PMB definition guideline for

Myelodysplastic Syndromes (MDS)

Version 1

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Disclaimer:

The Myelodysplastic Syndromes (MDS) benefit definition guideline has been developed for majority of standard patients and is aligned with best practice. These benefits may not be sufficient for outlier patients. Therefore, regulation 15h may be applied for patients who are inadequately managed by the stated benefits. The benefit definition does not describe specific in-hospital management such as theatre, anaesthetist drugs and supportive medication. However, these interventions form part of care and are Prescribed Minimum Benefits. Supportive medication for all haematology oncology conditions is detailed in a separate guideline available here.

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Table of Contents

Abbreviations

PMBs	Prescribed Minimum Benefits
DTPs	Diagnosis Treatment Pairs
MDS	Myelodysplastic Syndromes
AML	Acute Myeloid Leukaemia
WHO	World Health Organization
HIV	Human Immunodeficiency Virus
FBC	Full Blood Count
LDH	Lactate Dehydrogenase
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
INR	International Normalized Ratio
LFT	Liver Function Test
HLA	Human Leukocyte Antigen
HSCT	Haemopoietic Stem Cell Transplantation
ATG	Anti-thymocyte Globulin

1. Introduction

1.1. The legislation governing the provision of the Prescribed Minimum Benefits (PMBs) is contained in the Regulations enacted under the Medical Schemes Act, No. 131 of 1998 (the Act). With regards to some of the Diagnosis Treatment Pairs (DTPs), medical scheme beneficiaries find it difficult to be fully aware of their entitlements in advance. In addition, medical schemes interpret these benefits differently, resulting in a lack of uniformity of benefit entitlements.

1.2. The benefit definition project is undertaken by the CMS with the aim of defining the PMB package, as well as to guide the interpretation of the PMB provisions by relevant stakeholders.

2. Scope and purpose

2.1. This is a recommendation for the diagnosis, treatment and care of individuals with Myelodysplastic Syndromes (MDS) in any clinically appropriate setting as outlined in the Medical Schemes Act.

2.2. The purpose is to provide detailed clarification in respect of benefits and entitlements to members and beneficiaries of medical schemes.

Table 1: Possible ICD10 codes for patients with MDS in the curative and palliative setting

DTP code	ICD 10 code	ICD10 code description
901S	D46.0	Refractory anaemia without ring sideroblasts, so stated
901S	D46.1	Refractory anaemia with ring sideroblasts
901S	D46.2	Refractory anaemia with excess of blasts
901S	D46.3	Refractory anaemia with excess of blasts with transformation
901S	D46.4	Refractory anaemia, unspecified
901S	D46.5	Refractory anaemia with multi-lineage dysplasia
901S	D46.6	Myelodysplastic syndrome with isolated del(5q) chromosomal abnormality
901S	D46.7	Other myelodysplastic syndromes
901S	D46.9	Myelodysplastic syndrome, unspecified

3. Classification and description of MDS

MDS represents a myeloid clonal haemopathy with a relatively heterogeneous spectrum of presentation. The major clinical problems in these disorders are morbidities caused by cytopaenias and the potential for MDS to evolve into acute myeloid leukaemia (AML). The World Health Organization (WHO) 2016 classification for MDS identifies six subtypes of MDS:

i. MDS with single lineage dysplasia (MDS-SLD)
ii. MDS with ring sideroblasts (MDS-SR)
iii. MDS with multilineage dysplasia (MDS-MLD)
iv. MDS with excess blasts (MDS-EB)

v. MDS with isolated del(5q) +/- one other abnormality.
vi. MDS unclassifiable (MSD-U)

2016 WHO CLASSIFICATION OF MDS[a,b,1]

Subtype	Blood	Bone Marrow
MDS with single lineage dysplasia (MDS-SLD)[c]	Single or bicytopenia	Dysplasia in ≥10% of one cell line, <5% blasts[d,2]
MDS with ring sideroblasts (MDS-RS)	Anemia, no blasts	≥15% of erythroid precursors w/ring sideroblasts, or ≥5% ring sideroblasts if *SF3B1* mutation present
MDS with multilineage dysplasia (MDS-MLD)	Cytopenia(s), <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in ≥2 hematopoietic lineages, <15% ring sideroblasts (or <5% ring sideroblasts if *SF3B1* mutation present), <5% blasts
MDS with excess blasts-1 (MDS-EB-1)	Cytopenia(s), ≤2%–4% blasts, <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, 5%–9% blasts, no Auer rods
MDS with excess blasts-2 (MDS-EB-2)	Cytopenia(s), 5%–19% blasts, <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, 10%–19% blasts, ± Auer rods
MDS, unclassifiable (MDS-U)	Cytopenias, ±1% blasts on at least 2 occasions	Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, <5% blasts
MDS with isolated del(5q)	Anemia, platelets normal or increased	Unilineage erythroid dysplasia, isolated del(5q), <5% blasts ± one other abnormality except -7/del(7q)
Refractory cytopenia of childhood (Provisional WHO category)	Cytopenias, <2% blasts	Dysplasia in 1–3 lineages, <5% blasts

4. Epidemiology

4.1. Myelodysplastic syndromes (MDS) are clonal haemato-poietic stem cell disorders predominating in the elderly, characterised by ineffective haematopoiesis leading to blood cytopenias and progression to acute myeloid leukaemia (AML) in one-fourth to one-third of cases (Adès et al., 2014)

4.2. MDS is rare among children/adolescents and young adults, with an incidence rate of 0.1 per 100,000 people per year in those younger than 40 years of age, however, among individuals between the ages of 70 and 79 years, the incidence rate increases to 30.2 per 100,000 people, and further to 59.8 per 100,000 people among those 80 years of age and older (National Cancer Institute, 2016).

4.3. The South African National Cancer Registry does not report on the incidence of MDS, probably because it is considered a pre-leukaemia condition.

4.4. There are no known ethnic differences in the incidence of MDS; but in Asian populations, MDS tends to occur at an earlier age. Trisomy 8 also seems to occur more frequently in Asian populations compared with Western populations (Miyazaki et al., 2018).

4.5. The aetiology of MDS is only known in 15% of the cases. Environmental factors include previous exposure to chemotherapy, especially alkylating agents and purine analogues, radiotherapy or ionising radiation and tobacco smoking. Recognised occupational factors include benzene and its derivatives, and more cases of MDS are reported among agricultural and industrial workers (Fenaux et al., 2020).

5. Diagnostics and work up

5.1. Pathology work up

5.1.1. The evaluation and initial workup for suspected MDS consists of a comprehensive medical history, physical examination and a comprehensive range of laboratory investigations.

5.1.2. To establish the diagnosis of MDS, careful morphological review and correlation with the patient's clinical features are important, because a number of medications and viral infections (including HIV infection) can cause morphological changes in the marrow cells which are similar to MDS (Greg et al. 2002; Koca et al. 2008).

5.1.3. The following are PMB level of care (Fenaux et al., 2020):

- Full blood count (FBC), platelets, differential count, reticulocyte count, uric acid
- Lactate dehydrogenase (LDH)
- Examination of peripheral smear
- Serum erythropoietin level
- Partial thromboplastin time (PTT), Fibrinogen, international normalized ratio (INR)/ Prothrombin time (PT)
- Urea and Electrolytes (U&E)
- Full liver function tests (LFT)
- Cytogenetic analysis
- Molecular analysis
- Other viral studies (HIV, hepatitis B & C)
- Pregnancy test- where appropriate
- Iron studies, Vitamin B12, Folate
- Calcium, Magnesium, Phosphate
- Uric acid
- Glucose
- TSH, T4
- Human leukocyte antigen (HLA) typing for patient with potential haemopoietic stem cell transplantation (HSCT)

5.2. Histopathology

5.2.1. Molecular and cytogenic studies, flow cytometry and bone marrow aspirate with iron stain and bone marrow trephine biopsy are PMB level of care (Bellos & Kern, 2017; NCCN, 2021).

5.2.2. Flow cytometry – consideration should be given to obtain flow cytometry testing at initial evaluation of MDS to include antibody combinations to characterise blasts and to identify abnormal lymphoid populations, which may mimic blasts leading to erroneous myeloblast quantitation (Bellos & Kern, 2017).

6. Prognostic classification

6.1.1. Diagnostic criteria allow for categorisation of patients with MDS, however the highly variable clinical outcomes within these subgroups indicate prognostic limitations.

6.1.2. The morphological features contributing to this variability include the wide range of marrow blast percentages for patients with MDS, marrow cytogenetics, and the degree and number of morbidity-associated cytopenias (NCCN, 2021).

6.1.3. This has led to development of prognostic scoring systems, namely:

- **International prognostic scoring system (IPSS)**- To develop the IPSS for MDS, relative risk scores for each significant variable (marrow blast percentage, cytogenetic subgroups and number of cytopenias) were generated (Greenberg, 1997). By combining the risk scores for the three major variables, patients were stratified into four risk groups in terms of both survival and AML evolution: low, Intermediate-1, Intermediate-2 and high.

- **International prognostic scoring system – revised version (IPSS-R)** – refined the original IPSS by incorporating cytogenetic subgroups, separate subgroups for marrow percentage, and a depth of cytopenias measurement defined with cut-offs for hemoglobin levels, platelet counts and neutrophil counts (Schanz et al. 2012). The IPSS-R comprises of five risk groups: very low, low, intermediate, high and very high (Greenberg et al. 2012). Other parameters including age, performance status, serum ferritin, LDH and beta-2-microglobulin provided additional prognostic information for survival outcomes (Greenberg et al. 2012).

- **WHO Prognostic Scoring System (WPSS)**- World Health Organisation (WHO) classification-based prognostic scoring system incorporates the WHO morphologic categories, the IPSS cytogenic categories and the degree of RBC transfusion dependence (Malcovati et al. 2007). As with the revised IPSS-R, the WPSS also classifies patients into five risk groups differing in both survival and risk of AML. The five risk groups are: very low, low, intermediate, high, and very high. WPSS provides dynamic estimation of prognosis at any time during the course of MDS.

6.1.4. IPSS or IPSS-R risk categories are used in the initial planning of therapeutic options because they provide a risk-based patient evaluation (NCCN, 2021).

6.1.5. The South African guidelines stratified patients based on the older version of IPSS and acknowledged that at the time both the IPSS and WPSS were being revised (Louw et al., 2011).

7. Management of myeloproliferative neoplasms

7.1. Treatment is tailored depending on the risk factors. In patients identified as low risk, the treatment is aimed at haematological improvement and, for high-risk patients, the goal of therapy is to limit disease progression and improve survival. Supportive care, low intensity therapy, high intensity therapy, biological response modifiers, immunosuppressive therapy (IST) and stem cell transplant are recommended for MDS.

7.2. It is important for the users of this guideline to acknowledge that the management of MDS is complex and therefore the choice of treatment is at discretion of the treating provider as several factors are considered prior to initiating treatment.

7.3. The following is a list of recommendations for PMB level of care for MDS patients.

- Anti-thymocyte globulin (ATG)
- Cyclosporin
- Cytarabine
- Fludarabine
- Hydroxyurea
- Idarubicin
- Thalidomide analogues
- Erythropoiesis-stimulating agents (ESAs)
- Granulocyte-colony stimulating factor (G-CSF)
- Hypomethylating agents – for high risk patients

Lower-risk (IPSS-R very low, low and some intermediate risk)

7.4. In lower risk MDS, the risk of AML progression is lower, and the main priority is the treatment of symptomatic thrombocytopaenia, symptomatic neutropaenia, symptomatic anaemia and moderate and asymptomatic cytopaenias (Fenaux et al., 2021; Greenberg et al., 2000; Louw et al., 2011).

7.5. Supportive care, including the management of anaemia for MDS patients is PMB level of care. Guidance on supportive care is detailed in a separate document available here.

7.6. The 2011 South African guidelines included ESAs, G-CSF and IST for management of lower risk MDS (Louw et al., 2011).

7.7. ESAs are PMB level of care and the first-choice treatment of anaemia in lower-risk MDS without del(5q). There are no data showing that one ESA is superior to another, however, the efficacy of ESAs can be improved by using them in combination with G-CSF (Louw et al., 2011; Fenaux et al., 2021)

7.8. The South African guidelines, in alignment with international guidelines, recommend the use of lenalidomide in patients with del 5q (Fenaux et al., 2021; NCCN, 2021; Louw et al., 2011). Thalidomide is currently listed as an EML option, and not its analogue, lenalidomide. There have been considerable price reductions of lenalidomide, and schemes are encouraged to consider funding lenalidomide when deemed cost-effective.

7.9. In patients not responding to ESA and G-CSF, the South African guidelines include hypomethylating agents, IST, a clinical trial or allogeneic HSCT in selected patients (Louw et al., 2011).

7.10. Hypomethylating agents, namely azacitidine, has shown evidence of improved overall survival and an increase in the time to progression to AML. The benefits were apparent in subgroups who had unfavourable karyotypes. Although Azacitidine is not currently listed on the EML, there has been considerable price reductions and the availability of lower cost generics. Schemes are encouraged to consider funding azacitidine in the high- risk patients.

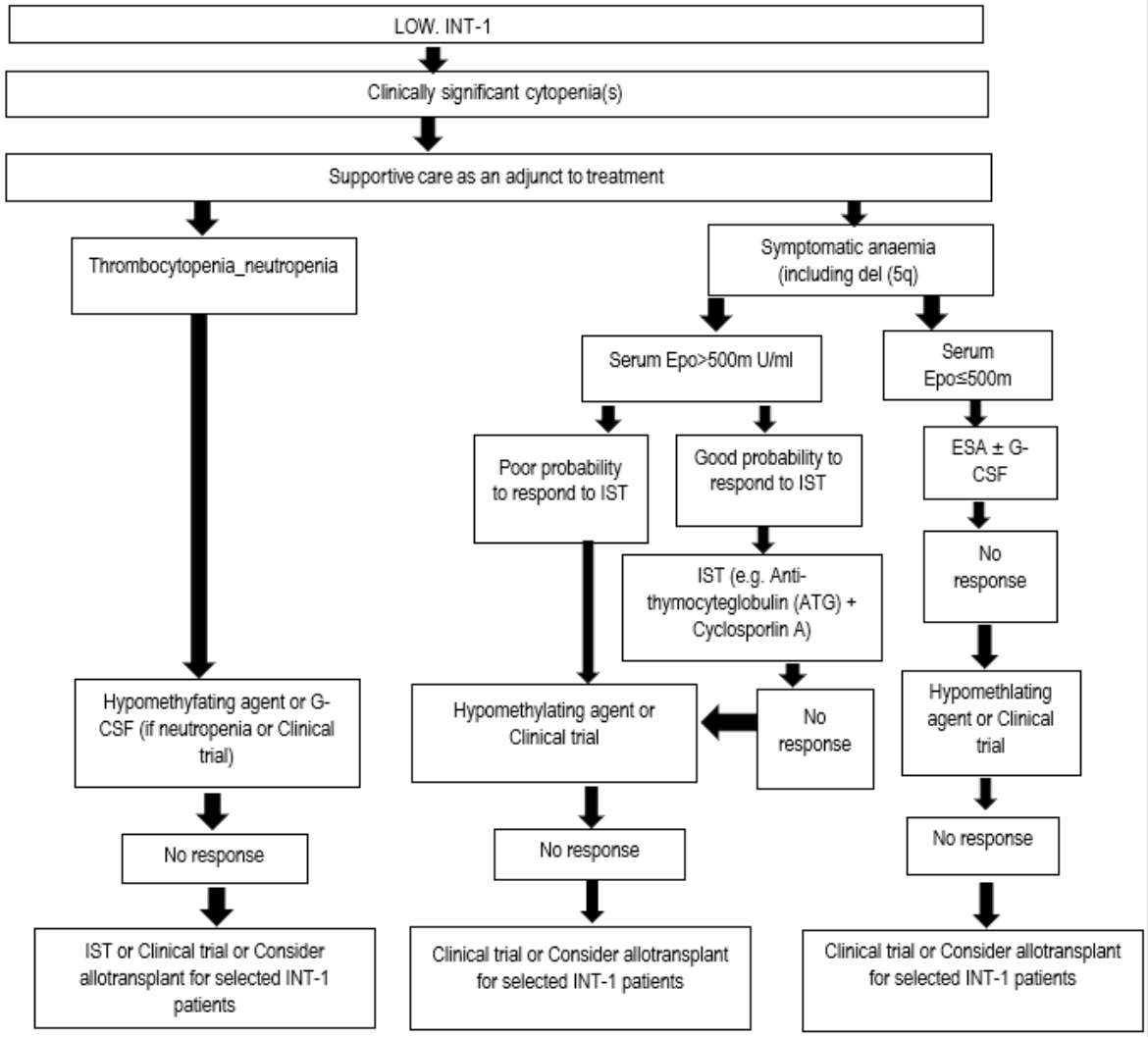

Figure 1: Algorithm for the management of the IPSS Categories LOW and INT-1.

ESA: Erthropiesis- stimulating agents
G-CSF: Granulocycle- colony stimulating factor
Epo: Erythropoietin
IST: Immunosuppresive therapy

Higher-risk MDS (IPSS-R very high-, high- and some intermediate-risk)

7.11. Higher-risk MDS carries a major risk of progression to AML and short survival, and treatment is aimed at modifying the disease course.

7.12. Based on the South African guidelines, therapeutic options for higher-risk patients include allogeneic HSCT, high-intensity therapy, low-dose chemotherapy, hypomethylating agents, and supportive care (Louw et al., 2011).

7.13. Intensive therapy (anthracyclines and cytarabine combinations) is usually limited to patients less than 65 years of age with more favourable karyotypes and no allogeneic stem cell donor. In patients with

unfavourable karyotype, hypomethylating agents are preferred. In older patients, azactidine is the treatment of choice (Louw et al., 2011, Fenaux et al., 2010).

7.14. As stated above in 7.10, azacitidine is recommended as PMB level of care for the high risk patients.

7.15. Treatment options for patients who are not candidates for intensive therapy are like those in low-risk patients, being azacitidine-based regimens, supportive care, low-dose cytarabine and participation in clinical trials (Louw et al., 2011). See diagram below from the South African guidelines:

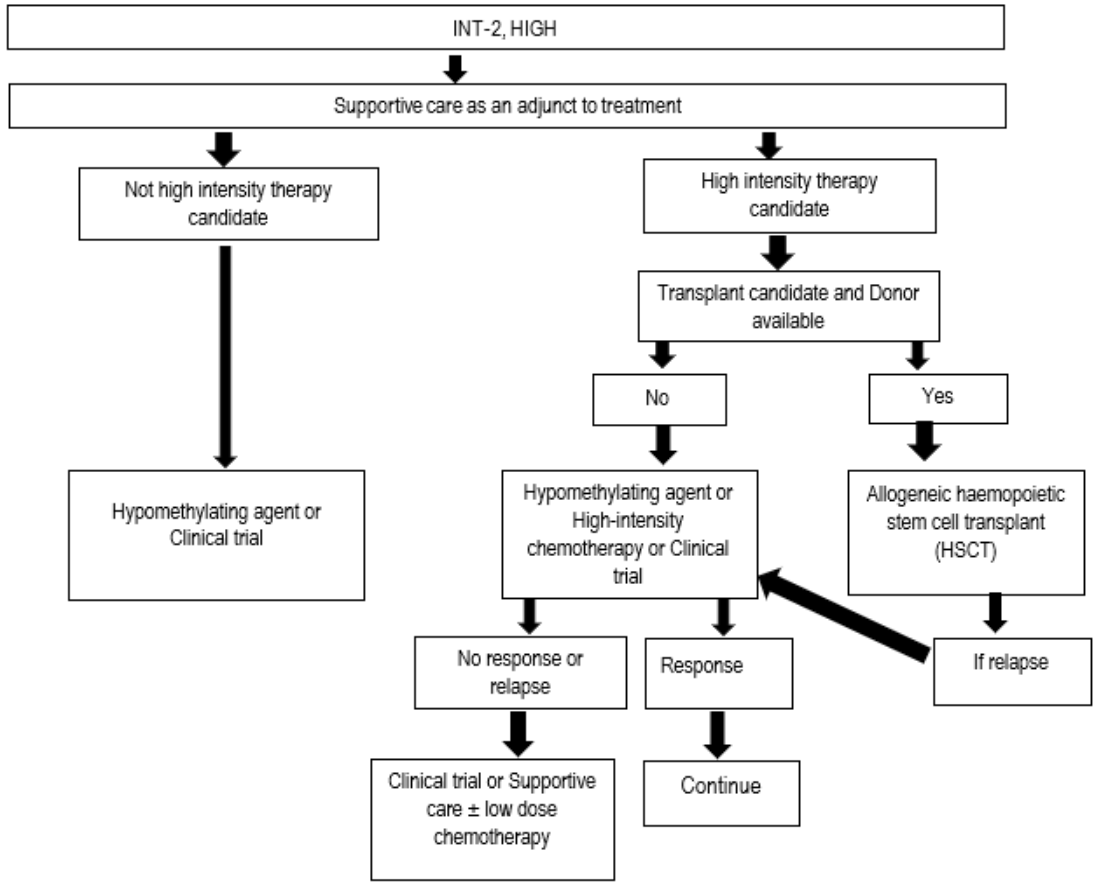

Figure 2: Algorithm for the management of the IPSS Categories INT-2 and HIGH.

8. Transplant

8.1. The only treatment associated with possible cure is allogeneic HSCT. However, it is associated with significant morbidity and mortality requiring careful selection of eligible patients (Fenaux et al., 2021).

8.2. Factors that influence the decision of allogeneic HSCT include patient age, performance status, absence of major co-morbid conditions, psychological status and the availability of an HLA-matched donor (Louw et al., 2011).

8.3. HSCT from an HLA-matched sibling, matched unrelated or alternative (including haploidentical or cord blood) donor is a preferred approach for treating select patients particularly those with high-risk disease (Luznik et al., 2008; Scott et al., 2006; Wallen et al., 2005). Allogenic HSCT is PMB level of care for eligible patients.

8.4. In patients who relapse after a prolonged remission following the first transplant, a second transplant may be considered.

8.5. The following medicines are PMB level of care for transplant:

- Fludarabine
- Busulfan
- Cyclophosphamide
- Anti-thymocyte globulin (ATG)
- Melphalan
- Cyclosporin
- Tacrolimus
- Methotrexate
- Etoposide
- Thalidomide
- Imatinib
- Ruxolitinib – indicated as 2nd line for graft vs host disease

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