Approach to thrombocytopenia and management of ITP

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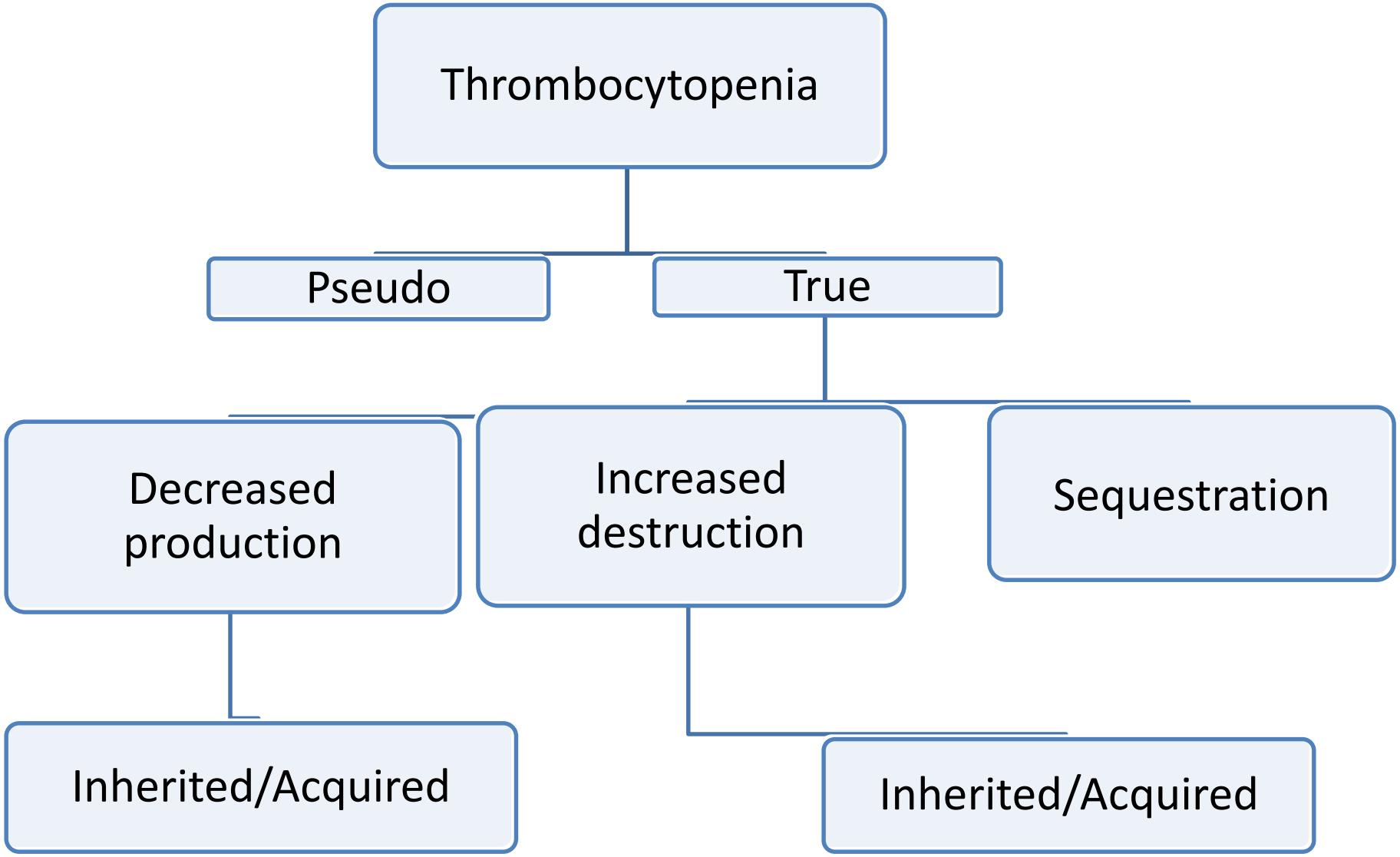
Causes of thrombocytopenia



Pseudothrombocytopenia

- 15-20% of all isolated thrombocytopenia.
- Platelet aggregation in the presence of EDTA.
- Detected on Blood smear by manual count.
- Repeat count on fresh citrated sample.

Decreased production-*Inherited*

Small platelets, MPV <7 fL	Normal platelets, MPV 7-11 fL	Large/giant platelets, MPV >11 fL
Wiskott-Aldrich syndrome *(X linked)*	Familial platelet disorder/acute myeloid leukemia *(AD)*	May-Hegglin anomaly *(AD)*
X-linked thrombocytopenia	Chromosome 10/THC2 *(AD)*	Fechtner syndrome *(AD)*
	Congenital amegakaryocytic thrombocytopenia *(AR)*	Epstein syndrome *(AD)*
	Thrombocytopenia and absent radii *(AR)*	Sebastian syndrome *(AD)*
		Mediterranean thrombocytopenia *(AD)*
		Bernard-Soulier syndrome *(AR)*
		Velocardiofacial/DiGeorge syndrome *(AD)*
		GATA1 mutation (X linked)
		Gray platelet syndrome *(AD)*
		Paris-Trousseau thrombocytopenia/Jacobsen syndrome *(AD)*

Decreased production-*acquired*

- Drug induced marrow suppression(chemotherapy)
- Radiation therapy
- Infection-Viral(HCV, HIV, CMV), bacterial(sepsis)
- Alcohol
- MDS
- Myelofibrosis
- Infiltration- granuloma,solid tumours
- Aplastic anaemia
- Haematologic malignancy- leukaemia, lymphoma, myeloma
- Nutritional-Vit B_{12} deficiency

Increased destruction-*acquired*

- ❑ Immune-
- Immune thrombocytopenic purpura
- Neonatal alloimmune thrombocytopenia
- Post transfusion purpura
- Drugs
- ❑ Nonimmune-
- Shortened circulation- DIC, TTP, HIT(immune component)
- Turbulent blood flow- haemangioma, abnormal cardiac valve, intra aortic balloon pump

Drugs causing thrombocytopenia

- Abciximab
- Acetaminophen
- Carbamezapine
- Chlorpropamide
- Cimetidine
- Danazol
- Diclofenac
- Efalizumab
- Eptifibatide
- Gold
- Valproate
- Hydrochlorothiazide
- Interferon-α
- Methyldopa
- Nalidixic Acid
- Quinidine
- Quinine
- Ranitidine
- Rifampin
- Tirofiban
- Trimethoprim/sulfamethoxazole
- Vancomycin
- Penicillin, cephalosporins

James N. George and Richard H. Aster

Hematology 2009

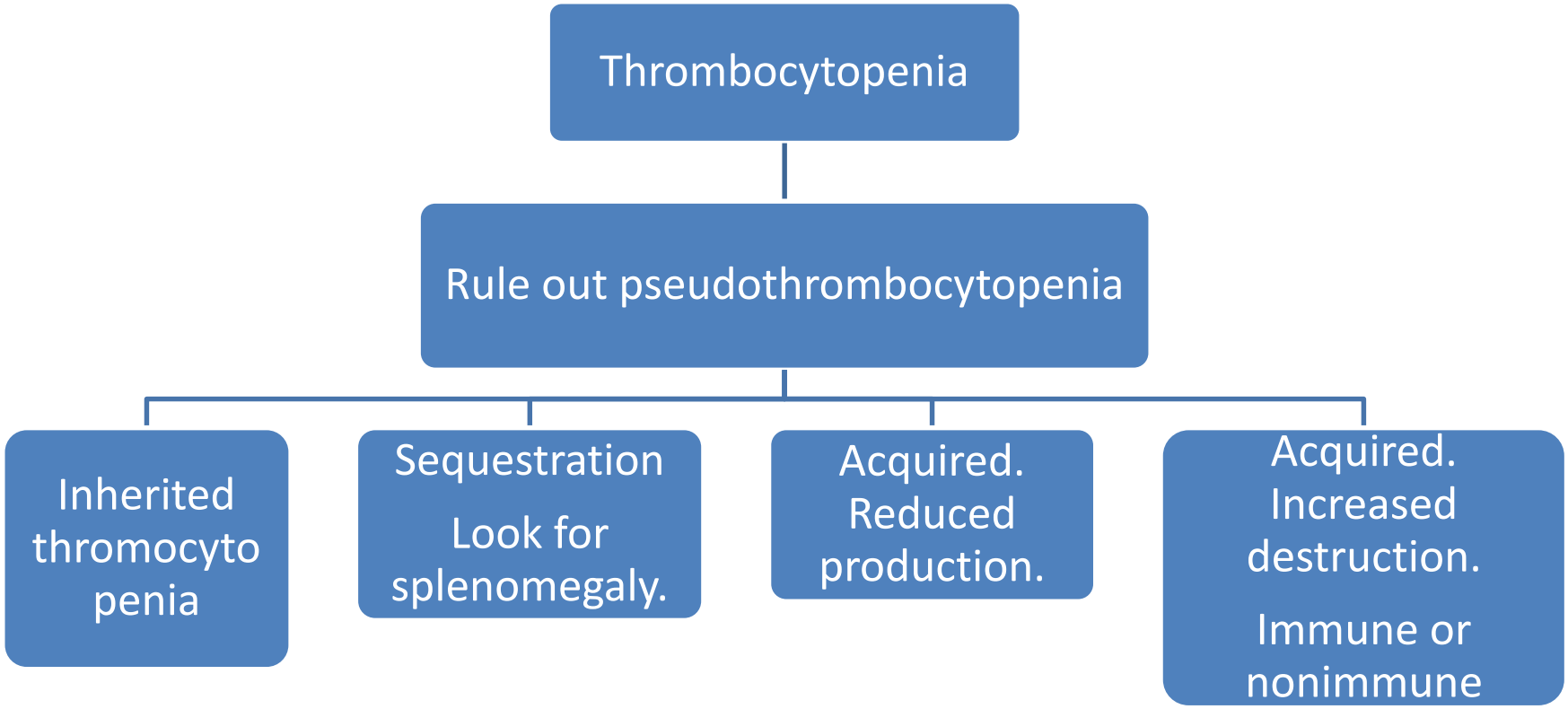
Initial evaluation in thrombocytopenia

Review bleeding history	Acquired	Congenital
Onset-epistaxis, gum bleed, purpura, menorrhagia	Recent	Lifelong
Medications	Changes	No
Bleed after trauma	Usually No in ITP	Yes
Family history	No	Yes
Normal previous platelet count	Yes	No
Response to treatment(steroid, IVIg, anti D)	Yes in ITP	No
Response to platelet transfusion	Poor increment in ITP	Good increment

Laboratory evaluation

- Complete blood count- MPV, other cytopenia.
- Peripheral blood smear-platelet number, morphology, clumps, white cell or red cell changes.
- Bone marrow examination.

Approach to thrombocytopenia



Management of ITP

Management of ITP

- Diagnosis of exclusion.
- History and physical examination.
- Laboratory evaluation including bone marrow examination.

Definitions of ITP

- **Primary**
- **Secondary**

- **Newly diagnosed ITP: within 3 months from diagnosis.**
- **Persistent ITP: 3 to 12 months from diagnosis. Includes patients not reaching spontaneous remission or not maintaining complete response off therapy.**
- **Chronic ITP: lasting for more than 12 months.**
- **Severe ITP: symptoms at presentation sufficient to mandate treatment, or occurrence of new symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dose**.

Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group *Blood. 2009;113:2386-2393*

Refractory ITP

Failure to achieve at least R or loss of R after splenectomy

Need of treatment(s) (including, but not limited to, low dose of corticosteroids) to minimize the risk of clinically significant bleeding.

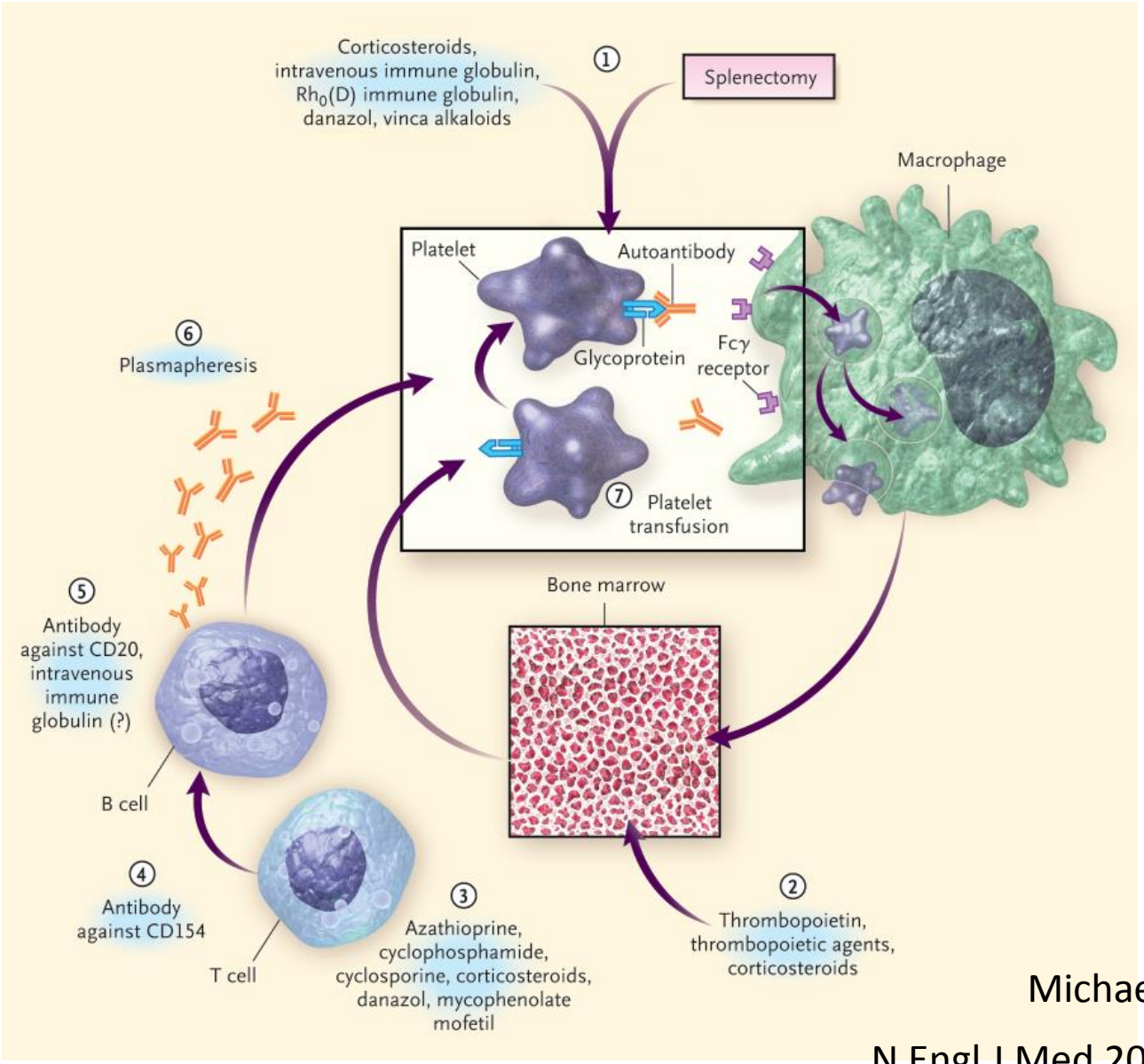
Need of on-demand or adjunctive therapy alone does not qualify the patient as refractory.

Primary ITP confirmed by excluding other supervened causes of thrombocytopenia

Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group

Blood. 2009;113:2386-2393

Approaches to the Treatment of ITP



Michael E. Bromberg

N Engl J Med 2006.355:1643-1645

When to treat ?

Trigger for treatment

- Platelet count <30,000/cmm
- Platelet count 30-50,000/cmm, symptomatic patient
- No treatment if platelet count >50,000/cmm

Criteria for assessing response to ITP treatments

CR	Platelet count $\geq$100 X 10^9/L Absence of bleeding
R	Platelet count $\geq$30 X 10^9/L and at least 2-fold increase from the baseline count Absence of bleeding
NR	Platelet count <30 X 10^9/L or less than 2-fold increase of baseline count Bleeding
Time to response	Time from starting treatment to time of achievement of CR or R.

Platelet counts should be confirmed on at least 2 separate occasions (at least 7 days apart when used to define CR, R or 1 day apart when used to define NR or loss of response.

Therapies for the treatment of ITP

First line (initial treatment for newly diagnosed ITP)	**Anti-D** **Corticosteroids:dexamethasone, methylprednisolone, prednisolone** **IVIg**	
Second line	**Azathioprine** **Dapsone** **Cyclosporin A** **Cyclophosphamide** **Danazol**	**Mycophenolate mofetil** **Rituximab** **Splenectomy** **TPO receptor agonists** **Vinca alkaloids**
Treatment for patients failing first- and second-line therapies	***Category A: Sufficient data*** **TPO receptor agonists** ***Category B:Minimal data*** ***Potential for considerable toxicity*** **Campath-1H** **Combination of first- and second-line therapies** **Combination chemotherapy** **HSCT**	

Treatment

FIRST LINE AGENTS

Steroids

Treatment strategy	Response rate	Time to initial response	Time to peak response	Duration of sustained response
Dexamethasone 40 mg daily(0.8 mg/kg) for 4 d every 2-4 wk for 1-4 cycles	Up to 90% of patients respond Initially	2-14 d	4-28 d	50%-80% reported, the latter with 3-6 cycles (during 2-5 y of follow-up)
Methylprednisolone 30 mg/kg/d for 7 d	As high as 95%	2-14 d	4-28 d	23% of patients have sustained platelet count (> 50 × 10^{9}/L) at 39 mo
Prednisolone 0.5-2 mg/kg/d for 2-4 wk	70%-80% of patients respond Initially	4-14 d	7-28 d	Remains uncertain; estimated 10-y disease free survival 13%-15%

Steroids

Toxicities-vary with length of administration:

- Mood swings
- Weight gain, anger, anxiety, insomnia, Cushingoid faces
- Dorsal fat, diabetes, fluid retention
- Osteoporosis, skin changes including thinning, alopecia, hypertension, GI distress and ulcers
- Avascular necrosis, immunosuppression, psychosis
- Cataracts, opportunistic infections, adrenal insufficiency
- Hypertension.
- Tolerability decreases with repeated dosing.
- Possibly lower rate of adverse events when used as short-term bolus therapy.

IVIg

Treatment strategy	Response rate	Time to initial response	Time to peak response	Duration of sustained response
0.8-1 g/kg/d for 1d or 0.4 g/kg/d for 5 d	Up to 80% of patients respond initially; half achieve normal platelet counts	1-3 d	2-7 d	Usually transient; platelet counts returning to pretreatment levels 2-4 wk after treatment; persists for months in a few patients

IVIg

Toxicities

- Headaches common: often moderate but sometimes severe
- Transient neutropenia, renal insufficiency, aseptic meningitis, thrombosis, flushing, fever, chills, fatigue, nausea, diarrhea, blood pressure changes and tachycardia
- IVIg preparations may contain small quantities of IgA, which occasionally causes anaphylactoid reactions in patients with IgA deficiency; in these cases use IgA depleted IV Ig

AntiD

Treatment strategy	Response rate	Time to initial response	Time to peak response	Duration of sustained response
50-75 µg/kg	Initial response rate similar to IVIg (dose dependent)	1-3 d	3-7 d	Typically last 3-4 wk but may persist for months in some patients

Toxicities

Common: hemolytic anemia (dose-limiting toxicity),fever/chills
Rare: intravascular hemolysis, disseminated intravascular coagulation, renal failure, rare death

Treatment

SECOND LINE AGENTS

Dapsone

Treatment strategy	Response rate	Time to initial response	Time to peak response	Duration of sustained response
75-100 mg po daily (1-2 mg/kg)	Response in up to 50% of patients	21-90 d	30-180 d	Sustained response in up to two thirds of responders off therapy

Toxicities

Infrequent and treatable/reversible: abdominal distension, anorexia, nausea, methemoglobinuria, hemolytic anemia in those with G6PD deficiency

Rare-motor neuropathy

Severe: skin rash may require drug to be stopped

Azathioprine

Treatment strategy	Response rate	Time to initial response	Time to peak response	Toxicities	Duration of sustained response
1-2 mg/kg (maximum: 150 mg/d)	Up to two-thirds of patients; 40% in anecdotal reports	30-90 d	30-180 d	Low incidence and generally mild: weakness, sweating, transaminase elevations, severe neutropenia with infection, pancreatitis	Up to a quarter of patients off therapy maintain response

Splenectomy

Treatment strategy	Response rate	Time to initial response	Time to peak response	Toxicities	Duration of sustained response
Splenectomy	80% of patients respond; approximately two-thirds achieve a lasting response	1-56 d	7-56 d	Hemorrhage, peripancreatic hematoma, subphrenic abscess, wound infection, death, pneumococcal infection, fever, overwhelming sepsis syndrome, thrombosis	Response sustained with no additional therapy in approximately two-thirds of patients over 5-10 y

Treatment

FAILURE OF SPLENECTOMY

TPO receptor agonists

Treatment strategy	Response rate	Time to initial response	Time to peak response	Duration of sustained response
romiplostim Doses 1-10 µg/kg subcutaneously weekly	**Overall platelet response rate: non-splenectomized, 88%; splenectomized, 79%**	**5-14 d**	**14-60 d**	**Up to 4 y with continual administration of the drug**

Toxicities

Adverse events in at least 20% of patients: headache, fatigue, epistaxis, arthralgia and contusion (similar incidence in placebo groups) Treatment-related serious adverse events: increased bone marrow reticulin, worsening thrombocytopenia upon discontinuation, thrombosis

TPO receptor agonists

Treatment strategy	Response rate	Time to initial response	Time to peak response	Duration of sustained response
eltrombopag 25-75 mg orally daily	Platelet responses (platelet count > 50 × 10^9/L on d 43 of study): 70% receiving 50-mg dose, 81% receiving 75-mg dose	7-28 d	14-90 d	Up to 3 y with continual administration of the drug

Toxicities
Adverse events in at least 20% of patients: headache Treatment-related serious adverse events: increased bone marrow reticulin, worsening thrombocytopenia upon discontinuation, thrombosis, liver function abnormalities in 13%

Rituximab

Treatment strategy	Response rate	Time to initial response	Time to peak response	Duration of sustained response
375 mg/m^2 weekly ×4 (lower doses may also be effective)	60% of patients; complete response in 40% of patients	7-56 d	14-180 d	Sustained response > 3-5 y in 15%-20% of responders. Responders may require retreatment months to years later

Toxicities

Low rate, usually mild-to-moderate first-infusion fever/chills, rash, or scratchiness in throat. More severe reactions include serum sickness and (very rarely) bronchospasm, anaphylaxis, pulmonary embolism, retinal artery thrombosis, infection, and development of fulminant hepatitis via reactivation of hepatitis B. Rare cases of progressive multifocal leukoencephalopathy

Cyclophosphamide

Treatment strategy	Response rate	Time to initial response	Time to peak response	Toxicities	Duration of sustained response
(1-2 mg/kg orally daily for at least 16 wk) or IV (0.3-1 g/m^2 for 1-3 doses every 2-4 wk)	24%-85% of patients	1-8 week	16 weeks	Most are mild to moderate: neutropenia, acute deep venous thrombosis, nausea, vomiting	Up to 50% show a sustained response

Vinca alkaloids

Treatment strategy	Response rate	Time to initial response	Time to peak response	Toxicities	Duration of sustained response
vincristine total dose of 6 mg (1-2 mg per infusion weekly) vinblastine total dose of 30 mg (10 mg per infusion weekly)	Highly variable transient response in 10%-75% of patients	7-14 d	7-42 d	Neuropathy (repeated dose,elderly) neutropenia, fever, inflammation/ thrombophlebitis at the infusion site	A normal platelet count was observed in 6 of 9 (9/12 had response) patients under longterm 3-36 mo monitoring; average, 10 mo

Mycophenolate mofetil

Treatment strategy	Response rate	Time to initial response	Time to peak response	Toxicities	Duration of sustained response
1000 mg twice daily for at least 3-4 wk	Up to 75% of patients; complete response in up to 45%	2-4 weeks	4-6 weeks	Mild and infrequent: headache (most common and doselimiting), backache, abdominal distension, anorexia, nausea	Sustained for short time after Treatment discontinuation

Danazol

Treatment strategy	Response rate	Time to initial response	Time to peak response	Toxicities	Duration of sustained response
200 mg 2-4 times daily	67% complete or partial response; 40% in anecdotal reports	14-90 d	28-180 d	Frequent side effects: acne, increased facial hair, increased cholesterol, amenorrhea, transaminitis	46% remained in remission at a median of 119 ± 45 mo and mean duration of danazol therapy was 37 mo

General management

- Tranexamic acid-extremely useful in the control of mucous membrane bleeding.
- Combination OCP- menorrhagia.
- Avoid IM injections.
- Avoid platelet transfusions

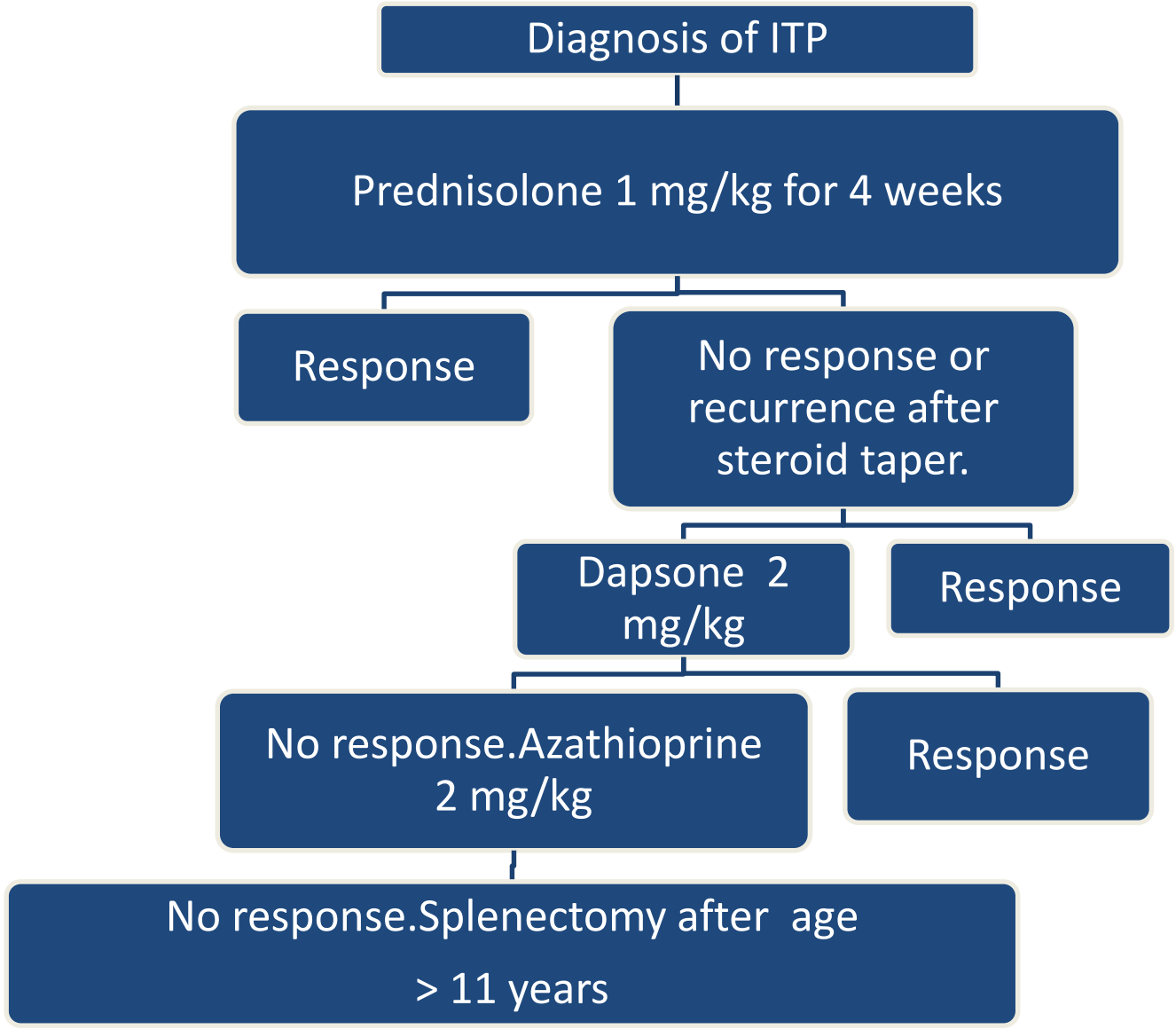
Special situations

- Pregnancy

  Steroid, IVIg/Anti D, Azathioprine, Dapsone.
- CNS bleed

  IVIg/Anti D, Dexamethasone, emergency splenectomy

Algorithm for management of ITP in children



Algorithm for management of ITP in adults