

## ***Understanding the Different Types of Myelodysplastic Syndromes (MDS)***

### **Introduction**

MDS is a group of disorders where your bone marrow does not work well, and the bone marrow cells fail to make enough healthy blood cells. People with MDS may not have the right amount of red blood cells, white blood cells, and platelets.

In patients with MDS many bone marrow cells do not develop into working blood cells. Instead, many of these cells die off in the bone marrow. This is why blood cell counts tend to be low in patients with MDS. The symptoms and the course of MDS may vary greatly from person to person. These differences depend on which blood cells are affected.



There are many different subtypes of MDS. Doctors use two different but related systems to classify the types of MDS. These systems give you and your doctor important information about your specific case. These two classification systems are:

1. French-American-British (FAB) Classification System
2. World Health Organization (WHO) Classification System

Doctors have also created a scoring system to help them understand how a patient's MDS is likely to progress over time. It is called the International Prognostic Scoring System, or IPSS for short.

Together, the classification systems and the scoring system help your doctor know:

- How serious your case is
- How long patients in your situation are likely to live
- What you can expect from MDS over time
- Which treatments are best for now, and at what point you should think about changing treatments

This reference summary explains the two systems for classifying MDS and the scoring system. It will help you understand the classification and scoring systems better.

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## History of MDS Classification

Before 1976, the term “MDS” didn’t exist. Doctors and scientists used other names for what we now call MDS. At that time, there was no standard way to split MDS into subtypes.

In 1976, scientists came out with the first system for classifying MDS into subtypes. This system is called the French-American-British or FAB classification system. It is based on how blood and bone marrow cells look.

In 1997, the International Prognostic Scoring System or IPSS was launched. This system turns patient data into a score. The score tells how quickly an MDS case is likely to progress and helps predict what may happen with the patient’s MDS in the future.

In 1999, the World Health Organization, or WHO, published a new classification system. This classification system was then revised in 2008. Its goal was to be more specific than the FAB in describing subtypes and in predicting what will happen to patients. This system is based on patient data from around the world and on the most up-to-date knowledge of MDS.



## FAB (French-American-British) Classification System

The FAB classification system is older than the WHO classification system. However, the FAB classification system is still used by some doctors today.

The FAB classification system is based on 4 main factors:

- The percentage of blast cells in the bone marrow.  
Blasts are the youngest or most immature white blood cells. In normal bone marrow, no more than 5 out of 100 white cells are blasts.
- The percentage of peripheral blood blasts. This is the percentage of blasts in the blood that is circulating in the body.
- The percentage of red blood cell precursors with abnormal iron deposits called ring sideroblasts which are very young red blood cells that have ring-shaped iron deposits in them
- The percentage of monocytes in the blood which are a type of white blood cell.

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The FAB system divides MDS into 5 subtypes. These subtypes include:



- Refractory anemia, also called RA
- Refractory anemia with ring sideroblasts, also called RARS
- Refractory anemia with excess blasts, also called RAEB
- Refractory anemia with excess blasts in transition, also called RAEB-t
- Chronic Myelomonocytic Leukemia, or CMML

The next few pages discuss the FAB system's 5 different sub-types.

The first FAB system subtype is refractory anemia, or RA for short. The RA subtype is diagnosed if:

- The number of blast cells in the blood are less than 1 percent
- The number of bone marrow blasts are less than 5 percent
- The percentage of ring sideroblasts in the bone marrow is less than 15 percent
- The number of blood monocytes is less than 1000 per milliliter



Blasts Cells in Blood		<1 out of 100
Bone Marrow Blasts		<5 out of 100



Ring Sideroblasts		<15 out of 100
Blood Monocytes	 x1000	<10000/mL

The second subtype is Refractory Anemia with Ring sideroblasts, or RARS for short.

This subtype is diagnosed if:

- There are less than 1 percent blast cells in the blood
- The number of bone marrow blasts are less than 5 percent
- More than 15 percent of young red blood cells in the bone marrow are ring sideroblasts
- The number of blood monocytes is less than 1000 per milliliter



Blasts Cells in Blood		<1 out of 100
Bone Marrow Blasts		<5 out of 100

Ring Sideroblasts		>15 out of 100
Blood Monocytes	 x1000	<10000/mL

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The third FAB system subtype is called Refractory Anemia with Excess Blasts, or RAEB for short. This subtype is diagnosed if:

- There are less than 5 percent blasts in the blood
- There are between 5 and 20 percent blasts in the bone marrow

Blasts Cells in Blood		<5 out of 100
Bone Marrow Blasts		5-20 out of 100




The fourth subtype is called Refractory Anemia with Excess Blasts in Transformation, or RAEB-t for short. This subtype is diagnosed if:

- There are between 5 and 20 percent blast cells in the blood
- There are between 21 and 30 percent blasts in the bone marrow

Blasts Cells In Blood		5-20 out of 100
Bone Marrow Blasts		21-30 out of 100

The final FAB system subtype is called Chronic Myelomonocytic Leukemia or CMML for short. This subtype is diagnosed if:

- There are fewer than 5 percent blasts in the blood
- More than 1,000 monocytes per cubic millimeter are in the blood
- There are between 0 and 20 percent blasts in the bone marrow

<5	
>1000	
0-20	

### WHO (World Health Organization) Classification System

The WHO classification system builds and expands on the older FAB system. It divides MDS into 7 subtypes based on tests of the blood and bone marrow. To help you understand the different subtypes we will first list the subtypes and then go into each in more detail. These seven subtypes include:

1. Refractory cytopenia with unilineage dysplasia. This includes refractory anemia or RA subtype, refractory neutropenia or RN subtype, and refractory thrombocytopenia or RT subtype. Dysplasia is when blood cells have an abnormal size, shape, or look.
2. Refractory anemia with ring sideroblasts or RARS
3. Refractory cytopenia with multilineage dysplasia or RCMD
4. Refractory anemia with excess blasts type 1 or RAEB-1
5. Refractory anemia with excess blasts type 2 or RAEB-2



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- 6. MDS with isolated deletion 5q
- 7. MDS unclassified

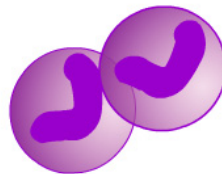
The next few pages show the different subtypes along with their related blood and bone marrow findings.

The first subtype listed in the WHO classification system is refractory cytopenia with unilineage dysplasia. If you have this type of MDS your blood tests will show a low blood cell count for one or two types of blood cells.

- If you have low red cell counts this is called refractory anemia, or RA for short.
- If you have a low white cell count this is called refractory neutropenia, or RN for short.
- If you have a low platelet count this is called refractory thrombocytopenia, or RT for short.



Red Blood Cells




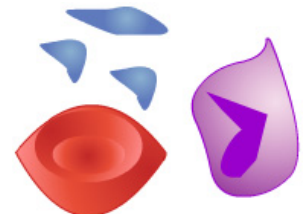
White Blood Cells



Platelets

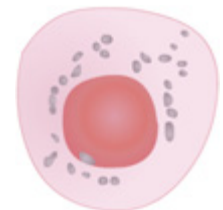
With RA, RN and RT your bone marrow tests will show that your bone marrow has less than 5 percent of very immature white blood cells, also called blasts. You will also have blood cells with an abnormal size, shape, or look. This is called dysplasia.

Blasts	<5/100
	<5 out of 100



Dysplasia

The second subtype is refractory anemia with ring sideroblasts, or RARS for short. Just like the RA subtype, your bone marrow tests will show that your bone marrow has less than 5 percent blasts. You will also have blood cells with an abnormal size, shape, or look called dysplasia. In RARS, however, more than 15 percent of the red blood cells are red blood cells with ring-shaped iron deposits in them.




Ring Sideroblast


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These cells are called ring sideroblasts. A special stain for iron needs to be performed on your bone marrow to see these iron deposits.


The third MDS subtype is called Refractory Cytopenia with Multilineage Dysplasia, or RCMD for short. You can have RCMD with or without ring sideroblasts. Blood tests show that patients with RCMD have either a low white blood cell count, or a low platelet count. People with RCMD also have bone marrow test results that show dysplasia in more than one cell type. Their bone marrow will contain less than 5 percent blasts. In people with more than 15 percent ring sideroblasts, the subtype is called RCMD-RS.

Blasts	<5/100
	<5 out of 100

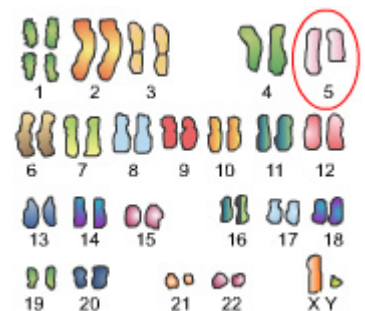
The fourth MDS Subtype listed in the WHO classification system is Refractory Anemia with Excess Blasts 1, also called RAEB-1. If you have RAEB-1 your blood test results will be similar to someone with RA. The difference between RA and RAEB-1 is in the bone marrow test results. RAEB-1 bone marrow test results show 5 percent to 9 percent blasts in the marrow.

Blasts	5-9/100
	5 out of 100 to 9 out of 100

The fifth subtype is called Refractory Anemia with Excess Blasts 2, or RAEB-2 for short. The blood results for this subtype are similar to the RA and RAEB-1 blood test results. However, the bone marrow tests show 10 percent to 19 percent blasts in the marrow.

Blasts	10-19/100
	10 out of 100 to 19 out of 100

The sixth MDS Subtype from the WHO system is called MDS with isolated deletion 5q. In this subtype the blood test results are similar to the RA subtype, but may include normal or high platelet counts. The cytogenetic testing done on bone marrow will show a loss of part of the long arm of chromosome 5, with no other chromosome abnormalities. Cytogenetic testing is the study of the chromosomes inside the nucleus of the cells.



Chromosomes

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Doctors do cytogenetic testing to look for changes in number or structure of chromosomes.

MDS with isolated deletion 5q subtype is more common in women age 65 and older who have mild to moderate degrees of anemia, low white blood cell counts, and normal to high platelet counts.

The final MDS Subtype is called Unclassified MDS. Unclassified MDS is diagnosed when a patient doesn't fit into one of the other categories. These patients can sometimes have unusual features in their bone marrow such as scarring, also called fibrosis. Only 1 percent to 2 percent of MDS patients have this subtype.



The WHO classification system made the following changes to the older FAB classification system:

- Added isolated deletion 5q Syndrome and Unclassified MDS
- Created the category of refractory cytopenia with unilineage dysplasia
- Created a category called RCMD (refractory cytopenia with multilineage dysplasia)
- Split RAEB-t into 2 subtypes depending on the number of blast cells present in the bone marrow
- Reclassified Chronic Myelomonocytic Leukemia or CMML into a new group of diseases known as MDS/MPD. CMML used to be considered a kind of MDS.

### **IPSS (International Prognostic Scoring System)**

The IPSS gives each patient a score to help their doctor understand how quickly their MDS is progressing and what is likely to happen to their disease over time. The score is based on several factors that are linked to MDS. They are:

- Percentage of blasts in the bone marrow
- Changes in cell chromosomes, also called cytogenetics
- Low blood cell counts

Each factor gets a score. Together, the scores tell which risk groups you fall into.

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Your IPSS score helps your doctor to answer the following questions:

- How severe is your case of MDS?
- How likely is your case to become acute myeloid leukemia or AML if treated only with supportive care?
- How long are you likely to live if you are treated only with supportive care?

Using the IPSS, a patient is given a score between 0 and 3.0. A patient can be put into one of four risk groups, two lower-risk and two higher-risk. Scores of less than 1.5 are considered lower-risk.

To come up with a score, the IPSS looks at three things:

1. The percentage of blasts in your bone marrow.
2. Whether your diseased bone marrow cells have abnormal chromosomes. The abnormal chromosomes in MDS cells are only in the diseased cells and cannot be passed down to a patient's children.
3. How many of your blood cell types are too low.

The first factor is the number of blasts you have in your bone marrow.

- If you have less than 5 percent blasts, then your IPSS blast score is 0.
- If you have 5 to 10 percent then your IPSS blast score is 0.5.
- If you have 11 to 20 percent then your IPSS blast score is 1.5.
- If you have 21 to 30 percent then your IPSS blast score is 2.0.

Factor	Value	IPSS Score
Blasts in bone marrow	less than 5 percent	0
	5 percent to 10 percent	.05
	11 percent to 20 percent	1.5
	21 percent to 30 percent	2.0
Cell DNA changes	Good	0
	Intermediate	.5
	Poor	1.0
Low Blood Counts (cytopenias)	2 or 3 cytopenias	.5

The second factor is chromosome changes in your cells. Chromosome changes are divided into three categories. Each is given a value. The categories include:

- Good which is a chromosome score of 0
- Intermediate which is a chromosome score of 0.5
- Poor which is a chromosome score of 2.0

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Patients with a good risk cytogenetic score have either a normal set of 23 chromosomes, a partial loss of chromosome 5 or 20 only, or a loss of the Y chromosome. In the good chromosome group, your IPSS chromosome score is 0.

Patients with an intermediate risk cytogenetic score have anything that doesn't fall into the good or poor value. In the intermediate chromosome group, your IPSS chromosome score is 0.5.

Patients with a poor risk cytogenetic score have lost all or part of one or two number 7 chromosomes, have the addition of a third copy of the number 8 chromosome, or have at least three different chromosome abnormalities. In the poor chromosome group, your IPSS chromosome score is 1.0.

The third factor is the number of low blood counts or cytopenias you have. Patients may have low blood counts which are not low enough to get points in this category. To get points for cytopenias, your hemoglobin needs to be less than 10 grams per deciliter, your neutrophils less than 1800 per milliliter, or your platelets need to be less than 100,000 per milliliter. Cytopenias are low blood counts. The blood count is considered low when the red blood cells are less than 36 percent of the total body volume of whole blood, the white blood cells are less than 1,800 per microliter, or the platelets are less than 100,000 per microliter. Neutrophils are the most common type of white blood cell.

Cytopenias		
	hemaglobin	<10g/dL
	neutrophils	<1,800/mL
	platelets	<100,000/mL

- If you have 0 to 1 cytopenias you have an IPSS cytopenia score of 0
- If you have 2 or 3 cytopenias you have an IPSS cytopenia score of 0.5

After your doctor has figured out your score for each factor he or she will add them up and give you your total IPSS score. This score tells you what risk group you fall into. For example:

- If your IPSS score is 0, you are in the low-risk group.
- If your IPSS score is 0.5 to 1, you are in the intermediate-1 risk group.
- If your IPSS score is 1.5 to 2, you are in the intermediate-2 risk group.
- If your IPSS score is greater than or equal to 2.5, you are in the high-risk group.

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## Conclusion

This presentation discussed two MDS classification systems and one prognostic scoring system.

- The FAB classification system uses blood cell blasts percentages and bone marrow blast percentages to define MDS subtypes.
- The WHO classification system updates the FAB system and uses blood and bone marrow test results to define MDS subtypes.
- The IPSS gives patients a score that lets them know what risk group they are in.

The WHO and FAB classification systems and the IPSS are important tools. Together, they give you and your doctor key information about your specific case of MDS. They tell you:

- How serious your case is
- How long patients in your situation live on average if given only supportive care
- What you can expect from your MDS over time
- Which treatments are best now, and at what point you should think about changing treatments



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