



# Management of infection prophylaxis in Dutch patients with myelodysplastic syndromes, a web-based case vignette questionnaire: The MINDSET study

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## Abstract

**Objectives:** Infections are a major cause of morbidity and mortality in patients with myelodysplastic syndromes (MDS). The objective of the MINDSET study was to evaluate haematologists' management of infection prevention in MDS patients using a case vignette study and to assess the availability of guidelines.

**Methods:** We conducted a web-based, nationwide survey amongst haematologists in the Netherlands between September and December 2021. The survey included a set of case vignettes. In addition, the availability of protocols was evaluated.

**Results:** Sixty responses were obtained (23.6%). These responses were well distributed across hospital types as well as level of experience. No protocols regarding infection prophylaxis specifically for MDS patients were received. In the case vignette of a 75-year-old MDS patient, respondents would primarily prescribe infection prophylaxis in case of recurrent infections (96.7%) and neutropenia (75.0% for absolute neutrophil count [ANC]  $< 0.2 \times 10^9/L$  and 53.3% for ANC  $< 0.5 \times 10^9/L$ ), especially in combination with hypomethylating agents (80.0%), lenalidomide (66.7%) or chemotherapy (51.7%). Respondents would predominantly choose antibacterial agents (85.0%), followed by antifungal agents (71.7%).

**Conclusions:** This study showed diverse reasons and considerations of haematologists regarding whether to prescribe infection prophylaxis in MDS patients. Given the seriousness of infections in MDS patients, patient-tailored recommendations might be valuable in clinical decision-making.

## KEYWORDS

anti-infective agent, infections, myelodysplastic syndromes, prophylaxis, survey

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## 1 | INTRODUCTION

Myelodysplastic syndromes (MDS), a group of clonal disorders in haematopoietic stem cells, are predominantly diagnosed in the elderly.<sup>1-4</sup> The median age of MDS patients at diagnosis is 70–75 years. These vulnerable patients often suffer from comorbidities.<sup>3-6</sup> MDS is characterised by ineffective haematopoiesis, resulting in cytopenia and dysplasia, and has been associated with an increased risk of infections.<sup>1,2,7-11</sup> Infections have been found to be a significant cause of death among MDS patients.<sup>1,2,7-11</sup> In particular, neutropenia and treatment with hypomethylating agents (HMA) have been associated with the occurrence of infectious complications.<sup>7-9</sup> In a recent study, we showed that, after diagnosis of MDS, patients had a 2.5-fold increased risk for receiving anti-infective agents compared to before diagnosis.<sup>12</sup>

Little is known about prophylactic use of anti-infective agents in MDS patients, with the exception of patients who have received chemotherapy similar to that for acute myeloid leukaemia (AML) or who received an allogeneic stem cell transplant (allo-SCT).<sup>7,12</sup> A number of studies have outlined recommendations for infection prevention in MDS patients,<sup>7,9,13-21</sup> however, these recommendations are not always translated into guidelines and no guidelines specifically for infection prevention in MDS patients exist today. This gap emphasises the importance of evaluating the management of infection prevention in MDS patients in daily clinical practice.

To evaluate haematologists' management of infection prevention in MDS patients, we designed an online survey. The focus of this survey was the haematologists' approach for the prevention of infections in MDS patients. The participants were presented with case vignettes of typical MDS patients with varying levels of neutropenia and comorbidities. By means of case vignettes, more information was gathered about decision-making when prescribing anti-infective agents prophylactically in clinical practice.<sup>22</sup> Furthermore, we evaluated the availability of local protocols for the prevention of infections in MDS patients in hospitals in the Netherlands.

## 2 | METHODS

### 2.1 | Data collection

We conducted a web-based nationwide survey amongst haematologists in the Netherlands between September 2021 and December 2021. The survey was called the MINDSET study to represent the following: Management of infections in Dutch patients with myelodysplastic syndromes: a questionnaire-based survey. The Medical Ethics Committee in Leeuwarden, the Netherlands, confirmed the execution of the study without requiring an ethical review. This study was conducted in accordance with Dutch regulations. As this was no clinical research, our study was not registered in [clinicaltrials.gov](https://clinicaltrials.gov).

The questionnaire-based survey was accessible through an anonymous weblink and distributed via email on behalf of the Dutch-Belgian Cooperative Trial Group for Haemato-Oncology (HOVON). The HOVON Foundation focusses on the improvement and

promotion of treatment methods for adult patients with haematological malignancies<sup>23</sup> and has 254 members, representing the vast majority of all haematologists in the Netherlands. Participation in the survey was voluntary and the contact details of the participants were not available to the researchers. After 5 weeks of the survey being available, a reminder was sent by HOVON via email. The survey was closed on 31 December 2021.

### 2.2 | Study measures

An online survey was developed and tested by the research group, with piloting amongst four haematologists to ensure the relevance of the questions and case vignettes and to assess the required time investment. We used Qualtrics XM to create the online survey. The Dutch version of the survey and an English translation are available in the Supporting Information Data S1. The survey consisted of 12 multiple choice questions (see Supporting Information Data S1). The first question was designed to identify haematologists who treated patients with MDS in the previous year. The following eight questions focussed on factors that may play a role in the decision-making of haematologists regarding infection prophylaxis in MDS patients, in other words, personal opinion and various patient-related factors such as comorbidities, cytopenia and treatment for MDS. Space was included for additional comments. A case vignette of a 75-year-old MDS patient with varying risk factors was presented, where participants had to indicate in which situation they would prescribe infection prophylaxis. The varying risk factors included the MDS risk group, recurring susceptibility to infections, varying levels of neutropenia, comorbidities and treatment for MDS. The final three questions were optional and concentrated on characteristics

**TABLE 1** Sociodemographic characteristics of questionnaire respondents

	N (%)
Total	60 (100)
Gender	
Male	32 (53.3)
Female	26 (43.3)
Not reported	2 (3.3)
Median age, years (range)	48 (34–66)
Age categories	
30–40	14 (23.3)
41–50	21 (35.0)
51–60	14 (23.3)
61–70	6 (10.0)
Not reported	5 (8.3)
Type of hospital	
University hospital	12 (20.0)
Medical teaching hospital	31 (51.7)
General hospital	17 (28.3)



of the participating haematologists, regarding gender, age (level of experience) and the type of hospital in which they work. In case respondents worked in multiple hospital types, only one type was chosen (e.g., university hospital over medical teaching hospital and medical teaching hospital over general hospital). Descriptive statistical analyses were performed using IBM SPSS version 24 and Qualtrics XM.

### 3 | RESULTS

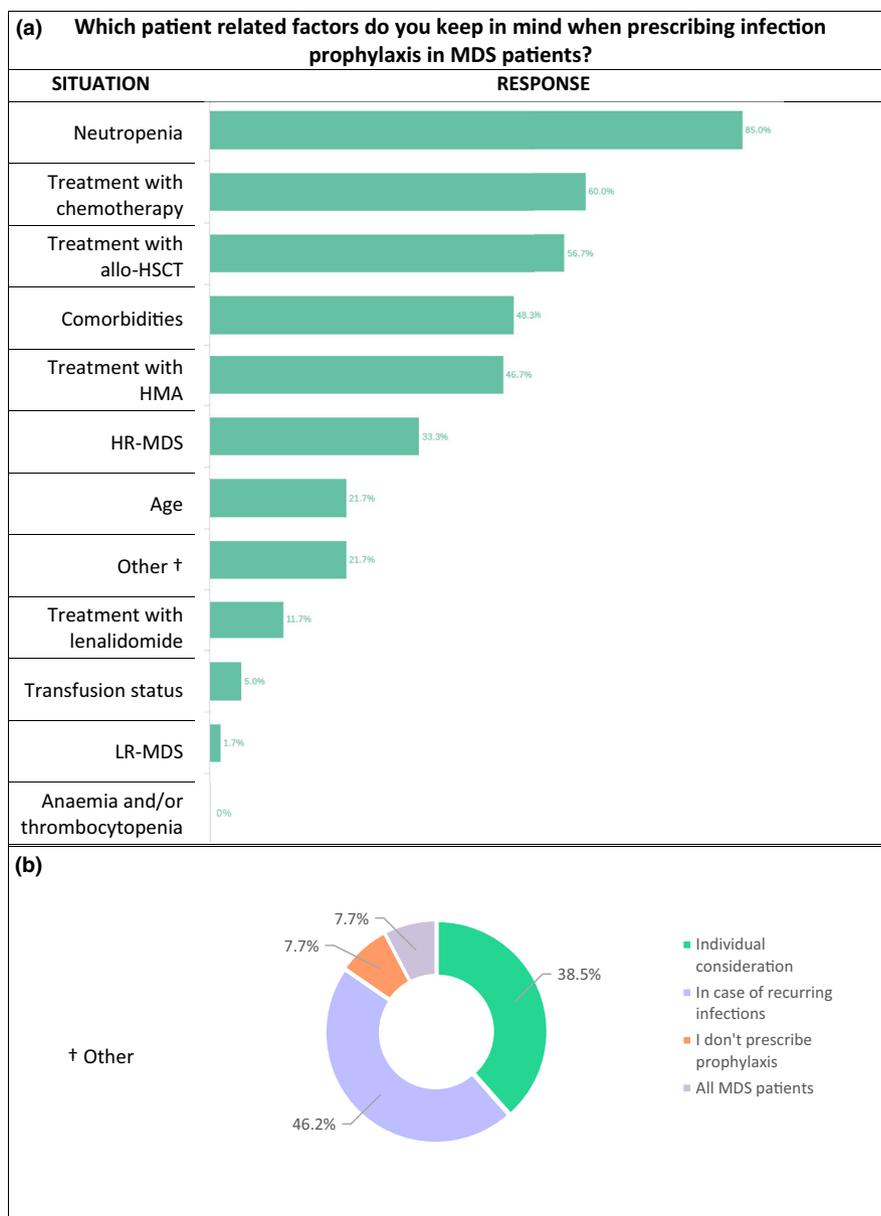
#### 3.1 | Respondents' characteristics

Of the 254 HOVON members who received the questionnaire, 60 haematologists returned them, for a response rate of 23.6%. The median age of the respondents was 48 years (range: 34–66) and 53.3% were male. Of the respondents, 20.0% worked in a university hospital, 51.7%

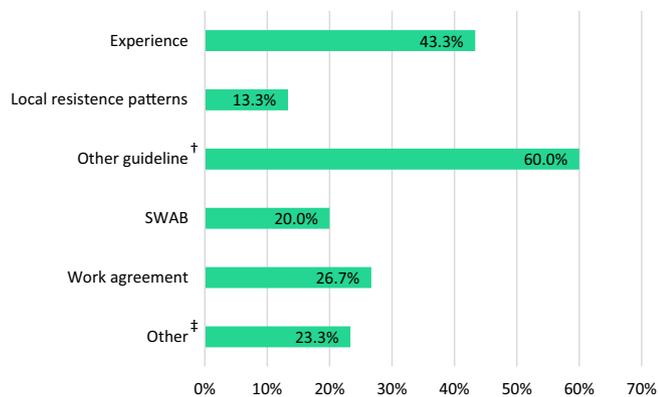
in a medical teaching hospital and 28.3% in a general hospital (Table 1). All respondents were familiar with treating MDS patients in the past year. Forty-eight respondents (80.0%) stated that infections are a significant complication in MDS patients, while 10 respondents (16.7%) did not agree and two (3.3%) were indecisive. The majority (98.3%) indicated that no protocol specifically designed for MDS patients regarding infection prophylaxis was available in their medical centre. One respondent (1.7%) mentioned a protocol for infection prophylaxis, but did not send this protocol to the researchers.

#### 3.2 | Important factors when considering infection prophylaxis

Neutropenia (85.0%), chemotherapy (60.0%), haematopoietic stem cell transplantation (56.7%), HMA (46.7%) and comorbidities (48.3%) were



**FIGURE 1** The answers to the question ‘Which patient-related factors do you keep in mind when prescribing infection prophylaxis in MDS patients?’ (A) List of possible patient-related factors. (B) Specification of ‘other’



**FIGURE 2** The answers to the question ‘Based on what information would you prescribe infection prophylaxis in MDS patients?’ <sup>†</sup>In case a guideline for another haemato-oncological disease was chosen, 31 respondents (51.7%) would use the guideline for AML and five (8.3%) would opt for a different guideline. <sup>‡</sup>In case respondents chose ‘other’: 8 respondents (57.1%) based their decision on individual consideration, 1 respondent (7.1%) on the SmPC of Azacitidine and 5 respondents (35.7%) would not prescribe standard prophylaxis

the most important factors for considering infection prophylaxis in MDS patients (Figure 1). Transfusion status (5.0%) and low-risk MDS (1.7%) were not considered important factors when prescribing infection prophylaxis. The majority of respondents (60.0%) based their decision to prescribe infection prophylaxis on another guideline—predominantly the guideline for AML—or their own experience (43.3%; Figure 2).

In case the respondents would decide to prescribe infection prophylaxis, they would predominantly choose antibacterial agents (85.0%), followed by antifungal agents (71.7%) and antiviral agents (25.0%). Four respondents (6.7%) would not prescribe any infection prophylaxis in MDS patients. One respondent specifically mentioned not prescribing standard infection prophylaxis because there was no protocol.

### 3.3 | Case vignette

In the case vignette of the 75-year-old MDS patient, respondents indicated they would primarily prescribe infection prophylaxis in case of recurrent infections (96.7%) and in case of neutropenia (75.0% for absolute neutrophil count [ANC] < 0.2 × 10<sup>9</sup>/L and 53.3% for ANC < 0.5 × 10<sup>9</sup>/L), especially in combination with HMA (80.0%), lenalidomide (66.7%) or chemotherapy (51.7%). The majority of respondents would not prescribe infection prophylaxis in case of comorbidities COPD (78.3%) or diabetes mellitus type 2 (91.7%; Figure 3).

## 4 | DISCUSSION

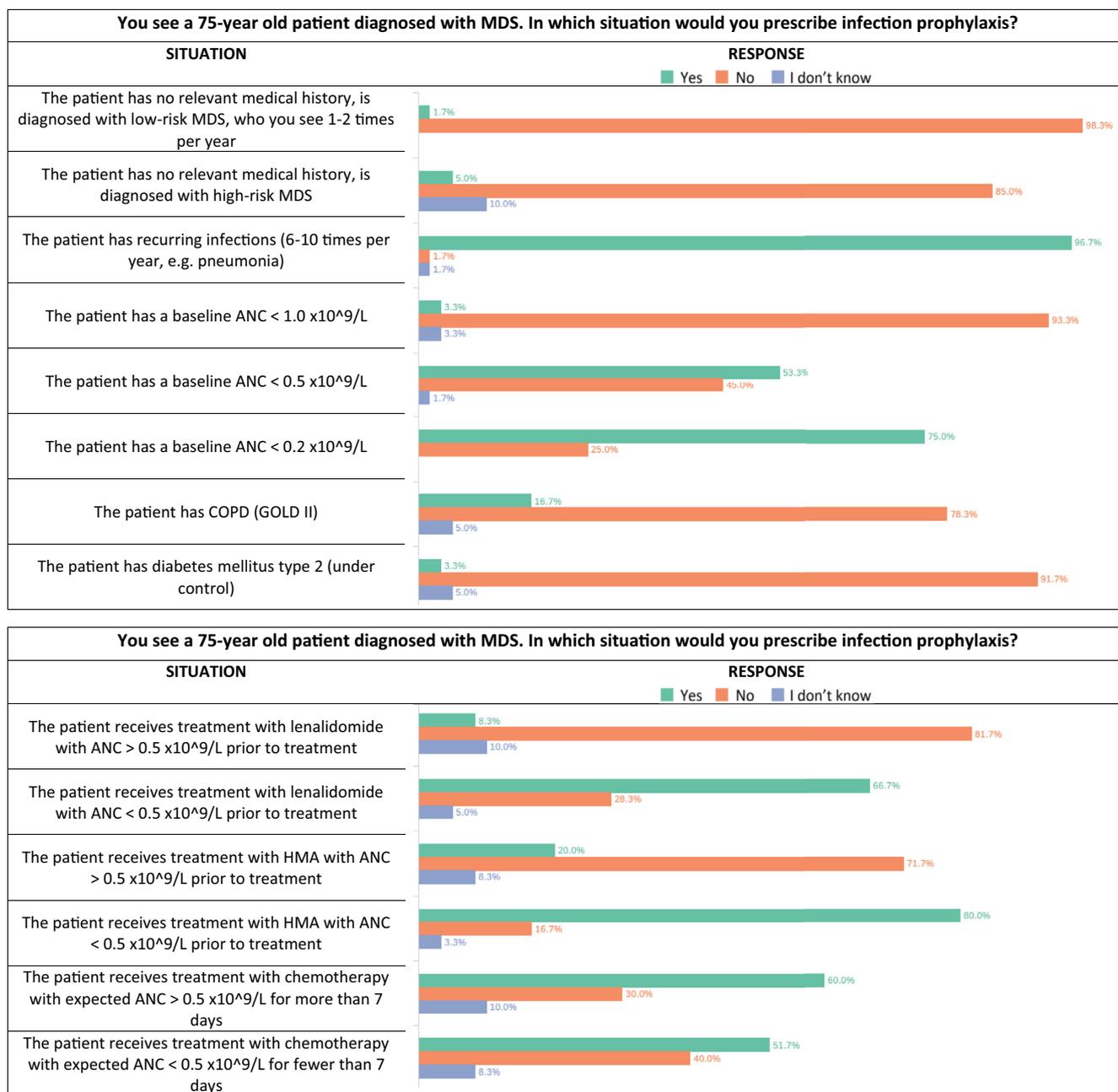
The aim of this study was to gain further insight into haematologists’ decision-making regarding infection prophylaxis in MDS patients with

varying comorbidities, the treatment of MDS and the management of other patient-related factors, as well as to assess the availability of related guidelines. The vast majority of haematologists regarded infections as a significant complication of MDS. Neutropenia, treatment of MDS, comorbidities and recurring infections were the most important factors for considering infection prophylaxis in MDS patients. Respondents would predominantly choose to prescribe antibacterial agents, followed by antifungal agents.

Nearly all respondents agreed that infection prophylaxis should be prescribed in case of recurring infections. Of note is that only half of the respondents indicated to take transplantation into account. In addition, almost half of the respondents would consider comorbidities when prescribing infection prophylaxis. However, in the case vignette of the 75-year-old MDS patient, most respondents indicated they would refrain from prescribing prophylaxis in case of relatively mild comorbidities such as COPD GOLD II and under-control diabetes. In the extant literature, neutropenia, myeloid blasts, treatment of MDS (HMA, lenalidomide or chemotherapy) and comorbidities have been associated with an increased risk of infection.<sup>7–9,13,19–21,24–26</sup> Our survey confirms that haematologists use these risk factors in daily practice and interpret comorbidities with caution when prescribing prophylaxis. As expected, when respondents would choose to prescribe anti-infective agents, they would predominantly select antibacterial and antifungal agents.<sup>7,12</sup> Half of the respondents indicated basing their decision to prescribe infection prophylaxis on the guidelines for AML. The Dutch national guidelines for AML indicate that prophylaxis with antibacterial and antifungal agents significantly improves the survival chances of AML patients.<sup>27,28</sup> Whether this is the case for MDS patients remains unknown.

There was great diversity in the haematologists’ reasons and considerations as to whether or not to prescribe infection prophylaxis, which may vary from the recommendations made in literature.<sup>7–9</sup> Similar results were observed in a recent study on the perceptions of haematologists regarding recommended care of MDS patients in Switzerland.<sup>29</sup> In that survey, no clear consensus on the topic of infection prophylaxis was found.<sup>29</sup> These outcomes suggest a lack of uniformity in the management of infection prevention in patients with MDS. The initiation of infection prophylaxis is preferably determined through patient-based risk factors and the preference of the haematologist, and some decisions regarding anti-infective prophylaxis may involve infectious-disease specialists. Guidelines or recommendations may lead haematologists in their consideration, however, to the best of our knowledge, guidelines specifically focussing on the prevention of infections in MDS are lacking.<sup>7,15–21,28,30</sup>

This is the first nationwide study to describe the perception of haematologists in the Netherlands with respect to the prescription of infection prophylaxis in patients with MDS. The availability of protocols for the prevention of infections in MDS patients were investigated, along with the empiricism in infection prevention in MDS, which can aid in transforming literature into practice.<sup>31</sup> This study represents an important contribution towards the development of more effective treatment methods and protocols surrounding the



**FIGURE 3** The answers to the question ‘You see a 75-year-old patient diagnosed with MDS. In which situation would you prescribe infection prophylaxis?’

prescription of infection prophylaxis not only in the Netherlands but worldwide. A limitation inherent in the study design was the relatively low number of participants ( $n = 60$ ; response rate 24%) and the possibility that haematologists with particular interest in the subject responded. Nevertheless, the study population represented haematologists of all hospital types and age groups, and a response rate of 20%–30% is considered quite successful for a web-based survey with no relationship to the respondents.<sup>29,32</sup> Our study did not yield information regarding the use of granulocyte colony-stimulating factor as a way to mitigate infections in neutropenic patients. Of note is that the Netherlands has a strict policy for prescribing anti-infective agents,

which may influence haematologists' opinions.<sup>33,34</sup> Therefore, our study results should be extrapolated with caution, as haematologists in other countries might share different perceptions on infection prevention in MDS patients.

In conclusion, this study reported the current opinions and insights of haematologists in the Netherlands with respect to infection prophylaxis in MDS patients. In addition, this study showed diverse reasons and considerations concerning whether to prescribe infection prophylaxis in MDS patients. Pronounced neutropenia, treatment of MDS, comorbidities and recurring infections were the most important factors for considering infection prophylaxis. Given the seriousness of



infections in MDS patients, patient-tailored recommendations might be valuable in daily clinical decision-making.

#### AUTHOR CONTRIBUTIONS

Johanne Rozema, Lars Vogelzang, Eric van Roon, Mels Hoogendoorn, Robby Kibbelaar and Arjan van de Loosdrecht designed the project. Johanne Rozema collected the data and wrote the manuscript. Johanne Rozema analysed the data. Eric van Roon, Mels Hoogendoorn, Robby Kibbelaar, Lars Vogelzang and Nic Veeger provided input in the data analysis. All authors contributed to critical revision and gave final approval of the manuscript.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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