

# MYELODYSPLASTIC SYNDROMES: A diagnosis often missed



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# THE MYELOYDYSPLASTIC SYNDROMES



# DEFINITION



The Myelodysplastic Syndromes are a group of myeloid neoplasms characterized by peripheral blood cytopenias and increased risk of leukaemic evolution.

Common features:

- Dysplasia in one or more myeloid cell lineages
- Ineffective haemopoiesis
- Peripheral cytopenias
- Increased risk of transformation to Acute Myeloid Leukaemia

# INCIDENCE



- 5 cases per 100,000 persons per year in the general population.
- Increases to 20-50 cases per 100,000 persons per year after the age of 60 years.
- Considering the progressive aging of the population, the number of MDS patients is destined to increase in the next decades.
- The Survey of Epidemiology and End Results (SEER) database underestimates the incidence of MDS by at least 3-fold.

# CHALLENGES



- The clinical presentation of MDS can be highly variable and patients with seemingly similar features often have very distinct disease courses.
- MDSs range from indolent conditions with a long natural history to subtypes analogous to Acute Myeloid Leukaemia.
- Clinical decision-making concerning treatment modalities and timing of interventions is problematic.
- The ability to accurately predict outcomes for individual patients is a cornerstone of MDS treatment.

# DIAGNOSTIC CONSIDERATIONS:



- The diagnostic approach should begin with the exclusion of non-malignant causes of cytopenias.
- A complete history should include information on prior chemotherapy, irradiation, radio-immunotherapy, radioiodine and occupational or hobby exposure to potential carcinogens, especially benzene.
- A history of medication, ethanol intake, smoking, tendency to bleeding or bruising and infections is important.
- In young patients, a family history should focus on conditions suggestive of inherited bone marrow failure disorders, such as Fanconi's anaemia and telomere disorders.
- A complete physical examination, specifically assessing splenic size, should follow.

# BLOOD TESTS OF VALUE IN THE DIAGNOSTIC WORK-UP OF MYELOYDYSPLASTIC SYNDROMES:



## HAEMATOLOGY AND BIOCHEMISTRY:

### Haematology:

- FBC with slide review
- Reticulocyte count

### Biochemistry:

- Vitamin B12 and Folate levels
- Iron studies
- LDH
- Bilirubin
- Haptoglobin
- Direct Coombs
- CRP
- Liver function studies
- U&E and creatinine
- Protein electrophoresis
- Beta-2 Microglobulin
- Thyroid function studies
- Hb electrophoresis

## VIRAL STUDIES AND OTHER INVESTIGATIONS:

### Viral studies:

- HIV
- Parvovirus B19
- CMV
- Hepatitis B and C

### Other:

- Paroxysmal Nocturnal Haemoglobinuria
- Specific genetic analysis (in patients in whom a suspicion about inherited bone marrow failure has been raised)

# BONE MARROW EXAMINATION:



Once the non-malignant causes have been excluded, the diagnostic approach to suspected MDSs includes:

- Morphological assessment of the peripheral blood and bone marrow precursors.
- Flow cytometry immunophenotyping.
- Bone marrow biopsy to assess overall marrow cellularity, megakaryocytes numbers, fibrosis and topography.
- Cytogenetic studies and FISH analysis to identify non-random chromosomal abnormalities.
- Repeated bone marrow examinations a few weeks, months or even years apart are sometimes required to establish the diagnosis and identify patients with rapid disease progression.

# DIAGNOSTIC DIFFICULTIES



- The diagnosis of MDS may be difficult in patients with a normal karyotype or non-informative cytogenetics who do not have robust morphologic markers such as ring sideroblasts or an excess of myeloblasts.
- If only unilineage dysplasia is present in the bone marrow, there is no increase in blasts in the peripheral blood or bone marrow, ring sideroblasts represent  $<15\%$  of the erythroid precursors, and none of the recurrent cytogenetic abnormalities are present, then an observation period of 6 months and repeat bone marrow investigation are recommended prior to making the diagnosis of MDS.
- This group of patients usually present with mild cytopenia only, and rapid progression is unlikely.

# THE WHO CLASSIFICATION OF MYELOID NEOPLASMS - revised 2008



## **MYELODYSPLASTIC SYNDROMES:**

- Refractory cytopenia with unilineage dysplasia (RCUD): refractory anemia (RA), refractory neutropenia (RN), refractory thrombocytopenia (RT)
- Refractory anemia with ring sideroblasts (RARS)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- Refractory Anemia with Excess Blasts-1 (RAEB-1)
- Refractory Anemia with Excess Blasts- 2 (RAEB-2)
- Myelodysplastic syndrome, unclassified (MDS-U)
- Myelodysplastic syndrome associated with isolated del(5q)

*\* Information is from Swerdlow et al. WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues, Fourth Edition IARC, Lyon, 2008.*

# CYTOGENETIC AND MOLECULAR GENETIC INVESTIGATIONS



- Cytogenetic analysis has a major role in determining clonality in patients with suspected MDS.
- Chromosomal abnormalities are observed in 50-60% of patients with MDS.
- The most frequent single cytogenetic abnormalities include del(5q), monosomy 7 or del(7q), trisomy 8 and del(20q).
- FISH analysis may compliment conventional cytogenetic analysis, and can detect abnormalities in up to 15% of karyotypically normal MDS patients.
- Recent developments in microarray techniques have allowed the application of single nucleotide polymorphisms (SNPs) for high-resolution genome-wide genotyping, and now is emerging as an important tool in the identification of chromosomal defects that are not detected by standard cytogenetics. The most commonly mutated genes in MDS include SF3A1, TET2, RUNX1, ASXL1, SRSF2, TP53, U2AF1 and NRAS/KRAS.

# RISK ASSESSMENT



Prognostic factors may be divided into:

- **characteristics of the MDS clone.**
- **patient's characteristics and general health condition**

## **Disease related factors:**

The definition of risk related to the characteristics of MDS is based on prognostic scoring systems combining multiple clinical and haematologic variables.

The International Prognostic Scoring System (IPSS) for MDS was first published in 1997, and has become the most widely adopted predictor of prognosis for patient with MDS. The International Working Group for Prognosis in MDS recently revised the IPSS on the basis of a large multicentric cohort of untreated patients with MDS, and this has been recently released (IPSS-R).

# IPSS.

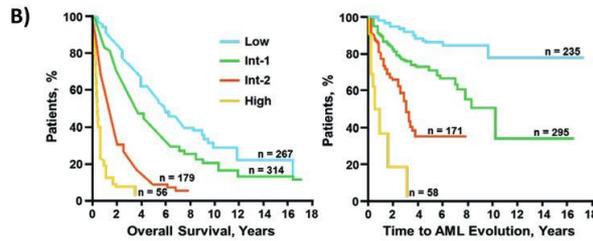
**A)**

Prognostic Category	IPSS Prognostic Score Value				
	0	0.5	1	1.5	2
Cytogenetics	Good	Intermediate	Poor		
BM blasts, %	< 5	5-10		11-20	21-30
Cytopenias	0/1	2/3			

**Cytogenetic groups**  
 Good: normal, -Y, del(5q), del(20q)  
 Intermediate: any not considered good or poor  
 Poor: complex (≥ 3 abnormalities), chromosome 7 abnormalities

**Cytopenias definitions**  
 Hemoglobin: <10 gm/dL  
 Neutrophils: < 1800<sup>3</sup>/L  
 Platelets: < 100 x 10<sup>9</sup>/L

Risk Category	Risk Score
Low	0
Int-1	0.5-1.0
Int-2	1.5-2.0
High	≥ 2.5

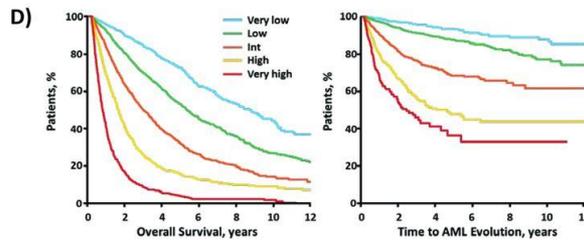


**C)**

Prognostic Category	IPSS-R Prognostic Score Value						
	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good		Good		Int	Poor	Very poor
BM blasts, %	≤ 2		> 2-< 5		5-10	> 10	
Hemoglobin, g/dL	≥ 10		8-< 10		< 8		
Platelets, x 10 <sup>9</sup> /L	≥ 100	50-< 100	< 50				
ANC, x 10 <sup>9</sup> /L	≥ 0.8	< 0.8					

**Cytogenetic groups**  
 Very good: -Y, del(11q)  
 Good: normal, del(5q), del(12p), del(20q), del(5q) + 1 additional  
 Intermediate: del(7q), +8, +19, t(17q), other abnormalities not in other groups  
 Poor: -7, inv(3)(3q)/del(3q), -7/del(7q) + 1 additional, complex (3 abnormalities)  
 Very poor: complex (> 3 abnormalities)

Risk Category	Risk Score (for age > 70)
Very low	≤ 1.5
Low	> 1.5-3
Intermediate	> 3-4.5
High	> 4.5-6
Very high	> 6



Rafael Bejar Hematology 2013;2013:504-510



# PATIENT RELATED PROGNOSTIC FACTORS



Different factors related to individual general health status may affect clinical outcome and decision-making in patients with MDS:

- age
- functional ability
- comorbidity,
- physical reserves
- nutritional status
- cognition.

# THERAPEUTIC INTERVENTION



A high proportion of MDS patients are not eligible for potentially curative treatment because of advanced age and/or clinically relevant comorbidities and poor performance status.

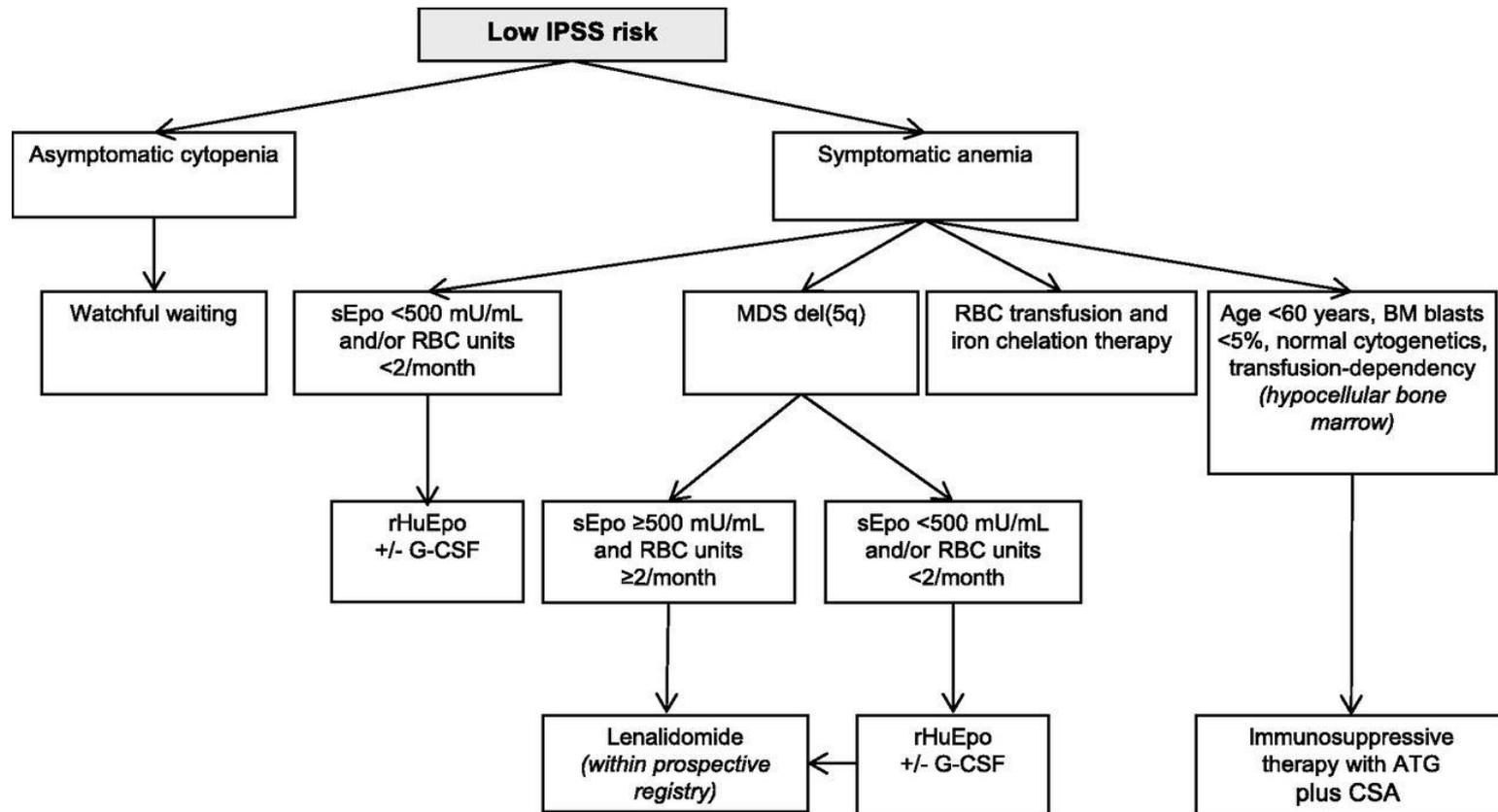
In these patients, the therapeutic intervention is aimed at preventing cytopaenia-related morbidity and preserving quality of life.

# THERAPEUTIC OPTIONS

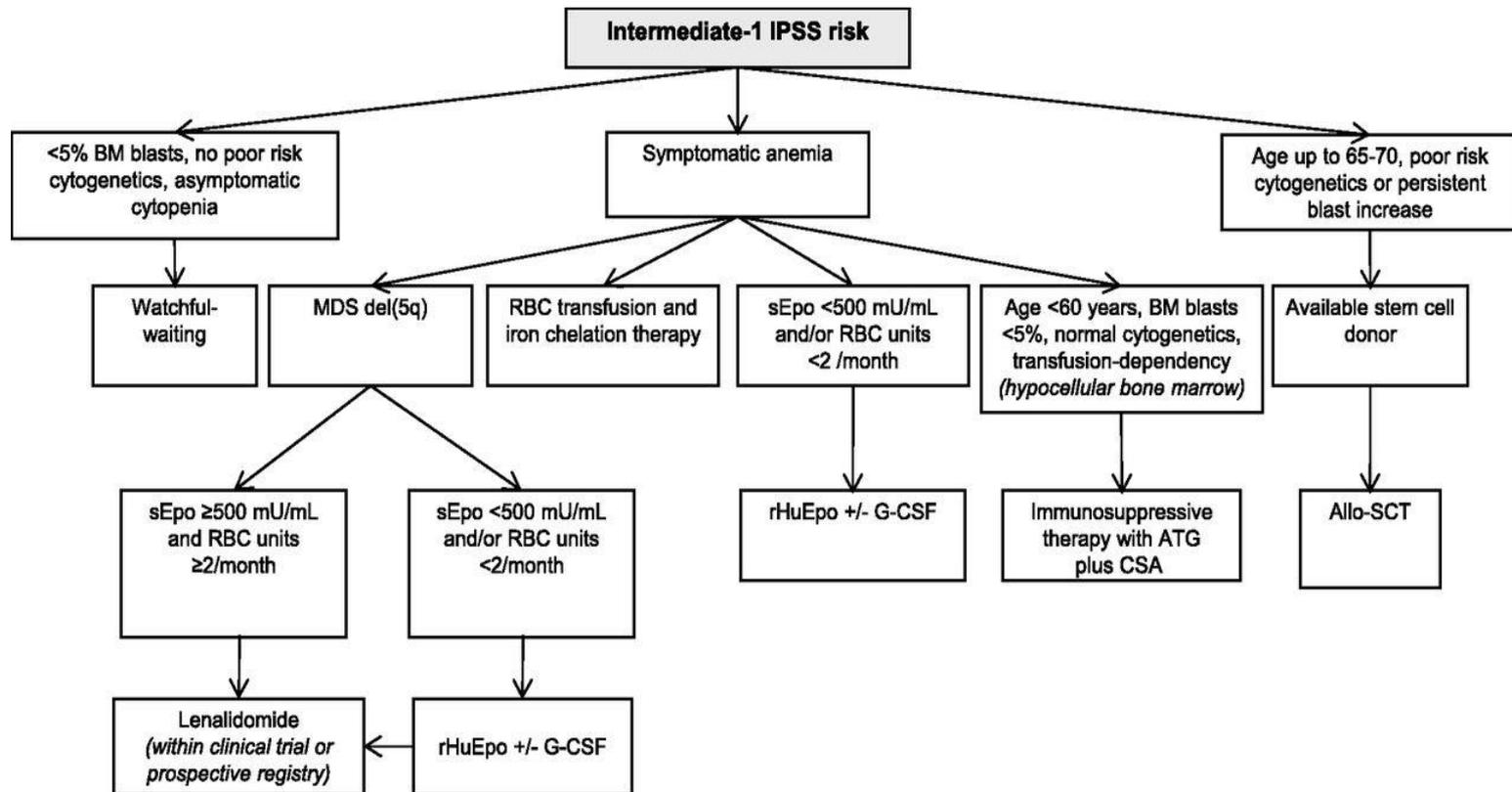


- Watchful waiting strategy.
- HLA typing
- Allogeneic SCT
- Remission induction chemotherapy
- Autologous SCT
- Low-dose chemotherapy
- Hypomethylating agents
- Haemopoietic growth factors
- Immunomodulatory drugs
- Immunosuppressive therapy
- Red cell transfusion and iron chelation therapy
- Platelet transfusion

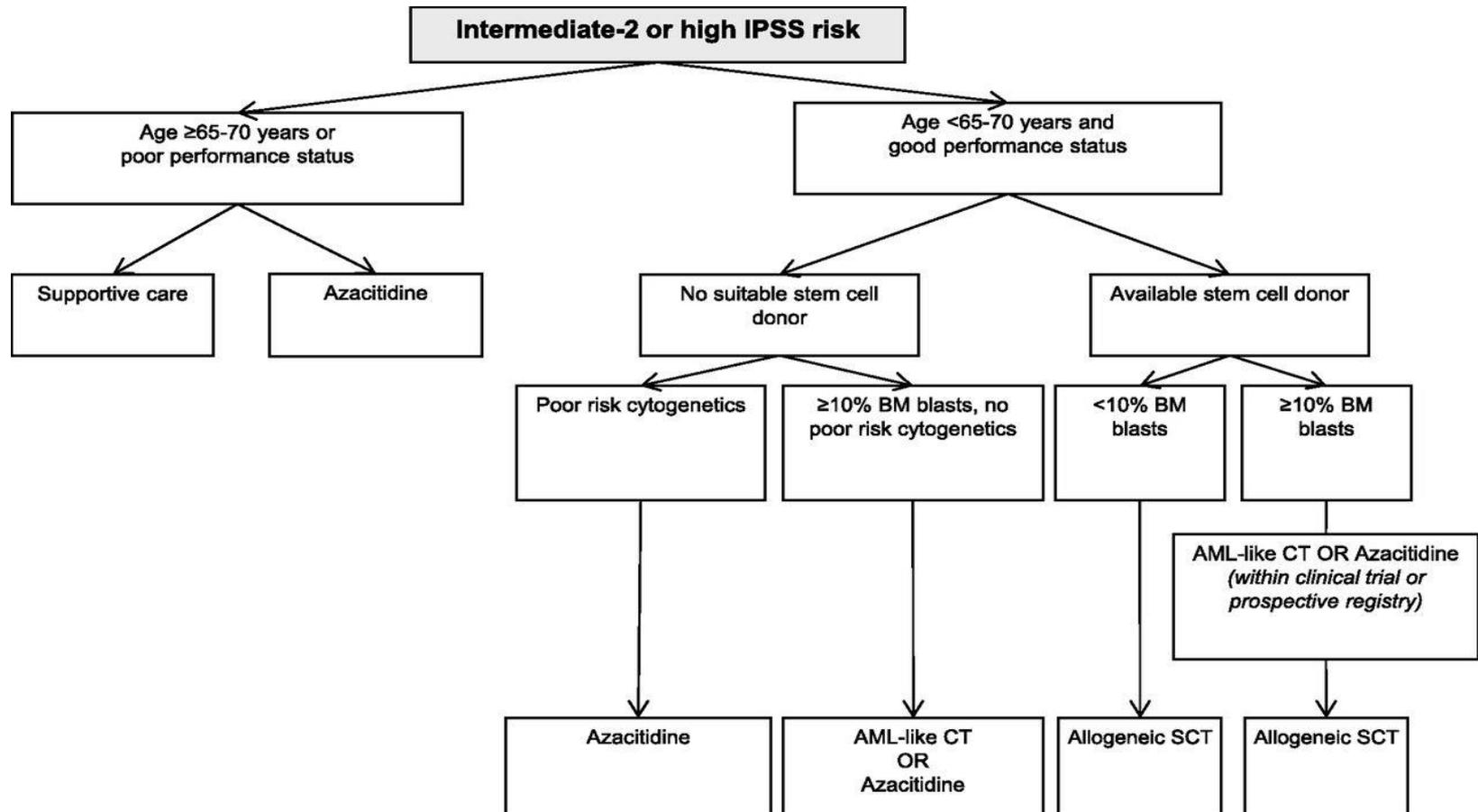
# Therapeutic algorithm for adult patients with primary MDS and low IPSS score



# Therapeutic algorithm for adult patients with primary MDS and intermediate-1 IPSS score.



# Therapeutic algorithm for adult patients with primary MDS and intermediate-2 or high IPSS score.

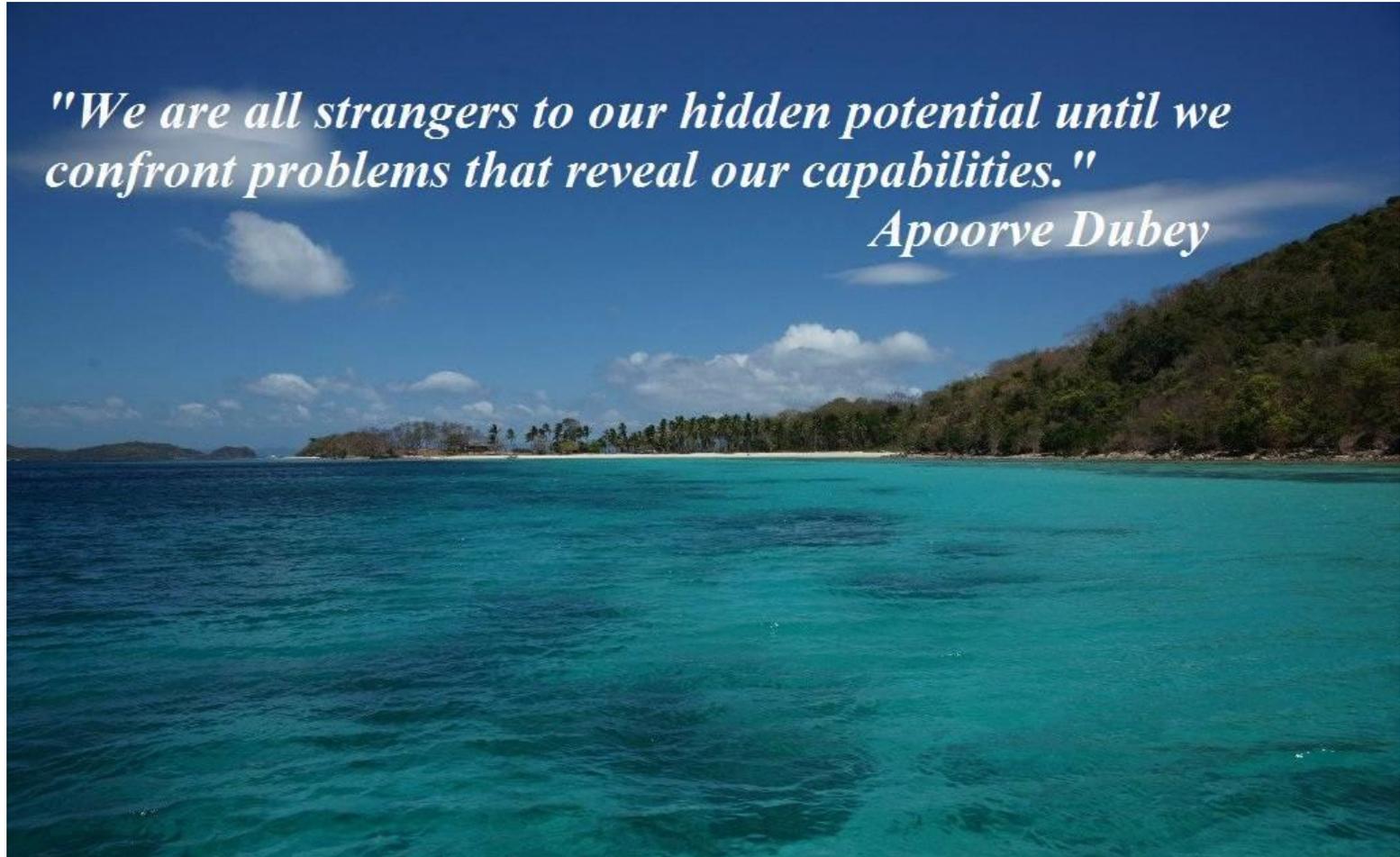


# IN CONCLUSION....



*"We are all strangers to our hidden potential until we confront problems that reveal our capabilities."*

*Apoorve Dubey*



# References



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