Aplastic Anemia Pathophysiology and Approach to Therapy

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Introduction

- Aplastic anaemia (AA) is the paradigm of the human bone marrow failure syndromes
- Fatal just a few decades ago, AA can now be cured or ameliorated
- The success is attributed to the better understanding of the pathophysiology and advanced treatment
- But, making a diagnosis and selecting among treatment options are not straightforward, and both physicians and patients face serious decision points
- Recent insights into pathophysiology have practical treatment implications

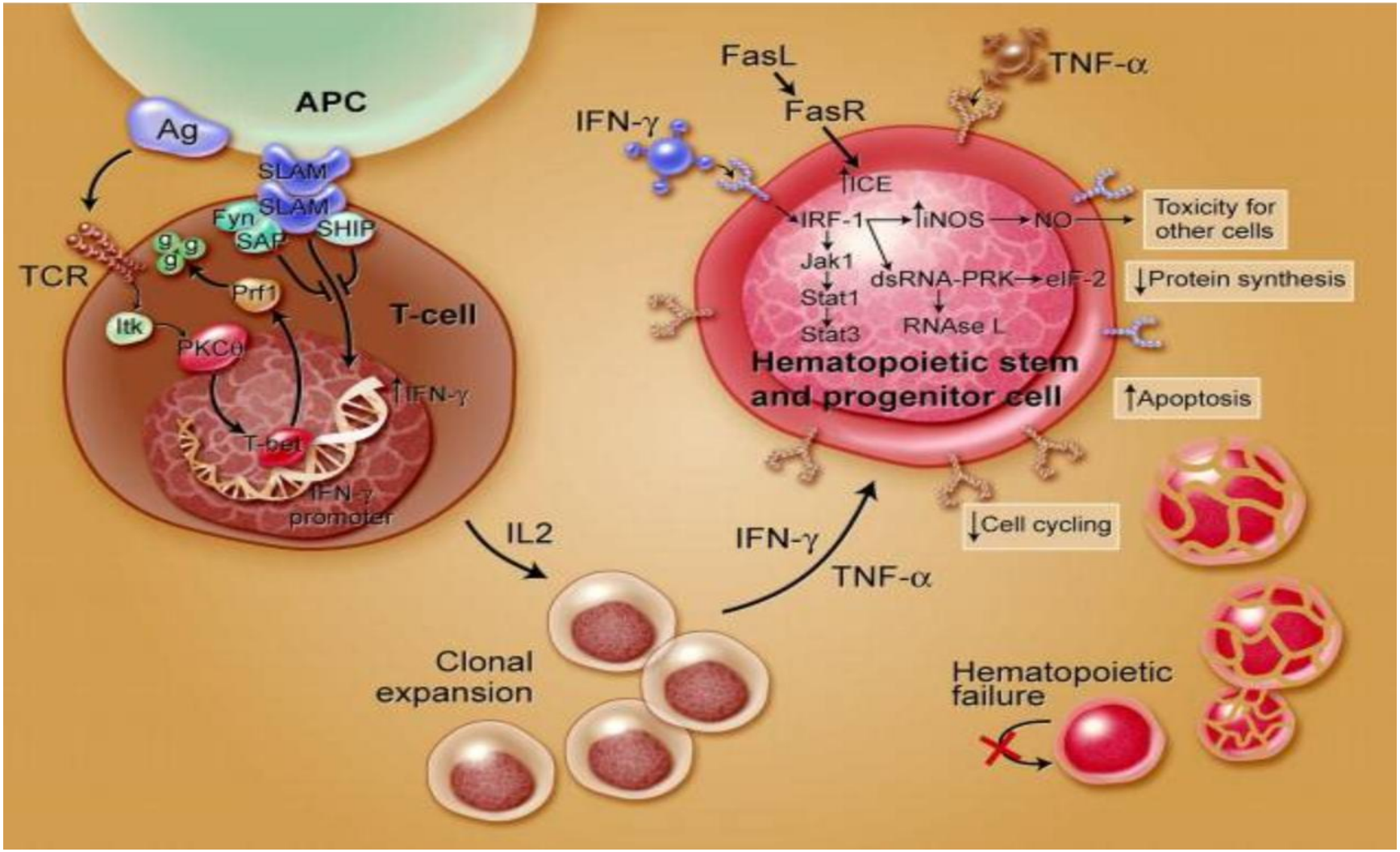
Pathophysiology

As basis of diagnosis and treatment

- Previously, an intrinsic defect of hematopoietic cells; external injury to hematopoietic cells; and defective stroma –all were held responsible.
- The role of an immune dysfunction was suggested in 1970, when autologous recovery was documented in a patient with aplastic anemia who failed to engraft after HCT.
- Technical advances in cell biology, flow cytometry, molecular biology, and immunology has led to a more unified and rational view of aplastic anemia's pathophysiology
- The pathophysiology is immune mediated in most cases, with activated type 1 cytotoxic T cells implicated.

Pathophysiology

As basis of diagnosis and treatment



Acquired Causes

- Idiopathic factors
- Infectious causes, such as hepatitis viruses, EBV, HIV, etc.
- Exposure to ionizing radiation
- Exposure to toxic chemicals, such as benzene or pesticides
- Transfusional graft versus host disease (GVHD)
- Orthotopic liver transplantation for fulminant hepatitis
- Pregnancy
- Eosinophilic fasciitis
- Anorexia
- Severe nutritional deficiencies (B12, folate)
- PNH, MDS, rarely-ALL

ALL

Congenital or Inherited Causes

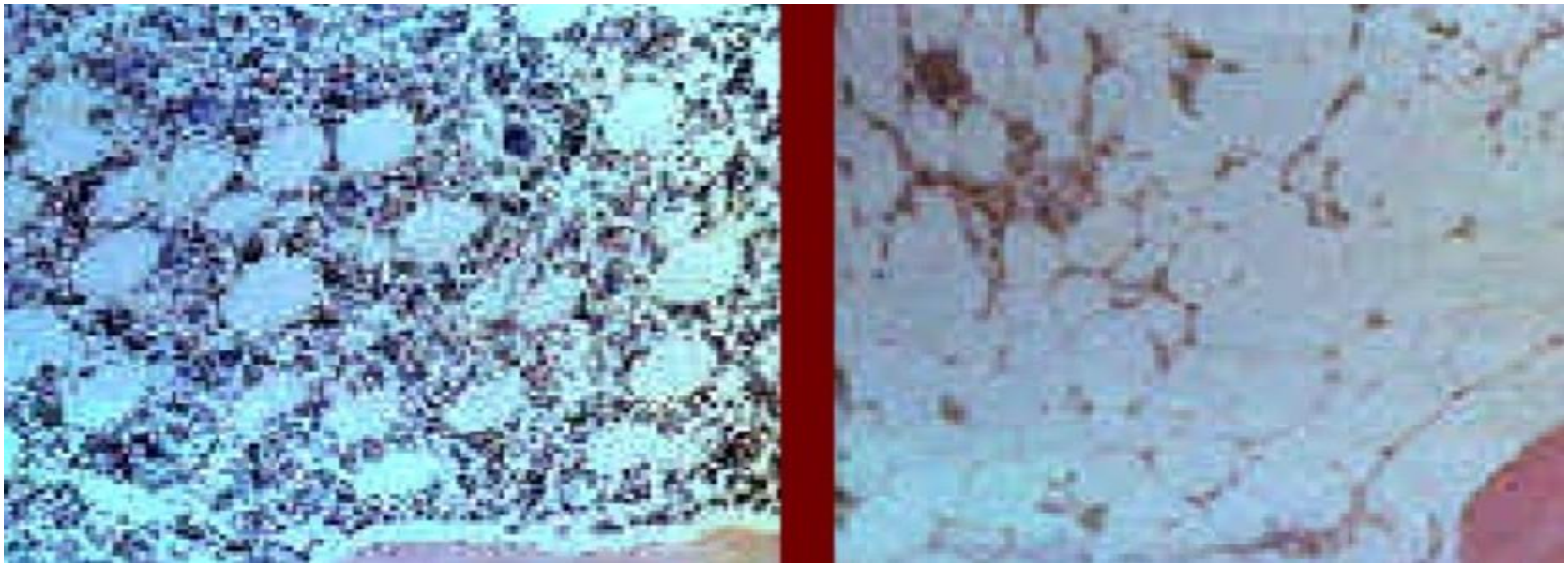
- A number of inherited (constitutional/genetic) disorders are characterized by bone marrow failure/aplastic anaemia (AA) usually in association with one or more somatic abnormality.
- Several loci have been identified
- History and physical –
  - Family with cytopenias, premature graying, pulmonary fibrosis
  - Short stature, physical abnormalities
- Examples:
  - Fanconi anaemia
  - *Dyskeratosis congenita*
  - *Familial AA*

Diagnosis

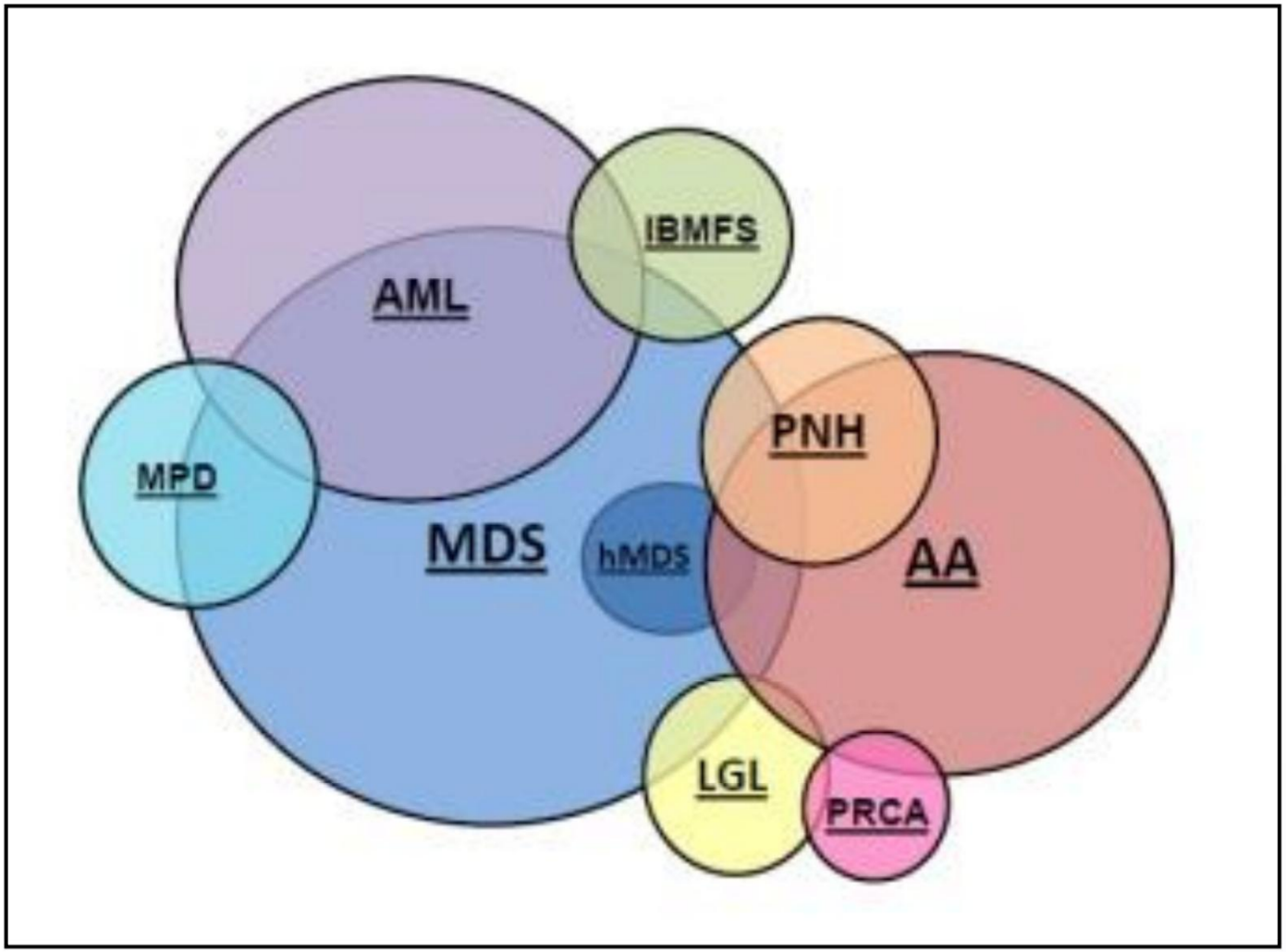
- There are three diagnostic steps in AA.
  - Confirm the suspicion of AA and exclude other bone marrow failure diseases
  - Define the severity of the disease
  - Characterize the AA

Diagnosis

- Presence of pancytopenia and proof of an empty bone marrow is mandatory.
- The diagnosis of Aplastic Anemia (AA) may be difficult and sometimes needs repeated marrow investigations.



Diagnosis: Confirm the suspicion



AA/MDS

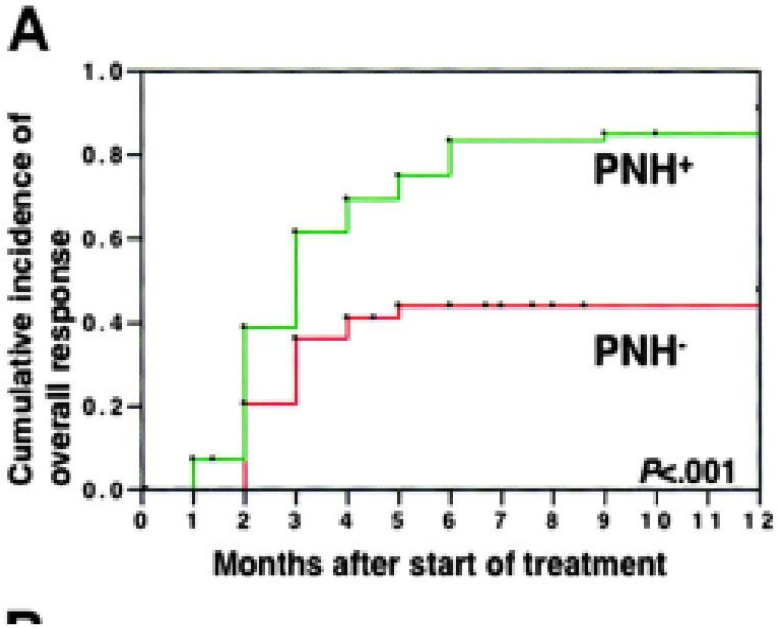
	AA	MDS
Splenomegaly at dx:	absent	possible
Cytopenia	present	present
Dysplasia	absent	present
Erythropoiesis	possible	possible
Myelopoiesis	absent	possible
Megakaryopoiesis	absent	possible
Blasts	absent	variable
CD34+ immunohistoch.	not increased	normal or increased
Marrow fibrosis	absent	possible

AA/PNH

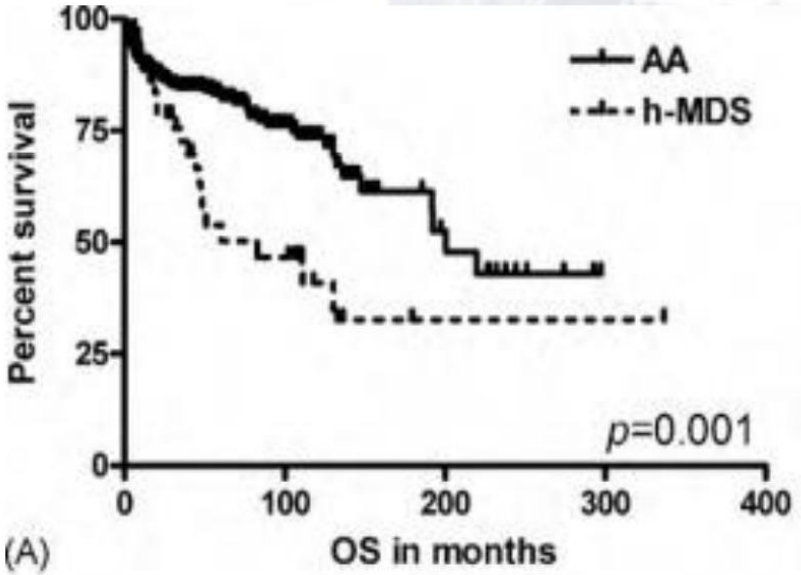
- Overlap in approximately 40% to 50% of cases
- More than 1% granulocytes deficient in glycosylphosphoinsoitol-linked proteins detectable by flow cytometry are considered abnormal
- Evidence of hemolysis: Complete blood count, reticulocyte count, serum concentration of lactate dehydrogenase (LDH), bilirubin (fractionated), and haptoglobin

Why It Matters

Time to Response with PNH clone present is shorter



Overall Survival is Shorter if hMDS compared to AA



Blood 2002; 100:1570-157; Blood 2002:100:3897-3902

JOHNS HOPKINS MEDICINE

Assess Severity

Classification of AA: Camitta Criteria

Peripheral Blood Cytopenias	Non-severe (Moderate) aplastic anemia (not meeting criteria for severe disease)	Severe aplastic anemia (any 2 of 3)	Very-severe aplastic anemia (meets criteria for severe disease and absolute neutrophils < 200)
Bone marrow cellularity	< 25%	< 25%	< 25%
Absolute neutrophil count		< 500 / μl	< 200 / μl
Platelet count		< 20,000 / μl	
Reticulocyte count		< 1.0% corrected or < 60,000 / μl	

JOHNS HOPKINS MEDICINE

Camitta BM et al Blood. 1976;48:63–70

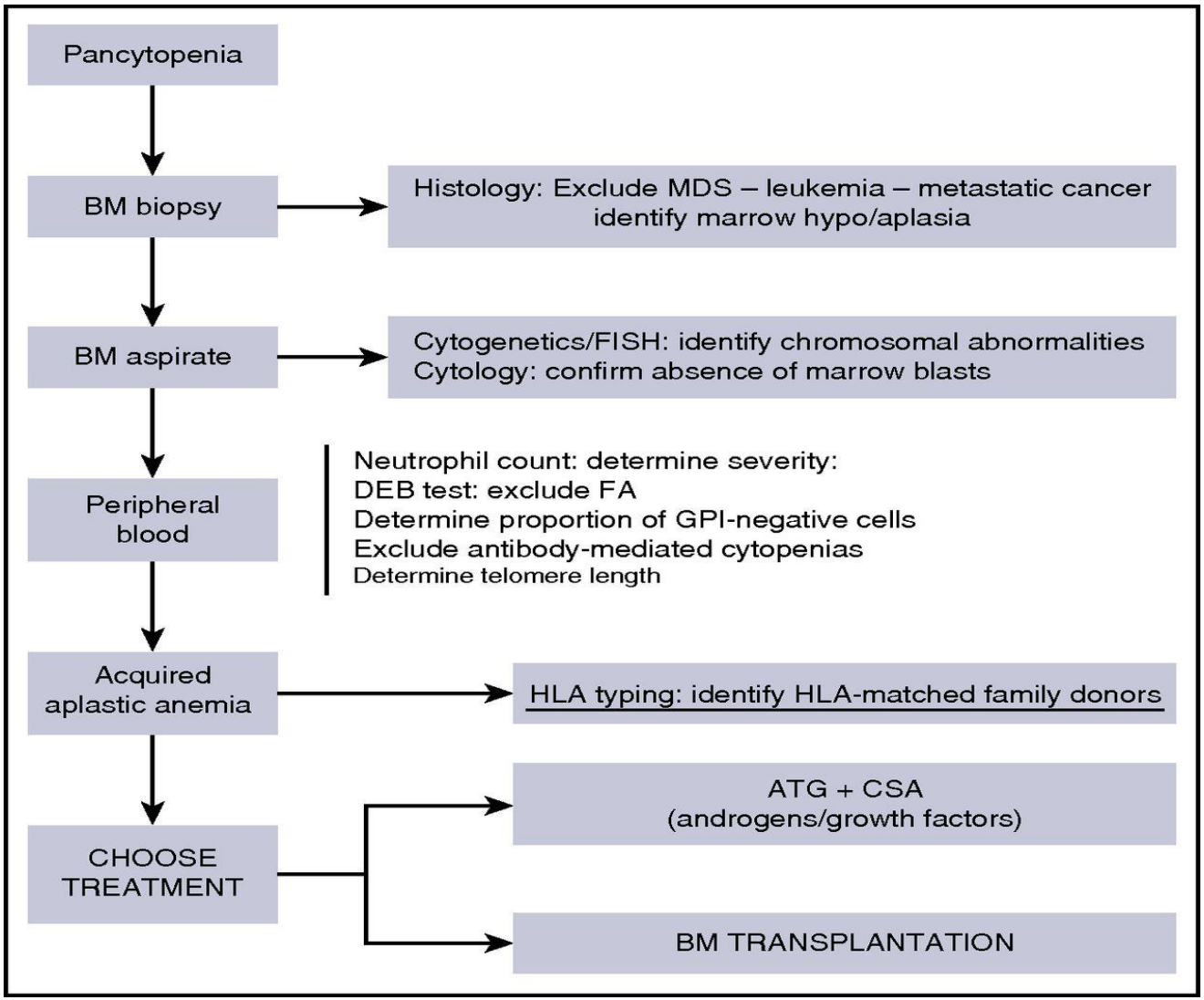
Characterize the AA

- Aplastic anemia and PNH
- Aplastic anemia and HLA-DR2 / HLA-DRB1*15
- Hepatitis associated Aplastic Anemia
- Aplastic anemia associated with other autoimmune disorders (AID)

Diagnostic Workup for AA

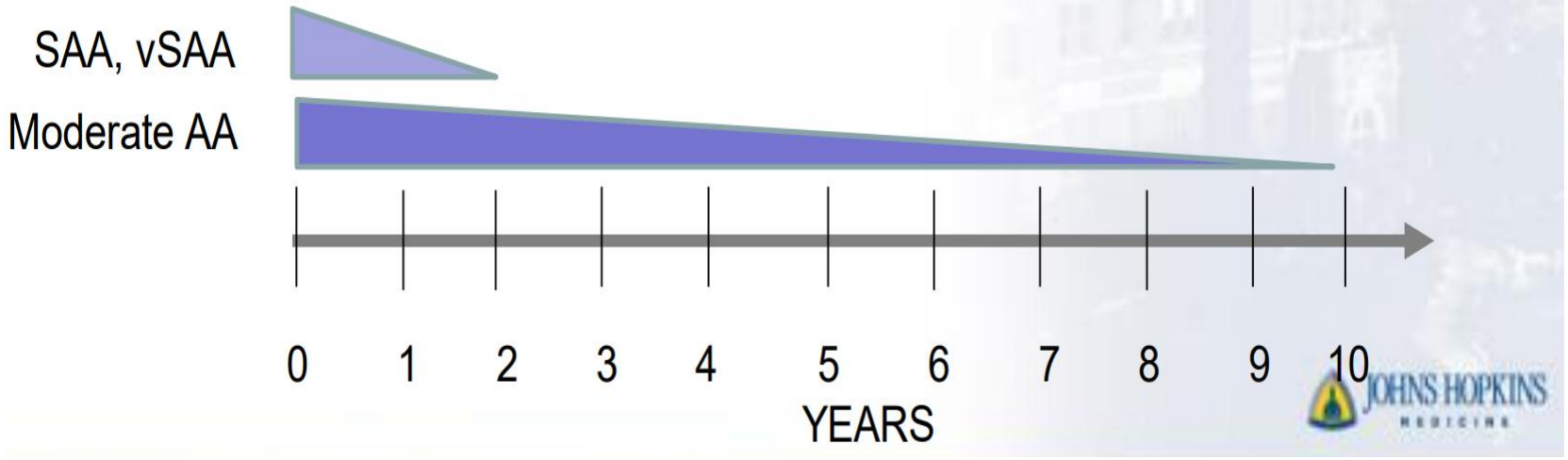
- Full blood count with reticulocyte count (automated or microscopic counting)
- Peripheral blood film examination
- PNH clone with a sensitive multicolor flow cytometry
- Viral hepatitis studies (serological and DNA/RNA)
- BM aspirate for morphology, cytogenetic, FISH-analysis (search for -7; +8), immunophenotyping, Pearls staining, viral (HIV, CMV, EBV) and microbiological studies.
- Marrow trephine biopsy assessing overall hematopoietic cellularity, single lineage cellularity, ALIP, blasts (CD34, CD117) and fibrosis.
- HLA-typing (search for HLA-DRB1*15) and family typing when patients eligible for HSCT

Diagnostic Workup for AA



When and whom to treat

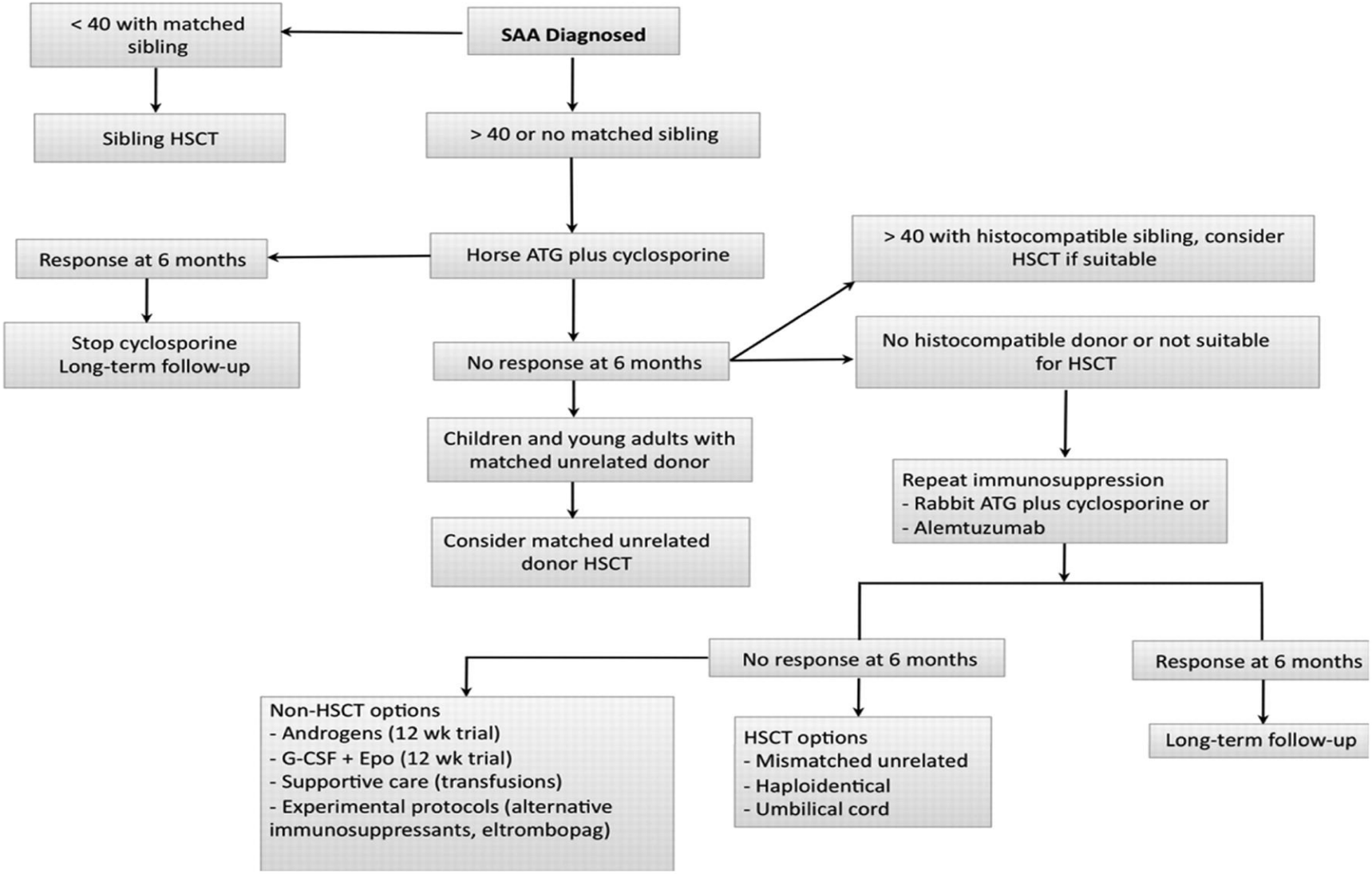
- Natural History of Untreated Disease



Moderate AA: Suportive Care

- General: Flowers and plants as potential source of fungal spores and Pseudomonas should be avoided. Low microbial food is recommended
- Individual hygiene rules should be applied
- Prevention and treatment of infections
- Blood counts should be monitored regularly, usually 3 times/week.
- Blood transfusion therapies: platelets, RBC
- GCSF is often used in neutropenic infections
- Androgen therapy: a proportion of non responders to IS therapy
- Psychological support

Treatment algorythm for SAA



Conclusions and Prospects

- Long-term survival of more than 75% of patients can be anticipated with therapy
- For HSCT: immediate challenge is the extension of stem-cell replacement to all patients, regardless of age, with a histocompatible sibling, and to others who lack a family donor using alternative stem-cell sources
- For immunosuppression: many new drugs and biologics have yet to be tested
- Measurement of telomere length and blood counts offer the possibility of rational risk stratification of treatment in future protocols.


SUCCESS!!
Thank You!!