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Review Article

Infections in Myelodysplastic Syndrome in Relation to Stage and Therapy

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Abstract. Infections remain a significant problem in myelodysplastic syndromes (MDS) in treated as well in non-treated patients and assume a particular complexity. The susceptibility to infections is due, in the absence of intensive chemotherapies, mainly to functional defects in the myeloid lineage with or without neutropenia. Furthermore, MDS includes a heterogeneous group of patients with very different prognosis, therapy and risk factors regarding survival and infections. You should distinguish risk factors related to the disease, like as neutrophils function impairment, neutropenia, unfavorable cytogenetics and bone marrow insufficiency; factors related to the patient, like as age and comorbidities, and factors related to the therapy. When the patients with MDS are submitted to intensive chemotherapy with and without hematopoietic stem cell transplantation (HSCT), they have a risk factor for infection very similar to that of patients with acute myeloid leukemia (AML), and mostly related to neutropenia. Patients with MDS treated with supportive therapy only or with demethylating agent or lenalidomide or immunosuppressive drugs should have a tailored approach. Most of the infections in MDS originate from bacteria, and the main risk factors are represented by neutropenia, thrombocytopenia, and unfavorable cytogenetics. Thus, it is reasonable to give antibacterial prophylaxis to patients who start the therapy with demethylating agents with a number of neutrophils <500 x 10^9/L, or with thrombocytopenia and unfavorable cytogenetics. The antifungal prophylaxis is not considered cost/benefit adequate and should be taken into consideration only when there is an antecedent fungal infection or presence of filamentous fungi in the surveillance cultures. Subjects submitted to immunosuppression with ATG+CSA have a high rate of infections, and when severely neutropenic should ideally be nursed in isolation, should be given prophylactic antibiotics and antifungals, regular mouth care including an antiseptic mouthwash.

Keywords: Myelodysplastic Syndrome, Infections; Azacitidine, Decitabine, Chemotherapy.

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Introduction. Infections remain a significant problem in myelodysplastic syndromes (MDS) patients treated as well non-treated, even if in reduction as a cause of death in the high-risk group.[1,2,3] At variance with acute myeloid leukemia (AML) the susceptibility to infections is due, in the absence of intensive chemotherapies, mainly to functional defects in the myeloid lineage[4-8] with or without neutropenia, which become essential risk factor when worsened by the treatments.[9]

In the study of Fianchi et al.,[6] the in vitro bactericidal and fungicidal activities of neutrophils isolated from 16 MDS patients showed a significantly reduced killing activity against *Escherichia coli*, against *Lactococcus lactis*, and more against *Candida albicans* in comparison to those from healthy individuals. The same patients were observed at a median time of 11 months (range 0–54) from the initial diagnosis; during this period, recurrent infectious episodes were recorded in 6 of them. No significant correlations were observed between the number and severity of infectious incidents and neutrophil counts. Interestingly, some functional defects could be reversed, a Maitake mushroom extract, administered to 21 patients with MDS, was able to enhance in vitro neutrophil and monocyte function in 18 of them.[7]

Accordingly, Merkel et al[8] in patients treated with azacytidine and decitabine, at the dose employed in MDS, found that platelet (PLT) count lower than 20 x 10^9/L, Hb level lower than 10 g/dL, and poor cytogenetics were the only statistically significant risk factors for infection. A low PLT count appeared to be the most significant risk factor, resulting in a 2.26-fold increase in infection risk, while poor cytogenetics and low Hb were associated with a 1.77- and 1.75-fold rise in infection rate, respectively. Surprisingly, low neutrophil count did not come up as one of the significant factors, at least in multivariate analysis.

In the past, most of the patients with MDS were treated with supportive therapies only. However the infections, bacterial, fungal and viral were frequently present, also independently from neutropenia.[1,2,6,8,10] The risk is significant in both high and low/intermediate risk MDSs.[1,2,10-14] In the series of M. D. Anderson Cancer Center[11] from 1980 to 2004, including 903 patients with low/intermediate MDS (median age at presentation of 66 years) in supportive care only, the causes of death (CODs) MDS-related was defined as infection, bleeding, transformation to AML, or disease progression. Remaining CODs were classified as non-MDS-related. The COD was identified as MDS-related in 230 of 273 (84%) patients. The most common disease-related CODs were infections (38%), transformation to AML (15%), and hemorrhage (13%). The most frequent non-disease-related COD was cardiovascular events (19 of 43 patients). Thus, the majority of patients with low- or intermediate-1 risk MDS will die because of causes related to their underlying disease.

In the Dusseldorf registry,[2,3] including low/intermediate and high-risk patients, of 1665 patients with a clearly documented cause of death, 1388 patients (83.4%) succumbed directly disease-related: AML (46.6%), infection (27.0%), bleeding (9.8%). Whereas, 277 patients (16.6%) died for reasons not directly related with MDS, including 132 patients with cardiac failure, 77 non-disease-related reasons, 23 patients with solid tumors, and 45 patients with possibly disease-related causes like hemochromatosis. By dividing the patients according to the WHO classification, infections were the cause of death in about the 30% of patients with very low, low and intermediate risk and about 15% with high and very high risk.[3] It is noteworthy that, in this same registry,[2] analyzing the survival and rate of leukemic progression of 4147 patients diagnosed during the last 30 years, an improvement of survival was found in those patients diagnosed after 2002 (30 vs. 23 months, $p<0.0001$). In detail, the improvement of the prognosis was restricted to high-risk MDS patients diagnosed between 2002 and 2014 in comparison to the patient group diagnosed between 1982 and 2001 (19 vs. 13 months, $p<0.001$), whereas the prognosis of low-risk MDS patients did not change significantly. This improvement was attributed primarily to a reduction of the death from infections.[2,3] Infections are bacterial mostly, but fungal infections are not rare, and the organs more frequently interested are the lungs, the skin and the gut (**Table 1**). Sepsis and bacteremia are also frequent.[1]

Recently appeared three exhaustive reviews on infections in MDS, they represent an important contribution to understanding this pathology.[12-14] However, they were not focused on the different therapies and stages of the disease. In this current review, considering the heterogeneity of this nosographic group, we have tried to relate on the risk of infections to the stages of the disease as evaluated by the International Prognostic Scoring System (IPSS) and the effect of the different therapies administered. So, we report the incidence of infections in the myelodysplastic syndromes classified according to the IPSS and its variations,[14-15] and the subsequent therapies by consulting the current English literature present in PUBMED, SCOPUS, and WEB of Science.

Table 1. Prevalence of Infectious complications in the MDS Follow-up Cohort of the USA from Medicare Standard Analytic Files (SAF). Adapted from Goldeberg et Al.[1] *J Clin Oncol 2010.*

	MDS		Overalll SAF Medicare Population		
No. of Subjects	512		1,379,185		
Characteristics of Infect. Complications	No	%	No	%	*P*
Sepsis	115	22.5	84,530	6.1	<.001
Bacteremia	80	15.6	110,904	8.0	<.001
Fungal Infection	49	9.6	66,129	4,8	<.001
Cellulitis	158	30.9	269,615	19.5	<.001
Renal Infections	18	3.5	19,860	1.4	<.001
Intestinal Infections	38	7.4	47,833	3.5	<.001
Pneumonia	204	39.8	272,487	19,8	<.001

Low and Intermediate Risk Myelodysplastic Syndrome. Patients with low and intermediate risk MDS have been treated in the past only with supportive therapy or by adding the Erythropoiesis-Stimulating Agents (ESAs), with or without granulocytic/granulocytic-monocytic growth factors, G-CSF or GM-CSF.[17,18] Also at present, this approach is considered the standard therapy excluding the 5q- syndrome,[19] which is generally treated with lenolidomide[19-22] and the hypoplastic forms, which can respond to immunosuppression with anti-thymocyte globulin, cyclosporine, and alemtuzumab.[23-29] After the failure of ESAs, other therapies can be instituted based on lenalidomide,[30] demethylating agents[9,31-33] and others not yet approved drugs. There is no clear guidance regarding the choice of lenalidomide or an HMA as initial disease-modifying therapy for patients with non-del(5q) LR-MDS, who mainly require treatment to reduce anemia and the need for transfusions.

The addition of G-CSF and Gm-CSF, even if is a common practice in myelodysplastic patients[9,17,18] with marked neutropenia has not a proved efficacy in preventing infections, and other drugs reducing granulocytes malfunctions should be tried.[34]

Recently, to avoid iron overload and organ damage has been proposed the addiction of chelation, particularly to low or intermediate 1 risk MDS patients.[35,36] Patients with iron overload disorders are known to be susceptible to lethal infections with bacteria that are considered only moderately pathogenic in other settings.[37] Two species of "siderophilic" bacteria are characteristic of such infections *Vibrio vulnificus* and *Yersinia enterocolitica*. These infections have been described in thalassemia or hemochromatosis patients with tremendous iron overload treated with deferoxamine but not in MDS.[37-39] It is possible that the infections from "siderophilic" bacteria in thalassemia and hemochromatosis can be in part attributed to the use of deferoxamine which, at variance with deferasirox and deferiprone enhances the growth of *Yersinia* in vitro or in vivo.[37] On the contrary, the use of iron-chelators could provide a complementary approach to overcome drug resistance in pathogenic bacteria by reducing the iron available by siderophilic bacteria.[39] However, the addition of iron-chelators seems to improve overall survival without reducing the deaths from infections,[35,36,40,41] even if a recent paper suggests that the time to its first manifestation was significantly longer in chelated patients.[37,42] Also, the hepcidin could play a role reducing infection by lowering the iron-free plasma level.[43]

Low grade/intermediate risk MDS treated with Immunosuppression. Immunosuppressive treatment may be a therapeutic option for selected patients with myelodysplastic syndrome characterized by hypoplastic bone marrow. Following the immunosuppressive therapy, authors reported a response between 30 to 60%.[23-29]

The most significant factors favoring the response to treatment are younger age, hypoplastic bone marrow, HLA-DR15 positivity and combination anti-thymocyte globulin (ATG) plus cyclosporine A (CsA) treatment.[23,24] The infections represented the primary cause of death, particularly in nonresponsive patients. Sloan et al.[23] reported response in 30% of 129 patients treated; 59 patients died, whom 33% died from leukemia and 61% from bleeding/and or infection

consecutive to marrow failure. In the study of 27 patients reported by Komrokji et al.[29] three died, of whom one of a preexisting line infection and one of pulmonary aspergillosis. The survey of Passweg et al.[24] is the only reporting a control group, treated with the only supportive therapy. This trial included mostly patients with low or intermediate1 risk group (80%), the response was about 30% versus 4% of the control. The incidence of neutropenia was the same in the two groups. In addition to the 40 deaths, 20 serious adverse events (SAEs) were reported (16 in the ATG+CSA arm and four in the Best Supportive Care (BSC) arm; *P*=.005). The deaths from infections were four in ATG+CSA arm and 2 in BSC arm.

Low grade/intermediate risk MDS treated with Lenolamide. Lenalidomide is considered the drug of choice in MDS patients with 5q deletion.[19-21]. Neutropenia and thrombocytopenia are the most treatment-associated adverse events and in the pivotal trial of List et al.[20] are reported respectively in 54.7% and 43.9% of subjects treated. Grade 4 ($<500x10^9$/L) was more common among patients receiving continuous daily dosing than among those receiving 21-day dosing (44.1% vs.17.4 %, P<0.001). However, neutropenia was accompanied by fever in only 4.1% of patients. During this trial, 11 patients died while receiving treatment or within 30 days after the last dose of lenalidomide; 3 deaths, attributed to neutropenic infection, were judged to be possibly treatment related by the treating physician. All other deaths were considered unrelated to the treatment. There were three deaths from congestive heart failure, one death from ischemic colitis, one death from AML, one death from procedure-associated intestinal perforation, one death from subarachnoid hemorrhage, and one sudden death. In the study of Fenaux et al.[21] grade 3 or 4 neutropenia and thrombocytopenia generally occurred within the first two cycles and subsequently decreased and were also the most common reasons for lenalidomide dose reductions. Furthermore, infection and febrile neutropenia were significant grade 3 or 4 adverse events. Also, in the evaluation of the same study made by Giagounidis et al.,[21] the most common grade 3–4 adverse event in patients treated with lenalidomide was myelosuppression. Grade 3–4 neutropenia was reported more frequently (75%) in patients treated with lenalidomide than in placebo group. So, infection (any grade) was reported in about 60 % in lenolamide groups and about 30% of patients in placebo groups. In this study, there were no treatment-related deaths because of neutropenic infection at variance with the study of List et al.[20] This difference was attributed to improved monitoring of neutropenia and management of febrile neutropenia, the dose reduction rules implemented, and possibly the use of G-CSF or GM-CSF. In the recent experience reported by Fenaux et al.[44] comparing the behavior of patients at different ages, the adverse events (AEs) in the ≥75 years group were compared with the <65 years group. The most common grade 3–4 AEs were neutropenia and thrombocytopenia. The incidence of grade 3–4 thrombocytopenia was significantly lower in patients aged <65 years than in patients aged ≥65 to <75 years. However, the incidence of grade 3–4 neutropenia was significantly lower in patients aged ≥75 years than in patients aged ≥65 to <75 years (p = 0.041). Dose reductions due to thrombocytopenia were more common in the ≥75 years group compared with that <65 years. G-CSF prophylaxis for neutropenia did not differ significantly across the age groups. The lower rates of neutropenia in the ≥75 years group may reflect the reduced total dose of lenalidomide in this age group rather than variations in G-CSF use. Although grade 3–4 neutropenia occurred less frequently in patients aged ≥75 years, infectious episodes were more common, a disparity possibly related to the known natural deterioration of the immune response in older individuals.[44]

Lenalidomide has also been utilized in patients with low-intermediate risk MDS without 5q deletion previously treated or not treated with ESA, with and without ESA.[29,45-47] The results are better if the patients were not previously treated or resistant to ESA.[29,36] Furthermore, the addition of ESA seems to improve the erythropoietic response.[45,46] Moreover in patients with non-del(5q) lower-risk MDS previously treated with ESAs, none of the most commonly used second-line treatments (demethylating agents and lenalidomide) improved OS.[47]

Also in these patients, lenalidomide, compared with placebo, was associated with a higher incidence of grade 3-4 treatment-emergent adverse events (TEAEs; 86% vs. 44%, and among them neutropenia was prevalent, 30%), but with not a

major risk of infection (p = .817). Only the frequency of pneumonitis could be major in patients treated with lenalidomide (5.6% vs. 2.5%).[48]

Low grade/intermediate risk MDS treated with Demethylating Agents. Azacytidine (AZA) and decitabine (DAC) are approved in the USA both for low Intermediate-1 as well intermediate-high risk MDS in Europe only for Intermediate-2 and high-risk MDS. In patients with low/intermediate risk, they have been utilized mostly as second-line therapy in patients primarily or secondarily resistant to ESA, and transfusion dependent (TD).[9,31,32,47,49,50] There are some difficulties in understanding the role of the demethylating agents in infections in this setting of patients. In fact, in the American literature, most trials reporting AZA or DAC experience include low-risk and high-risk patients without distinguishing the response and the side effects of the therapy in the two settings. Furthermore, in the abundant word literature is rare to find demethylating trials in which there is a control group treated with the supportive therapy only. So, even if there is concordance in finding that neutropenia is the most important hematological toxicity, hitting about 35% of all patients treated and that the infection is the main cause of death, it is difficult to understand how many patients acquired an infection because of the therapy, being evident that there is not, in MDS, a strict correlation between neutropenia and infections. The prospective phase II study of Tubiasson et al.[49] evaluated the efficacy of AZA in 30 patients with MDS low/intermediate risk, refractory to full-dose Epo+/-granulocyte colony stimulation factors for 48 weeks a and with a transfusion need of >4 units over eight weeks. AZA 75 mg/sqm days for 5 days each 28-day cycle, was given for six cycles; non-responding patients received another three cycles combined with Epo 60.000 units per week. The most important hematological toxicity was neutropenia. Nineteen patients suffered from severe neutropenia (ANC<$0.5x10^9$/L) at any time point during treatment, four of which were severely neutropenic before the treatment was started. The most commonly reported non-hematological adverse events were infections (n=30) and the related adverse events were neutropenic fever (n=12) and fever (n=6). Thirty-eight serious adverse events were reported in 18 patients during the study period. The main serious adverse event criterion (n=36) was in-patient hospitalization. The vast majority (n=28) of the serious adverse event was related to infection with or without neutropenia. Two patients died. Cause of death for the first patient is unknown; he suffered a sudden death after two cycles of AZA and had at the onset of the disease a moderate cytopenia aggravated during treatment. Cause of death for the second patient was septicemia with *Escherichia coli* during AZA-associated severe neutropenia. Authors conclude that AZA can induce transfusion independence (TI) in severely anemic MDS patients, but efficacy is limited, toxicity substantial and most responses of short duration. Thus, this treatment cannot generally be recommended in lower-risk MDS. The study of Fili et al[30] prospectively evaluated the efficacy and safety of AZA, administered at a lower cumulative monthly dose [5-days AZA (5d-AZA); 75 mg/sqm days for 5 days each 28-day cycle,], in 32 patients with IPSS low- or Int-1–risk MDS who were symptomatic and/or unresponsive to previous treatments. The overall response rate was 47% (15 of 32) on intention-to-treat and 58% (15 of 26) for patients completing the treatment program. In this latter group, 5 (19%) achieved complete remission (CR), and 10 (38%) had hematologic improvement, according to the International Working Group (IWG) criteria. Neutropenia, observed in 15 of 32 patients (47%), was the most common hematologic toxicity, and four patients died for infections and/or bleeding. In the experience of Sanchez-Garcia et al.,[50] 40 patients with MDS (IPSS score low or Int-1), with the absence of del5q, transfusion dependent (TD) anemia, and unresponsive to ESAs were assigned randomly to supportive therapy or to AZA 75mg/sqm, subcutaneously for 5 days of each 28-day cycle for nine cycles. Though the erythroid hematological improvement (HI-E) was confirmed in 44.4% of randomized to AZA and in 5.5% of patients receiving best supportive cure (p< .01), the event-free survival was not different between the two groups. Manageable hematological toxicity was seen in 52.2% of patients in AZA arm with seven patients experiencing severe AEs. In the BSC arm, eight patients also developed AEs related to the natural course of MDS. In particular, febrile neutropenia and/or pneumonia were reported in 22% of patients treated with AZA and

in 11% of those treated with supportive treatment only.

The patients with low-risk MDS can also respond to a low dose of demethylating agents. Jabour et al.[51] compared the safety and efficacy of low-dose DAC vs. low-dose AZA in this group of patients. Adults with low- or intermediate-1 risk MDS or MDS/myeloproliferative neoplasm (MPN), including chronic myelomonocytic leukemia, were randomly assigned using a Bayesian adaptive design to receive either AZA 75 mg/sqm intravenously/subcutaneously daily or DAC 20 mg/m2 intravenously daily for three consecutive days on a 28-day cycle. More myelosuppression was encountered in patients treated with DAC, resulting in cycle delays and dose reductions, however, the ORR was better in them, being 70% respect 49% in patients treated with AZA (P = .03). Cycle delays and dose reduction were required in 38% and 12% of patients treated with DAC and 20% and 5% of patients treated with AZA. The number of infections was not so different in the two groups. Infection or neutropenic fever occurred in 7% and 5% of patients treated with DAC and AZA, respectively.

A large cooperative study evaluated the outcome of low-risk MDS patients 5q-negative after the failure of ESA.[52] Out of 653 subjects failing or relapsing after ESA, 450 were treated with second-line therapy. Of them, 194 received hypomethylating agents (HMA), 148 lenalidomide and 108 another treatment. None of these treatments improved the overall survival significantly. In all three groups, the infections were the predominant cause of death, 26% in patients treated with HMA, 23% in those treated with lenalidomide and 22% in the third group. In conclusion at variance with high/intermediate-2 MDS patients with low-risk MDS, resistant to ESAs, do not have any advantage from demethylating agents, and probably the advantage in remission is counterbalanced by an increased rate of infections. The reduction of infections as a cause of deaths could be a way to improve the prognosis.

Intermediate 2 and High Risk MDS. The standard treatment for Intermediate 2 and high risk MDS is represented by the AZA and DAC.[53-56] The approval by the US Food and Drug Administration (FDA) of the hypomethylating agents (HMAs) AZA and DAC was made in 2004 and 2006, and by the European Medicines Agency (EMA) in 2009 and 2012 respectively. However, patients without comorbidities, particularly if young, can also be treated with intensive therapies, mainly to obtain a remission before being submitted to hematopoietic stem cell transplantation.[55] However recently, even AZA has also been utilized pre-transplant in order to achieve a remission or a hematologic improvement.[55,57] Only recently have been published some studies dedicated explicitly to infections in patients treated with AZA[58-65] or DAC.[67]

Patients treated with AZA. In the first trials demonstrating the superiority of the AZA in high risk MDS versus supportive therapy[53] or the best current therapy[54,55] it was shown a reduced or comparable rate of infections in the patients treated with AZA. In the Silverman et al.[53] experience, the rate of infection per patient-year was 0.64 in the AZA group and 0.95 in the observation group. Clinically significant infections were similar to the most common sites of infection (lung, urinary tract, and the bloodstream, skin) typically observed in patients with MDS, with no apparent increase in the AZA group. In the observation group, infection with pneumonia/sepsis was the cause of death in month 3 of one (2%) of the 41 observation patients who did not cross over during the study. Among 150 AZA-treated patients, infections were the cause of death in three patients (2%). In the trial of Fenaux et al.[54], the most common grade 3–4 events were peripheral blood cytopenias for all treatments. The rate of infections treated with intravenous antimicrobials per patient-year in the AZA group was 0·60 (95% CI 0·49–0·73) compared with 0·92 (0·74–1·13) in the conventional care group (relative risk 0·66, 95% CI 0·49–0·87; p=0·0032). The advantage of in term of infection of AZA respect to any other therapy was particularly evident in high risk MDS having a percentage of blasts between 20 and 30% in the bone marrow, and so classified at present as AML according to WHO.[66]

A few studies have been dedicated specifically to the incidence and risk factors of infections in patients treated with AZA.[8,58-66]

In the retrospective study of Merkel et al.,[8] aimed to evaluate the incidence and predisposing

risk factors for infections in AZA-treated, were included 184 patients [157 high-risk MDS and 27 AML, with a median age of 71.6], treated with AZA in 18 Israeli medical institutions between 2008 and 2011. Overall, 153 infectious events were reported during 928 treatment cycles administered to 100 patients. One hundred fourteen, (75%) events required hospitalization and 30 (19.6%) were fatal. In a univariate analysis, unfavorable cytogenetics, low neutrophil, hemoglobin and platelet counts were found to be associated with infections in multivariate analysis, only low Hb level, low PLT count, and unfavorable cytogenetics remained significant. Before therapy, poor cytogenetics, PLT count below 20 x 10^9/L and a neutrophil count below 0.5 x 10^9/L were predictive of the risk of infection during the first two cycles of therapy (**Table 2**). Infectious events were more frequent after doses of 75 mg/sqm for seven days than 75 mg/sqm for five days, regardless of the patient's age.[58] In this study, the causative pathogen was identified as bacterial in 25 (54.3%) and as viral or fungal in 2 (4.3%) and 2 (4.3%) cases, respectively. No pathogen was identified in 17 (37%) cases. Infections were significantly more prevalent among patients who presented with platelet counts < 20,000 (43.6% vs. 23.6%; P < .012) and poor risk cytogenetics (40.7% vs. 19.8%; P < .008). Patients treated with AZA who previously received intensive chemotherapy seem to be at the highest risk for fungal infection (invasive

Table 2. Risk Factors for infections in MDS High-risk. += risk factor; ± =no risk factor.

Risk Factors		**A U T H O R S**				
Male gender	± ± + ±	*Merkel (8)*	*Sullivan (9)*	*Lorenzana (63)*	*Ofran (58)*	
Age	± ± + ± +	*Merkel (8)*	*Sullivan (9)*	*Fenaux (43)*	*Lorenzana (63)*	*Shuck (59)*
High risk/ Blast count/ poor cytogenetics	+ + +	*Merkel (8)*	*Sullivan (9)*	*Trubiano (62)*	*Lorenzana (63)*	*Ofran (58)*
Neutropenia	+ + + ±	*Merkel (8)*	*Sullivan (9)*	*Lorenzana (63)*	*Ofran (58)*	
Thrombocytopenia	+ ± + ±	*Merkel (8)*	*Sullivan (9)*	**Ofran (58)*	*Stamatoullas. (61)*	
COPD	+	*Sullivan (9)*				
Comorbidities	+ ±	*Lorenzana (63)*	*Shuck (59)*			
Diabetes	±	*Sullivan (9)*	*Stamatoullas (61)*			
Hypoalbuminemia	+	*Stomatoullas (61)*				
Previous Chemotherapy	+ + ±	*Falantes (60)*	*Trubiano (60)*	*Stomatoulas.(61)*		
Hypomethylating agents	± ± +	*Silverman (53)*	*Fenaux (54)*	*Sanchez-Garcia (50)*		
Intensive Chemotherapy	++	*Fenaux (54)*	*Sullivan (9)*			
Iron Overload	+ + ± +	*Kontoyiannis (86)*	*Kanda (87)*	*Jacobi (91)*	*Leitch (36)*	*Lyons (40)*
Anemia/transfusion dependence	+ + + ±	*McQuilten (4)*	*Merkel (8)*	*Lorenzana (63)*	*Ofran (58)*	
Antimicrobial prophylaxis	+ + ± ±	*Lee (69)*	*Lorenzana (63)*	*Ofran (58)*	*Pomares (64)*	

Table 3. The rate of infections related to the number of cycles.

Author	**Patients treated**	**AZA N° Cycles**	**N° Infections, %**	**N° Deaths from Infections, %**
Merkel (8)	184	928	153 (16.48)	30(24.39)
*Lorenzana (63)	76	283	59 (20.08)	12 (20.33)
Trubiano (62)	68	884	124 (14.02)	16(12.90)
^Falantes (60)	64	523	72 (13.76)	2
Shuck (59)	77	614	81(13,19)	6 (7.79)
Ofran 1 (58)	106	106	36 (33.96)	
Ofran 2 (58)	67	67	10(14.9)	

*AML, Blasts>20%= 37 % . MDS patients had more infections but less total deaths than AML. ^AML 35%. AZA: Frontline 71.9 %; 28.1 % following Intensive Chemotherapy. Ofran 1. Standard dose AZA. Data regarding the first cycle only Ofran 2. Reduced dose AZA (5 days). Data regarding the first cycle only.

Aspergillosis); (p .015), so primary antifungal prophylaxis might be recommended in this group of patients.[60]

The importance of a previous therapy was not confirmed in a multivariate analysis by Stamatoullas et al.,[62] who found a major risk of infection in subjects with hypoalbuminemia and hypergammaglobulinemia. However, Trubiano et al., in a paper of 2017, report a retrospective review of patients receiving ≥1 cycle of AZA for MDS (49), or AML (19). Sixty-eight patients received 884 AZA cycles. Bacterial infections occurred in 25% of cycle-1 and 27% of cycle-2 AZA therapy. Febrile neutropenia complicated 5.3% of AZA cycles, bacteremia 2%, and invasive Aspergillosis 0.3%. Using Poisson modeling, a very high IPSS-R (RR 10.26, 95% CI 1.20, 87.41, p= .033) was identified as an independent risk factor for infection. Infection-related attributable mortality was 23%. In this series the burden of infection is high in AZA-treated patients and is associated with high attributable mortality. Over 25% of AZA cycles 1 and 2 were complicated by infection, predominantly bacterial, rates dropping to <10% after cycle-5 (**Table 3, Figure 1**). Among the microbiologically-confirmed infections were prevalent the bacteria (49) in this order *E. coli*, *Coagulase-negative Staphylococcus*, *Enterococcus spp*., *Staphylococcus aureus, Pseudomonas spp.*, *Clostridium difficile*, *Stenotrophomonas maltophilia*; and among the fungal infections *Aspergillus spp* was the most common. (**Table 4**)

Shuck et al.[59] of Dusseldorf group retrospectively evaluated the clinical course of 77 patients with MDS treated with AZA between 2004 and 2015 (median age 69 years). In total, 614 AZA cycles were administered, and 81 cycles with at least one infection complication (IC) were individuated. The median number of cycles was 6 (range 1–43). Median OS after the start of AZA was 17 months (range1–103). Infection rates were higher in the first 3 cycles with bacterial infections leading (**Table 3**), (**Figure 1**). The better patients' hematological response to AZA with less IC occurred, and fewer days with antimicrobial treatment were needed. Compared to progressive disease, the stable disease made no significant improvement in the occurrence of IC and days in the hospital. Older age was associated with more IC and longer time in the hospital. Comorbidities or IPSS-R did not influence IC. The incidence of IC correlated with hematological response and age. The stable disease led to longer OS, but the incidence of IC was comparable to progressive disease and survival seemed to be bought by a considerable number of IC. IC rates were highest in the first 3 cycles (**Figure 1** and **Table 3**).

Taking into account the high risk of infection bacterial and antifungal prophylaxis has been suggested in different protocols, but there is not a randomized trial demonstrating the utility of antibacterial and antifungal prophylaxis during AZA treatment. Lorenzana et al. compared in a retrospective, single-center study, the impact of prophylaxis on the incidence of infection and morbidity in all consecutive higher-risk MDS and AML patients, during the first 4 AZA cycles. Seventy-six patients, corresponding to 283 AZA cycles, were studied. Antimicrobial prophylaxis was administered in 117 cycles (41%). There were significant differences between the cycles with and without prophylaxis. Cycles with prophylaxis showed lower neutrophil counts and more severe disease characteristics. The majority of patients (75%) received combination therapy with quinolones and antifungals. There were infectious events in 43% of the patients. Globally, prophylaxis did not decrease the incidence of infection (17 vs 24%, p = 0.22). However, when only cycles starting with a neutrophil count below 0.5×10^9/L were analyzed, the incidence of infection was significantly lower (16 vs. 51%, p < 0.001). Risk factors for infection were neutropenia (OR 9.6 [2.63–34.7], p < 0.001) and comorbidity index (OR 1.62 [1.02–2.56], p = 0.003). Prophylaxis decreased the risk of infection (OR 0.13 [0.03–0.56], p = 0.006), with a significant interaction with neutropenia (OR 16.7 [2.5–109.8], p = 0.003). Median overall survival was comparable between patients with or without infections. However, the development of infections led to more hospital admissions, increased red blood cells and platelet requirements, and a delay in subsequent cycles. In the multivariate analysis, a neutrophil count below 0.5×10^9/L (OR 12.5 [2.6-50]) and antimicrobial prophylaxis (OR 0.1 [0.02-04]) were independent factors for the development of infection. Authors conclude that infectious events have a significant impact on the early clinical course of AZA-treated patients by increasing hospital admissions and transfusion requirements. Antimicrobial prophylaxis may prevent infections, leading to a decreased need for supportive care in these

Table 4. Microbiologically-confirmed infections during Azacytidine/Decitabine therapy according to different authors.

Authors	Sullivan (9)	Falantes (60)	Ofran (58)	Ali (69)	Trubiano (62)	Total
Isolations number	**109**	**17**	**22**	**91**	**68**	
Gram+	42		(?)	51	24	**117**
MRSA	16			2		18
Coag-neg. Staphylococ.	14	1		23	7	45
Staphylococcus aureus					4	4
Enterococcus spp	14			12	7	33
Bacillus spp.					1	1
Haemophilus influenzae					1	1
Clostridium difficile	7			3	3	
C. jekeium				5	1	6
Streptococcus spp.	4			4	1	9
Lactobacillus spp.				2		2
Gram-	47		**9**	**26**	**16**	**108**
Pseudomonas spp.	13		3	8	4	28
E. coli	14	7	3	6	7	37
Enterobacter spp.	4	1		2	2	9
S. maltophilia				4	3	7
Klebsiella Pneumonitis	7		3			10
B. fragilis				1		1
Achromobacter spp.				1		1
Citrobacter spp.				2		2
Other/not specified	9		9	1	9	**28**
Mycobacteria				2		
Fungal isolates	11	8	2	6	8	**34**
Candida	6	2		2		
Aspergillus spp.	3	5		1	5	
Fungal – mixed growth	2				2	
Mucormycosis				1	1	
Fusarium				1		
Pneumocystis jirovecii		1				
Parasitic					5	**5**
Viral	8		2	8	4	**22**

patients with poor outcome. On the contrary, Pomares et al.[64] found a very low risk of fungal infection in patients with high-risk MDS and AML treated with AZA, since the incidence rate of proven/probable invasive fungal infection (IFI) was 0.21% per treatment cycle and 1.6% per patient treated for the whole series, and 0.73% per treatment cycle and 4.1% per patient treated in those with severe neutropenia MDS. Therefore, they think that this very low risk of IFI does not justify the use of antifungal prophylaxis.

Patients treated with Decitabine (DAC). In the randomized trial[67] comparing low-dose DAC versus best supportive care in elderly patients with intermediate- or high-risk MDS ineligible for intensive chemotherapy grade 3 to 4 febrile neutropenia occurred in 25% of patients on DAC versus 7% of patients on BSC. Grade 3 to 4 infections occurred in 57% and 52% of patients on DAC and BSC, respectively. This trial did not demonstrate the superiority of DAC in overall survival; however, this treatment was associated with improvements in patient-reported quality-of-life (QOL) parameters. The type of infection found in 27 patients with MDS and 58 with AML (older or unfit) treated with DAC low dose ten days was investigated in a prospective clinical study of Washington University School of Medicine.[68] Prophylactic antimicrobial therapy was recommended, but not stipulated as part of the

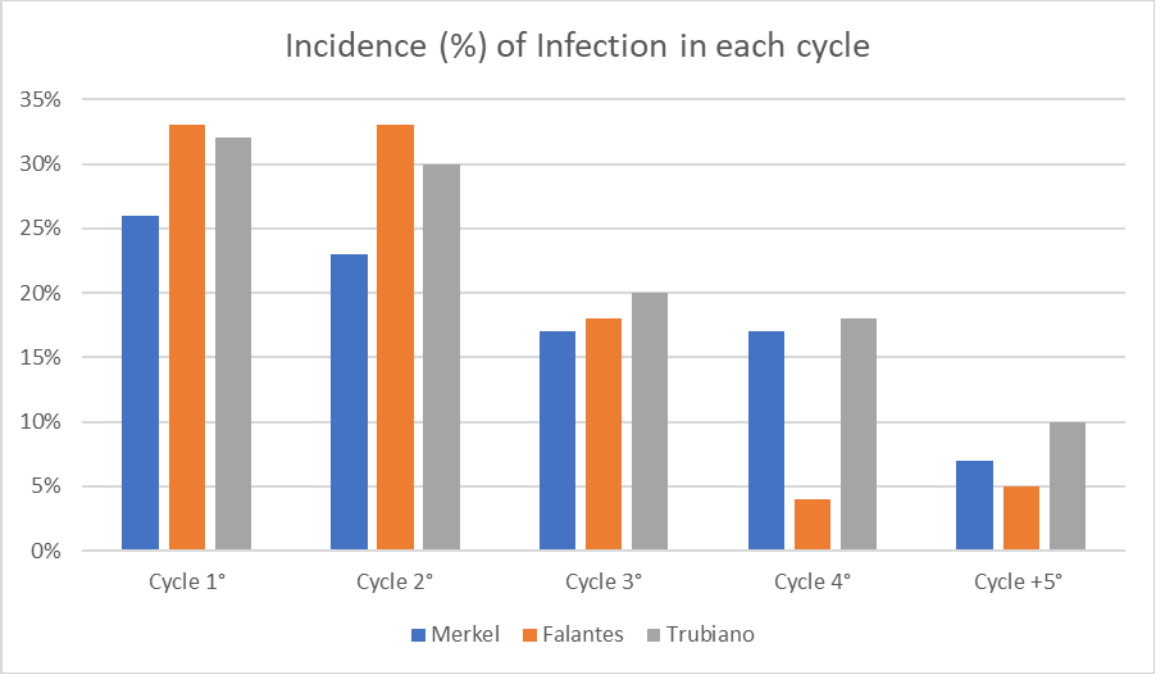

Figure 1. Incidence of infections in high risk MDS patients treated with azacytidine after the different cycles according to the articles of Merkel,[8] Falantes[60] and Trubiano.[62]

study. Recommended prophylaxis consisted of acyclovir, ciprofloxacin, and fluconazole Culture results were available for 163 infection-related complications that occurred in 70 patients. Ninety (55.2%) events were culture-negative, 32 (19.6%) were gram-positive bacteria, 20 (12.3%) were gram-negative bacteria, 12 (7.4%) were mixed, 6 (3.7%) were viral, 2 (1.2%) were fungal, and 1 (0.6%) was mycobacterial. Infection-related mortality occurred in 3/24 (13%) of gram-negative events, and 0/51 gram-positive events. (**Table 3**) On average, nearly one-third of patients experienced an infection-related complication with each cycle, and the incidence did not decrease during later cycles. In summary, in patients receiving 10-day DAC, infectious complications are common and may occur during any cycle of therapy. Although febrile events are commonly culture-negative, gram+ infections are the most frequent source of culture-positive infections, but gram-negative infections represent a significant risk of mortality in AML and MDS patients treated with DAC. Comparing the infections incidences, a higher incidence of infections was noted in MDS patients (96.3%) respect to AML patients (77.5%, P = 0.032). However, AML patients also had shorter survival compared with MDS patients.

The role of antibiotic prophylaxis during DAC treatment for MDS was studied in a group of 28 MDS patients treated with DAC in a University Hospital of Seoul (Korea).[69] The primary endpoint was the incidence of febrile episodes. The total number of DAC cycles given to 28 patients was 131, and febrile episodes occurred in 15 cycles (11.5%). Antibiotic prophylaxis was given orally in 95 cycles (72.5%). Febrile episodes were significantly less frequent among patients who received antibiotic prophylaxis (7.4%) than in those without prophylaxis (22.2%) (P = 0.017). Causative microbial agents were isolated in 6 cycles: methicillin-sensitive *Staphylococcus aureus* in 2 (blood in 1 and central venous catheter (CVC) in 1) and each one of *Staphylococcus epidermidis* (blood), *Klebsiella peumoniae* (urine), *Enterococcus faecalis* (urine), and *Stenotrophomonas maltophilia* (sputum) (**Table 4**). According to this report, antibiotic prophylaxis reduces the incidence of febrile episodes in patients who received DAC treatment for MDS, especially at earlier cycles and in the presence of severe cytopenia.[69]

Intensive Treatment. Like AML, high-risk MDS commonly require intensive chemotherapy to achieve disease complete remission. In the past high dose chemotherapy was the standard therapy for fit patients, with age <60.[70] The main cause of infections after intensive chemotherapy in both MDS and AML is the neutropenia, so in this circumstance, there is no a difference in prevention and treatment of infections between patients affected by MDS and AML.[70-74] It is

noteworthy that most of the fungal infections are reported in MDS patients with high blasts infiltration treated with intensive chemotherapy.[75] So the experiences with intensive therapy of patients with MDS or AML are frequently reported together, furthermore, before the WHO classification of 2008, the subjects with blast infiltration between 20 and 30% were classified in the MDSs.[76] However, the rate of the relapse of patients with MDS was very high, so, similarly to leukemia, trials were made utilizing intensive chemotherapy as a pre-transplant procedure followed by an allogeneic hematopoietic stem cell transplant (HSCT)[70,77] However, the pretreatment with high dose chemotherapy of patients with MDS entails a series of side effects, among them, infections are prevalent, which reduce the number of patients susceptible to stem cell transplantations.[77] Furthermore, the patients pretreated with chemotherapy have an overall survival similar to those transplanted upfront.[78,79] Therefore, even if the subjects in remission have a better prognosis, today the upfront transplant is preferred and the pretreatment with chemotherapy is suggested only in presence of a percentage of bone marrow blasts >10, when the reduced dose conditioning regimen is chosen.[80] To decrease the toxicity a reduced intensity conditioning (RIC) regimen is becoming more and more frequent,[80-82] even if a recent study of Seattle group[81] suggests that the eradicating regimen should be considered the standard. RIC has a higher relapse rate than standard conditioning but a lower the toxicity and non-relapse mortality.[80,81] Bacterial complications are more frequently observed in eradicating regimens, whereas no differences have been reported in CMV reactivation, EBV reactivation, or other viral o fungal infections.[81] According to some investigators the antifungal prophylaxis with fluconazole could be not necessary,[83] in patients treated with RIC but in general it is applied[82] and antifungal prophylaxis should be performed with posaconazole delayed-release tablets during remission induction chemotherapy.[84] Relapse rate is generally is higher in RIC regimens. Some particular risk factors for infection have been reported in the patients transplanted because of MDS. The Seattle group reported increased infection-related mortality in patients with MDSs with neutropenia < 1.5 x 10^9/L at baseline.[85] All patients included in this analysis received a myeloablative conditioning regimen. All patients were monitored for the onset of infections during the first 100 days after HSCT. Monitoring included bacterial and fungal blood cultures and chest radiographs when patients developed a fever (38.3 C°, orally). Additionally, all patients receiving >0.5 mg/kg of corticosteroid therapy were monitored with weekly bacterial and fungal blood cultures and chest radiographs. For *Pneumocystis jiroveci* prophylaxis all patients received trimethoprim/sulfamethoxazole as first-line therapy, dapsone as second-line therapy, from the time of engraftment until six months after HSCT or until six weeks after all immunosuppressive medications had been discontinued. All patients received fluconazole or itraconazole for prevention of candidiasis from the time of conditioning until day 75 after HSCT. Infections were considered causes of death when they occurred in the absence of GVHD, relapse, graft failure, and graft rejection. Overall, the neutropenic cohort had significantly increased rates of bacterial and fungal infections in comparison to non-neutropenic patients within the first 100 days after HSCT (rate ratio [RR] 1.59, P = .001 and RR = 2.89, P = .01, respectively). Most fungal infections were caused by the *Aspergillus* species (27 of 32), and the remaining fungal infections were because of *Candida glabrata* (2 of 32) and *Mucorales* spp. (3 of 32). The propensity for neutropenic patients to develop bacterial infections varied by type of organism. There was an increase in the rate of infections with gram-positive organisms but not with gram-negative rods. The increased rate of fungal and gram-positive bacterial infections among the neutropenic patients was most prominent more than 60 days after HSCT. The rate ratio for fungal infections remained unchanged after adjustment for aGVHD grades II-IV (RR 5 2.76, 95% confidence interval [CI] 1.1-6.7, P 5 .01), indicating there was no evidence of confounding by aGVHD. Another important risk factor advocated for an increased peritransplant mortality, and in particular due to the infections is the iron overload [86-91] The ferritinemia (SF) is considered the standard method for measuring iron overload. However, the optimal parameters and time points for the measurement of iron overload (IO) in allogeneic stem cell transplantation (ASCT) patients are still under discussion. Non-transferrin-bound iron (NBTI) could be a better marker to predict the effect for a higher risk of

bloodstream infections than SF, as well the superconducting quantum interference device (SQUID) biomagnetic liver susceptometry correlates with ferritinemia. and a significant association between SQUID, measured before HSCT and fungal infection was also found.[90,91]

Another possibility to improve the response to HSCT, reducing the toxicity and the infections associated with high dose chemotherapy, is the pretreatment of high risk MDs patients with demethylating agent.[92,93] At variance with intensive chemotherapy[77] pretreatment with demethylating agents does not reduce the number of patients susceptible to HSCT significantly.[92-94] In a recent trial Voso et al. for the Italian group GITMO demonstrate that HSCT is feasible after AZA in the majority of patients with HR-MDS/AML/CMML-2 (74% of subjects with donor enrolled in the trial). Causes of death in the non-HSCT group were disease progression or relapse (16 of 26 patients, 61.5%), followed by infectious (7 patients), and hemorrhagic complications (3 patients). Serious adverse events impeded HSCT in three patients and consisted of infection in two cases and an intra-abdominal hemorrhage in one patient. Mortality was transplant-related in 16 patients (30%, GVHD: 4 patients, infectious complication: 6 patients, multi-organ failure: 4 patients, other causes: 2 patients), disease relapse in 9 patients (17%), and second malignant disease in 1 patient. So, in this experience, the infections were the causes of deaths in 15 patients out of 97 patients enrolled. Similarly, in the more restricted pilot study of Tampa group (25 patients whom 21 transplanted), toxicities of 5-AZA treatment were low and included febrile neutropenia (5%), *Clostridium difficile* colitis (5%), nodular pneumonia (presumed fungal, 5%), perirectal abscess (5%), deep venous thrombosis (5%), and cerebrovascular accident (5%), without mortality. Causes of death of transplanted patients included four disease relapses, three infectious complications, and three with GVHD and infections. Central line-associated bloodstream infections commonly complicate the care of patients with AML and MDS after HSCT. However, you should distinguish between pathogens usually acquired following high dose chemotherapy because of disruption of mucosal barriers during the vulnerable neutropenic period, such as enteric gram-negative bacilli and *Streptococcus viridans*, that afterward localize in a central line, and pathogens which localized directly in the central line.[95] Although both types of central venous catheter (CVC) infection are characterized by a high rate of mortality (>70) the time of insurgency, the species of bacteria and fungus are different, and so should be the modality of prevention.[95]

Conclusions. Infections remain a major problem in MDSs and assume a particular complexity. In fact, MDS include a heterogeneous group of patients with very different prognosis, different therapy and different risk factors regarding survival and infections. About this last point, we should distinguish risk factors related to the disease, like as neutrophils function impairment, neutropenia, unfavorable cytogenetics and bone marrow insufficiency; factors related to the patient, like as age and comorbidities, factors related to the therapy. When the patients with MDS are submitted to intensive chemotherapy with and without HSCT, they have a risk factor for infection very similar to that of patients with AML. The age and comorbidities should be considered the most important risk factor, and you should follow the same guideline for the acute myeloid leukemia patients. Patients with MDS treated with supportive therapy only or with demethylating agent or lenalidomide or immunosuppressive drugs should have a tailored approach. Considering that most (about 80%) of the infections in MDS originate from bacteria, and the major risk factors are represented by neutropenia, thrombocytopenia and unfavorable cytogenetics, it is reasonable to give an antibacterial prophylaxis in patients who start the therapy with demethylating agents with a number of neutrophils <500, or with thrombocytopenia and unfavorable cytogenetics. This recommendation is imperative in the first cycles of therapy during which the infections are more frequent. The antifungal prophylaxis is not considered cost/benefit adequate and should be taken into consideration only when there is an antecedent fungal infection or presence of filamentous fungi in the surveillance cultures. Subjects submitted to immunosuppression with ATG+CSA have a high number of infections, although there are no guidelines we think that they should be treated like with aplastic anemia. Therefore, patients who are severely neutropenic should ideally be nursed in isolation when in

hospital, and likely, should be given prophylactic antibiotics and antifungals, regular mouth care including an antiseptic mouthwash (such as chlorhexidine or saline). Prophylactic antibiotics, either two non-absorbable (e.g., colistin and neomycin) or quinolones (e.g., ciprofloxacin), may be initiated but the preference should be according to local policy. A mold-active azole, preferably itraconazole or posaconazole, should be used as prophylaxis, in the presence of positive surveillance cultures. The use of lenalidomide, although can give neutropenia, which in general is not durable, does not increase the infection rate.

An unresolved problem is how to prevent infections in low-risk MDS on no therapy or supportive therapy. Patients with MDS low-risk transfusion dependent frequently have iron overload and are more at risk of infection. Chelating agents can reduce iron overload and so probably increase the overall survival. However, no convincing data are demonstrating a decrease of infections after chelation therapy also in the presence of a decrement of ferritin level. Pharmacological enhancement of some neutrophil functions is possible and could be a new tool to reduce infections.

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