-phase MDS [4,7,25,26]. Although no experience in the use of any antimicrobial prophylaxis has been reported in this specific setting to our knowledge, a primary antibacterial and antifungal prohylaxis limited to this early period may be hypothesized, also considering that the early interruption of the HMA treatment due to a complication may negatively impact on the overall outcome of the disease.

Secondary antibacterial, antifungal and anti-herpetic prophylaxis and the use of G-CSF have been suggested in patients with a history of severe infections.

An important issue when certain drugs are coadministered is represented by the possible pharmacokinetic drug-drug interaction. Considering that HMAs and lenalidomide are not a substrate of human CYP450 enzymes and are not subjected to direct conjugative metabolism there is no drug–drug interaction when coadministered with CYP and P-gp inhibitors, inducers, or substrates. Consequently, no precaution is required when any antibacterial, antifungal and antiviral drugs are administered concomitantly with HMAs and lenalidomide.

#### 5.1.2. Recommendations

- Primary antibacterial, antifungal and anti-herpetic prophylaxis is generally not recommended.
- In patients at higher risk of infection (in particular those with chronic obstructive pulmonary diseases, recent antibacterial treatments and severe neutropenia at baseline), candidate for treatment with HMAs, primary antibacterial (ciprofloxacin or levofloxacin) and mold-active antifungal (oral posaconazole or voriconazole) prophylaxis could be advisable during the initial 2–3 cycles of treatment, with the aim of preventing an infectious complication and the consequent interruption of HMA treatment.
- Secondary antibacterial, antifungal and anti-herpetic prophylaxis in patients with previous severe infections could be advisable.
- MDS patients with chronic HBV infection (HBsAg-positive or HBV DNA-positive), regardless of the disease risk, should always be considered at high risk of HBV reactivation and should be treated with tenofovir or entecavir, under the supervision of an infectious disease or hepatology expert.
- Low-risk MDS patients with resolved HBV infection (HBsAg-negative and HBV DNA-negative but anti-HBc-positive) receiving only supportive care and erythropoietin treatment should be managed according to guidelines for immunocompetent persons [61].
- MDS patients with resolved HBV infection receiving treatment with lenalidomide or HMA may be considered at low risk of HBV reactivation, and antiviral treatment is not recommended, but monitoring of seroreversion and/or viremic rebound (defined as determination of HBV DNA, serum HBsAg levels and alanine transaminase every 3 months), and the subsequent introduction of pre-emptive therapy are suggested.
- Anti-HBV prophylaxis should be initiated before or concomitantly with treatment start and should be continued for the duration of treatment. MDS treatment should not be delayed in subjects with chronic or active HBV infection.
- Close monitoring of liver function tests and HCV RNA is recommended in HCV-infected patients receiving HMAs. Antiviral treatment should be considered for HCV RNA positive patients and hepatic disease, according to the specific indication, as soon as possible under the supervision of an infectious disease or hepatology expert.
- The use of G-CSF in neutropenic patients is not recommended as primary infection prophylaxis, although its short-term use may be considered in neutropenic patients with active or recurrent infections.

### 5.2. Does iron chelation play a role in the prevention of infections in MDS patients?

#### 5.2.1. Preliminary considerations

IO due to chronic red cell transfusions and, to a lesser extent, to increased gut absorption of iron as a consequence of ineffective erythropoiesis, is a hallmark of MDS [62]. It has been suggested that, among other damage, IO may also increase the risk of infections in patients with MDS: [4] (i) through a direct effect of non-transferrin-bound, free iron (i.e., labile plasma iron) on pathogens, which have an impaired ability to acquire iron essential for their growth (which would instead be facilitated in hosts with excess iron loads); (ii) by affecting the natural resistance to infections, that could be reduced by excess labile plasma iron through complex mechanisms, including inhibition of cytokine production and nitric oxide formation, as well as by impairment of macrophage, neutrophil and lymphocyte functions [63–65].

In the clinical setting, although not yet formally demonstrated by prospective trials, numerous retrospective studies have reported that iron chelation therapy (ICT) may improve survival of MDS patients, at least those with lower-risk disease, probably mainly by repairing/preventing liver and heart toxicity [66,67]. Little attention has been paid, instead, to the potential benefit of ICT in reducing the risk of infections [68]. Among the most relevant studies, prevalence of infections during a 3-year follow-up period (between 2003 and 2005) of US Medicare beneficiaries was found to be significantly higher in patients with MDS requiring transfusion support (81%), compared with transfusion-independent cases (55.7%; $P < 0.001$) [28]. Similarly, Smith et al. analyzed 4351 MDS patients included between 2007 and 2009 in the Surveillance, Epidemiology, and End Results (SEER) database. A significant increase in incidence of infections per person per year was found in transfused patients, regardless of treatment [37].

More recently, Lyons et al. reported a 5-year analysis of another US registry including 599 lower-risk, transfusion-dependent MDS patients. In this paper, the difference in causes of death between the non-chelated and chelated patients was statistically significant ($P = 0.0014$), and was primarily driven by the higher rates of death due to MDS/AML and malignancy, but also from infections, in the non-chelated group [67]. Of interest, severe infections were not reported in a retrospective analysis of 51 patients with higher IPSS-R risk treated with the oral chelator deferasirox during the course of their disease, most of whom received concomitant azacitidine [69].

#### 5.2.2. Recommendations

- IO should be documented at least by ferritin serum levels ($> 1000$ ng/L) and enumeration of transfusions received ($\geq 20$).
- Given the possible multi-targeted effects, ICT should not be denied to any clinically eligible MDS patients with documented IO, although a possible positive effect on infection rates and severity

should not be a primary intention for this treatment.
- The use of deferoxamine for this purpose is not recommended, as this molecule can act as a siderophore, thereby promoting growth of pathogenic fungi such as *Mucor* [70]. This is not the case with the newer oral chelator deferasirox, which is approved in MDS.

### 5.3. Which vaccinations should be administered to MDS patients?

#### 5.3.1. Preliminary considerations

Although specific epidemiologic data are lacking, MDS patients are considered at increased risk of contracting, suffering complications, and dying from seasonal influenza and pneumococcal diseases. Advanced age and comorbidities, in addition to the hematologic disease-related immunologic impairment, represent important risk factors for these infections. In a retrospective cohort study (2006–2010) in three large and geographically diverse US populations, the rates of pneumococcal disease in adults with chronic diseases or immunocompromising conditions were compared with rates in healthy adults [71]. Rates of pneumococcal pneumonia (defined as a pulmonary infection confirmed by the isolation of *Streptococcus pneumoniae* from sputum) among persons with diseases of white blood cells aged 50–64 years and ≥65 years were 13.3 and 8.4 times the rates observed in age-matched healthy controls, respectively. The rates of invasive pneumococcal disease (confirmed by *S. pneumoniae* isolation from blood or cerebrospinal fluid but not sputum) were 15.3 and 13.3 times the rates in age-matched healthy counterparts, respectively.

The efficacy of vaccinations in immunocompromised patients is highly variable and the strength of evidence is limited by a small number of studies and remains an area of clinical uncertainty. Although several experiences in patients with lymphoproliferative disorders showed reduced response to certain vaccines, there are no data on the rates of immunization in MDS patients receiving vaccination against influenza virus and *S. pneumoniae*. Considering that immune deficiency in MDS is mainly related to disorders of the monocytic and myelocytic lineages immunity and that B cell dysplasia and defect in immunoglobulin production is not considered as a major issue in MDS [72], a satisfactory response to vaccines in MDS patients could be hypothesized. Treatment with recombinant human erythropoietin was associated with an improved immune response to the influenza vaccine in hematologic patients, with titers similar to those of healthy subjects [73]. Influenza and *S. pneumoniae* vaccinations are safe, and evidence, although weak, is in favor of vaccinating adults with cancer. For these reasons, vaccination against influenza virus and *S. pneumoniae* is recommended for immunocompromised hematologic patients, including those affected by MDS [74,75]. Considering that reduction of exposure to vaccine-preventable infections is important for risk reduction, guidelines also recommend influenza vaccination of caregivers, household members and healthcare contacts to provide a “circle of protection.”

There is no specific indication in the use of vaccines other than those against influenza and *S.pneumoniae* in the MDS population. Adult MDS patients may receive other vaccines according to the standard adult immunization schedule [76]. It is important to remember that live attenuated viral vaccines (i.e. measles, mumps, rubella, varicella and zoster vaccines) are contraindicated in patients with severe immunodeficiency (while adjuvanted varicella-zoster virus subunit vaccine is not contraindicated in immunocompromided subjects).

#### 5.3.2. Recommendations

- Vaccination against influenza should be performed annually and is also recommended for household members.
- Vaccination against *S. pneumoniae* with 13-valent pneumococcal conjugate vaccine should be performed at the time of diagnosis of the hematologic disease regardless of the decision to start treatment, and in any case before initiating any active therapy. A second vaccination with 23-valent pneumococcal polysaccharide vaccine after 2 months may be considered.

## 6. Conclusions

In this report, a panel of experts in MDS judged whether the body of evidence was sufficient to provide recommendations regarding infection control during the course of disease and concluded that there is a lack of sufficient information with regard to all aspects, starting from epidemiology. The lack of randomized clinical trials testing screening and infectious prophylaxis represents uncertainties in the optimization of infectious disease management thus forcing the panel to use the methods of consensus for shaping the recommendations of this work. As a consequence, this document was mainly based on the expertise and knowledge of experts in the field coordinated by the methods of group decision and represents the first, albeit weak, consensus report on the topic.

The development of new drugs, which include targeted therapy and immunologic modifying agents undergoing investigation, may induce treatment-related neutropenia and other adverse events which may result in a change in the risk profile of infections in MDS. The future treatment landscape of a once mainly untreated disease warrants a particular sensitization towards infectious epidemiology, screening, risk assessment and prophylactic approach. Implementation of such information in registries and clinical trials are highly recommended to better define guidelines on the assessment and treatment of infections in MDS patients.

### 6.1. Practice points

- New treatment strategies for MDS need a parallel progress in the best approach to prophylaxis and supportive therapy for infections, particularly in high-risk patients treated with HMAs.
- Infectious risk assessment should be defined before and during active treatment of MDS. In particular, baseline severe and prolonged neutropenia, transfusion-related iron overload, relevant co-morbidities, infectious history and recent hospitalization should be considered.
- Primary antibacterial, antifungal and antiviral prophylaxis is generally not recommended, however, in patients at higher risk of infection candidate for treatment with HMAs, primary antibacterial and mold-active antifungal prophylaxis could be advisable during the initial 2–3 cycles of treatment, with the aim of preventing an early infectious complication and the consequent interruption of HMA treatment.
- Iron chelation therapy in patients with iron overload should be administered in view also of a possible positive effect on infection rates and severity
- Vaccination against *S.pneumoniae* should be administered, possibly at the time of MDS diagnosis, and vaccination against influenza should be performed annually to the patients but also to the household members.

### 6.2. Research agenda

- Continuous investigation on epidemiology and risk assessment of infections is required to detect change in the risk profile of infections in MDS
- Implementation of such information in registries and clinical trials are highly recommended to better define guidelines on the assessment and treatment of infections in MDS patients.

Potential conflicts of interest

C.Girmenia. has received honoraria from Gilead Sciences, Astellas Pharma, Basilea, MSD, Pfizer Pharmaceuticals, and Celgene.
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## Contribution of the authors

CG, RL, MTV and VS were chairmen of the project; all authors contributed to the literature review, writing and revision of the manuscript

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