
بسم الله الرحمن الرحيم


IRSTH
Iranian Society of Thrombosis and Hemostasis
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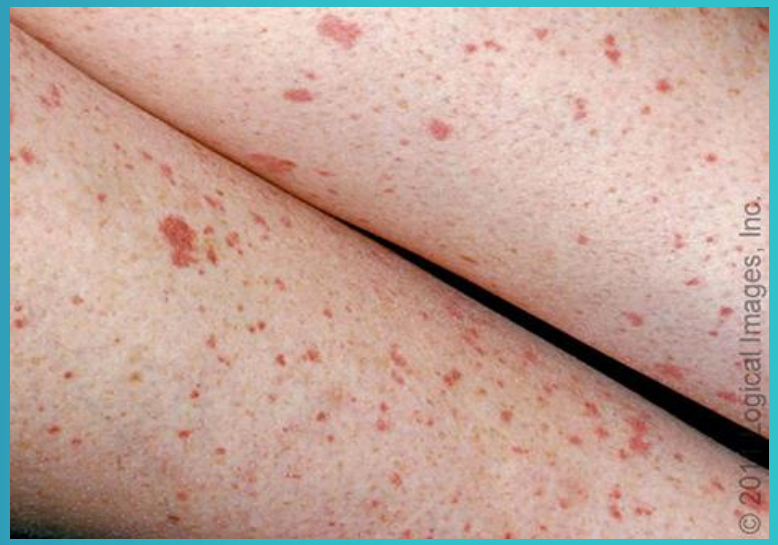
Challenges in Pediatric ImmuneThrombocytopenia



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TERMINOLOGY

Immune thrombocytopenia (ITP) of childhood is characterized by isolated thrombocytopenia
(platelet count <100,000/microL
with normal white blood cell count and hemoglobin).

The current term **Immune ThrombocytoPenia** preserves the widely-recognized acronym ITP and acknowledges the immune-mediated mechanism of the disorder, while allowing that patients may have little or no signs of purpura or bleeding

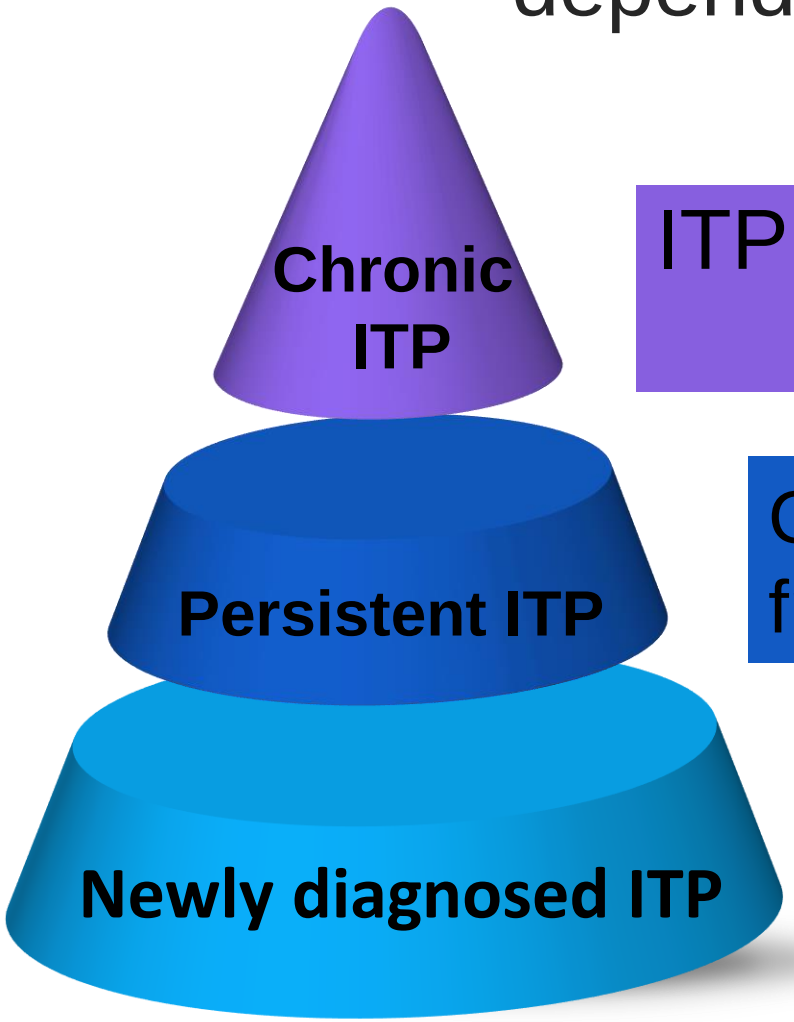
ITP was previously known as idiopathic thrombocytopenic purpura or immune thrombocytopenic purpura.

TERMINOLOGY

Primary Immune thrombocytopenia (ITP) – ITP in the absence of other causes or disorders that may be associated with the thrombocytopenia is known as primary ITP

Secondary ITP – Secondary ITP refers to immune-mediated thrombocytopenia with an underlying cause, including drug-induced, or associated with systemic illness : SLE, CVID, HIV.

Primary ITP is categorized into three phases, depending on the duration of the disease course :



ITP lasting more than 12 months

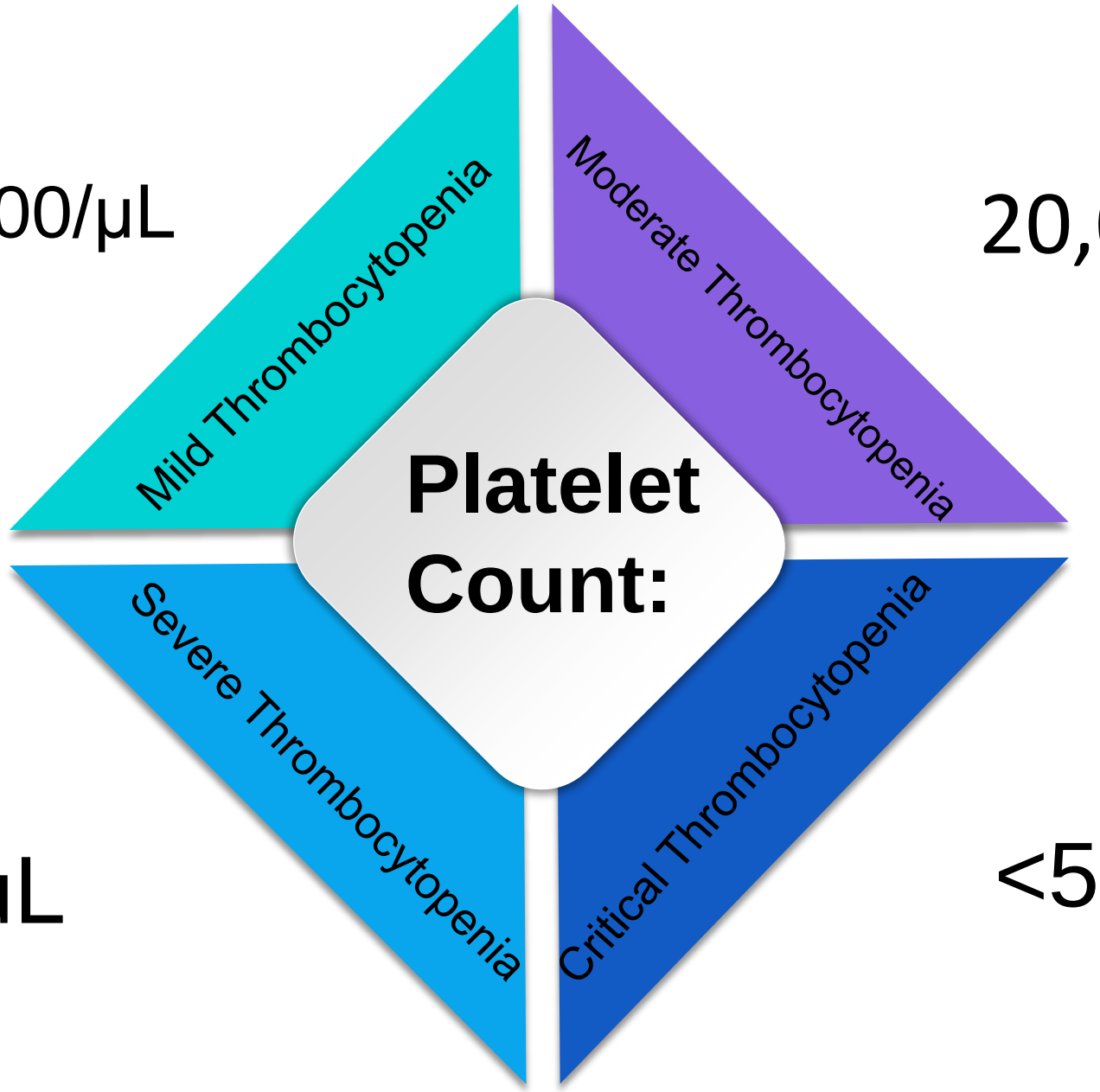
Ongoing ITP between 3 and 12 months from initial diagnosis

ITP within 3 months from diagnosis

TERMINOLOGY

30,000–50,000/µL

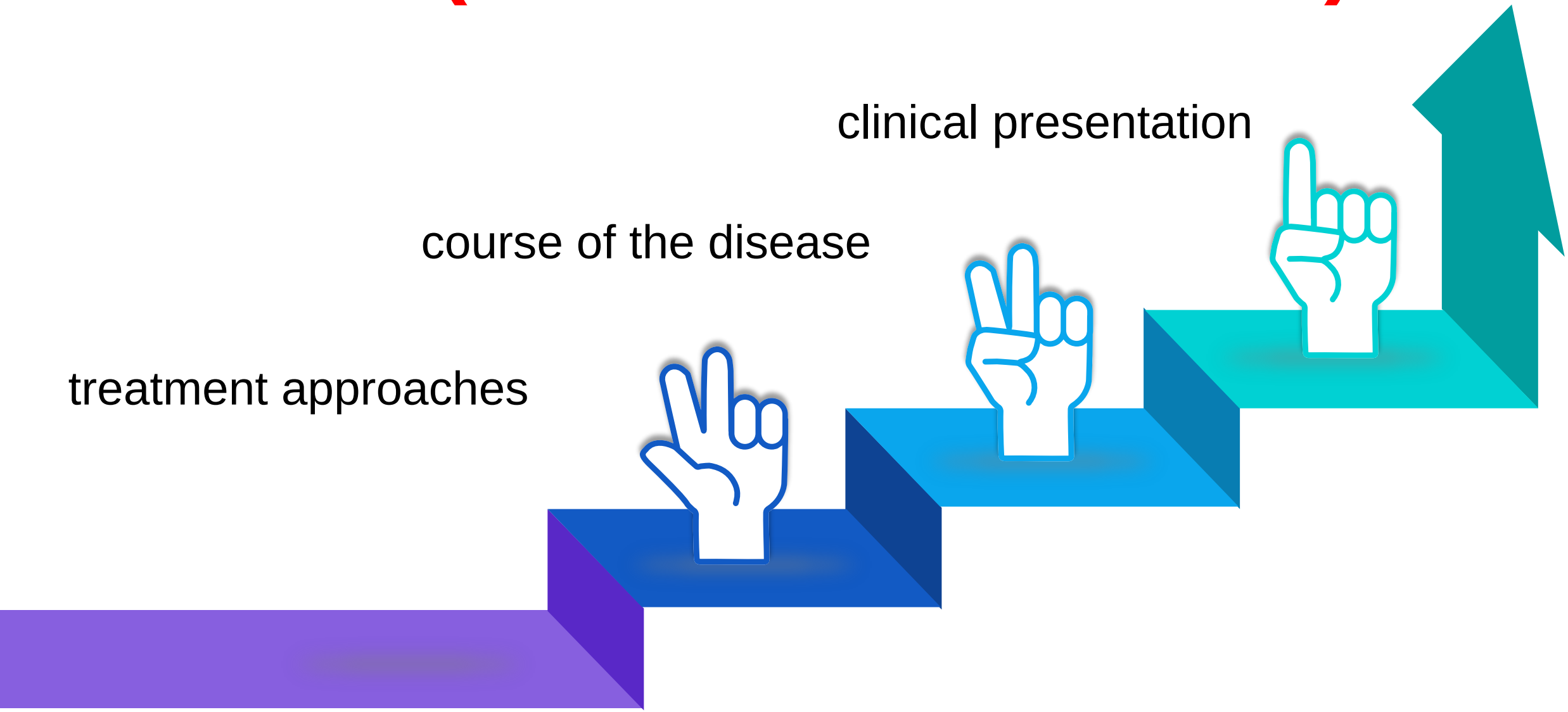
20,000–30,000/µL



<10,000/µL

<5,000/µL

ITP (Adults vs Childrens)



Main differences between ITP in children and adults

Differences Between Pediatric and Adult ITP

Feature	Pediatric ITP	Adult ITP
Typical age	2–7 years	>30 years
Onset	**Acute, sudden**	**Insidious, gradual**
Preceding viral infection	Common	Uncommon

Main differences between ITP in children and adults

Disease course	Usually **self-limited**	Often **chronic**
Progression to chronic ITP	<20%	>60–70%
Sex predominance	Equal	Female > male
Bleeding severity	Usually mild	Variable, may be severe
Intracranial hemorrhage	Very rare	Rare (slightly higher)

Main differences between ITP in children and adults

Treatment decision based on	**Bleeding symptoms**	Platelet count + bleeding
Bleeding score used	Buchanan–Adix	WHO / ISTH
First-line management	Observation / IVIG	Corticosteroids
Response to therapy	Excellent	Variable
Splenectomy	Rare	More common in refractory cases
Relapse rate	Low	High

Diagnostic challenges in pediatric ITP

Non-Specific Symptoms
Overlap with Viral Infections
Absence of Clear Diagnostic Markers
No Specific Test for ITP
Normal Bone Marrow Function
Need to exclude other potential causes of thrombocytopenia

Conditions that may be misdiagnosed as ITP :

Leukemia

Viral Infections (e.g., Epstein-Barr Virus, HIV, Hepatitis)

SLE, ALPS

Bone Marrow Failure Syndromes

CVID

MDS

Drug-Induced Thrombocytopenia

TTP

HUS

HSP

Genetic Disorder: WAS

Storage Disease

Indications for bone marrow examination :

Bone marrow examination is **not routinely** necessary for children with a **typical** **presentation of ITP**

It is performed in selected patients to exclude other causes of thrombocytopenia, such as **malignancy or marrow failure**.

Indications for bone marrow examination :

Based on the available data,
treatment with glucocorticoids
is not considered an indication for BMA
if the child otherwise has typical features of ITP

However, expert opinion varies and some centers choose to perform a bone marrow examination for all patients before initiating steroid treatment.

Indications for bone marrow examination :

Bone marrow examination performed in the following patients:

- Patients with atypical clinical or laboratory
- lymph node enlargement
- splenomegaly
- bone or joint pain
- fevers, weight loss
- neutropenia
- leukocytosis, atypical lymphocytes, or marked anemia)

Indications for bone marrow examination :

- Patients who are **refractory to treatment**
- Patients who develop new findings during follow-up that are not consistent with ITP
- who stop responding to ITP therapies that had previously been effective
- Patients in whom treatment with a thrombopoietin receptor agonist is being contemplated.

Indications for bone marrow examination :

- Inadequate or transient response to ITP treatment and is planned to undergo ***splenectomy,***
- Not resolved by 12 months but who has never required treatment and thus cannot be labeled as "**refractory to treatment**”.

Immature platelet fraction :

The immature platelet fraction (IPF) is an automated laboratory test used for quantifying platelet production and turnover.

The IPF assay uses nucleic acid-specific dyes to detect young platelets that contain residual RNA **(reticulated platelets).**

It is increasingly available on automated blood cell counters.

Immature platelet fraction :

The utility of the IPF in evaluating children with suspected ITP is unclear.

Some experts have suggested that IPF might be useful in cases where the diagnosis of ITP is uncertain, particularly to help distinguish ITP from bone marrow failure states, including leukemia and acquired or inherited aplastic anemia.

Immature platelet fraction :

If the diagnosis of ITP is uncertain,
bone marrow examination is the most reliable and established method for excluding a diagnosis of leukemia or aplastic anemia.

However,
the IPF may be helpful when used in conjunction with other tests

Pseudo-thrombocytopenia :

It occurs due to technical or lab-related factors:

- ✓ Platelet Clumping
- ✓ Antibody-Related Pseudo-Thrombocytopenia (EDTA-Dependent)
- ✓ Platelet Satelitis
- ✓ Incorrect Blood Sample Handling
- ✓ Spurious Results Due to Automated Counting Machines (**Giant platelets**)
- ✓ Cold Agglutinin Syndrome

Challenges in the Treatment of ITP :

The treatment of ITP in children can be complex due to the:

Disease’s unpredictable nature,

Varying responses to treatment,

And the potential for side effects.

Challenges in the Treatment of ITP :

The main challenges in the treatment of ITP in children

1. Variability in Treatment Response
2. Side Effects of Long-Term Medications
3. Need for Second-Line Therapies
4. Chronicity of ITP in Some Children
5. Risk of Severe Bleeding
6. Difficulty in Predicting Disease Course
7. Emotional and Psychological Impact

Treatment Challenges

Management of children with newly diagnosed ITP is based chiefly upon the :

- severity of bleeding symptoms
- The degree of thrombocytopenia
- impact of the ITP on quality of life
- values and preferences of the family

Treat the Patient, Not the Platelet

Platelet count does not equal disease burden

Bleeding phenotype is variable

Fatigue and QoL often underestimated

Modified Buchanan and Adix bleeding score for pediatric immune thrombocytopenia ...

Modified Buchanan and Adix bleeding score for pediatric immune thrombocytopenia (ITP)

Grade	Severity	Description
٠	None	No bleeding of any kind
١	Minor	Few petechiae (≤١٠٠ total) and/or ≤٥ small bruises (≤٣ cm diameter) No mucosal bleeding
٢	Mild	Many petechiae (>١٠٠ total) and/or >٥ large bruises (>٣ cm diameter)
٣	Moderate – Low risk	Blood crusting in nares, painless oral purpura, oral/palatal petechiae, buccal purpura along molars only, mild epistaxis ≤٥ minutes
	Moderate – High risk	Epistaxis >٥ minutes, hematuria, hematochezia, painful oral purpura, significant menorrhagia
٤	Severe	Mucosal bleeding or suspected internal hemorrhage (lung, muscle, joint, etc) that requires immediate medical attention or intervention
٥	Life-threatening/fatal	Documented intracranial hemorrhage or life-threatening or fatal hemorrhage at any site

ITP: immune thrombocytopenia.

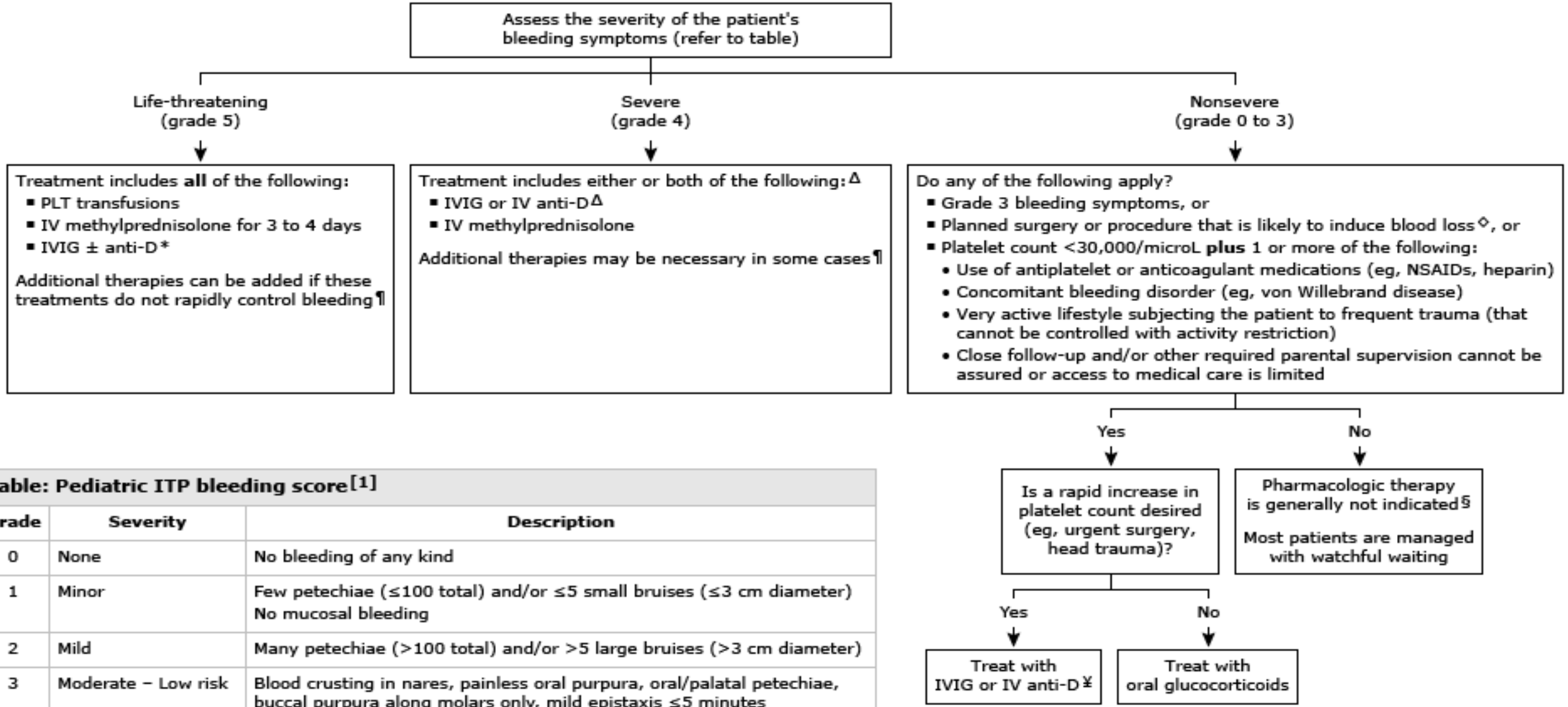


Table: Pediatric ITP bleeding score[1]

Grade	Severity	Description
0	None	No bleeding of any kind
1	Minor	Few petechiae (≤100 total) and/or ≤5 small bruises (≤3 cm diameter) No mucosal bleeding
2	Mild	Many petechiae (>100 total) and/or >5 large bruises (>3 cm diameter)
3	Moderate – Low risk	Blood crusting in nares, painless oral purpura, oral/palatal petechiae, buccal purpura along molars only, mild epistaxis ≤5 minutes
	Moderate – High risk	Epistaxis >5 minutes, hematuria, hematochezia, painful oral purpura, significant menorrhagia
4	Severe	Mucosal bleeding or suspected internal hemorrhage (lung, muscle, joint, etc) that requires immediate medical attention or intervention
5	Life-threatening/fatal	Documented intracranial hemorrhage or life-threatening or fatal hemorrhage at any site

Treatment	Initial response* (days)[1]	Peak response¶ (days)[1]	Initial response rate	Toxicities/risks	Sustained response
First-line options for newly diagnosed or persistent ITP					
Watchful waiting	A few days to 3 to 6 months		Spontaneous complete remission occurs in 50% within one month of presentation and 75% by six months	Risk of preventable hemorrhage (low risk); need for activity restriction; familial anxiety.	Relapse after spontaneous remission is unlikely.
IVIG$^{\Delta}$ **Life-threatening bleeding: 1 gram/kg per day IV for one to three days** **Non-life-threatening bleeding: 0.8 to 1 gram/kg IV, as a single dose**	1 to 3	2 to 7	**Initially effective in >80% of patients**	Side effects include headache (can be severe [eg, aseptic meningitis]), nausea, vomiting, fever, chills, body aches. These can be minimized with premedication and prolonging infusion time.$^{\Delta}$ Transient neutropenia also may occur.	One-third of patients fall below acceptable platelet threshold after 2 to 6 weeks.
Anti-D$^{\Delta\Diamond}$ **75 micrograms/kg IV, as a single dose**	1 to 3	3 to 7	**Initially effective in 70 to 80%**	Headache (less common than with IVIG), fever, chills, nausea, and vomiting. Side effects may be reduced with premedication.$^{\Delta}$ Mild hemolysis is common (eg, fall in hemoglobin by 1 to 2 g/dL). DIC and severe hemolysis or renal failure may rarely occur. Anti-D is contraindicated in patients who are Rh-negative or DAT-positive, or have had splenectomy.	**Similar to IVIG, although longer responses have been described with repeat dosing.**
Methylprednisolone 30 mg/kg as a single daily dose IV for 3 to 4 days (maximum 1000 mg per day)	2 to 14	7 to 28	**Initially effective in 75 to 80%**	Behavioral change, sleep disturbance, hypertension, impaired glucose tolerance.	In one-quarter to one-third of patients, platelet counts fall below acceptable thresholds after 2 to 6 weeks.
Prednisone 4 mg/kg per day orally for 7 days, followed by rapid tapering§ (maximum 240 mg/day)	4 to 14	7 to 28	**Initially effective in up to 75%**	Same as for methylprednisolone above. Prolonged usage may cause weight gain, osteopenia, cataracts, and growth failure.	In many patients, platelet counts fall below acceptable platelet thresholds after tapering, unless the course of prednisone is prolonged.
Dexamethasone 24 mg/m^2 for 4 days orally or IV§ (maximum 40 mg/day)	2 to 14	4 to 28	**Initially effective in up to 75%**	Same as for methylprednisolone above.	In one-third of patients, platelet counts fall below acceptable thresholds after 2 to 6 weeks.

Second-line options for chronic ITP

Rituximab[3] 375 mg/m^2 weekly for four weeks	7 to 56	14 to 180	Initial response in 40 to 50%	Urticarial rash, headache, fever, and chills (mild and transient). Serum sickness in up to 10% of children.	25% long-term response (2 or more years after treatment).
Thrombopoietin receptor agonists (eg, eltrombopag, romiplostim)	5 to 7	Not established	Approximately 80% of patients achieve a response	Transaminitis, mild respiratory illness, headache, epistaxis, cataract (rare).	The response lasts only as long as the drug is continued; these drugs do **not** typically induce remission.
Splenectomy	1 to 56	7 to 56	**60 to 70% long-term response**	Complications include sepsis and portal vein thrombosis.	70 to 80% of responders maintain platelet response over 4 years.

Target platelet count :

For patients who are managed with pharmacotherapy, treatment is aimed at increasing the platelet count *above a threshold that stops bleeding or reduces the risk of serious bleeding.*

The **goal** of these treatments is **not** to achieve a normal platelet count.

Target platelet count :

Generally use a target of **≥20,000 to 30,000/microL**
in most cases
(except in the case of life-threatening bleeding or surgery,
for which higher platelet counts may be necessary).

In particular, long-term steroid use is virtually never indicated
in children and other options should be pursued in
patients requiring treatment longer than **one to two** months.

Response to treatment :

Expected response

— Approximately 75 to 90 percent of patients respond to initial treatment with first-line therapies.

Genetic variations in the immunoglobulin G (IgG) Fc receptor IIb (FCGR2B) appear to influence the response to IVIG and the likelihood of achieving early complete remission.

Patients expressing the **FCGR2B-2321 allele** have a high likelihood of **complete response**, whereas patients who express homozygous FCGR2B-232T are less likely to respond

Poor response to initial therapy :

For patients who do not have an adequate response to the initial treatment in the setting of persistent platelet count <20,000/microL), **management includes:**

1-Changing to or adding another first-line agent
2- Assessment for other causes of thrombocytopenia

Antiplatelet & anticoagulants in ITP

Antiplatelet medications (eg, aspirin, ibuprofen, other [NSAIDs]) and **anticoagulants** (eg, heparin, enoxaparin, warfarin, DOACs) generally should be **avoided** if the platelet count is **very low (ie, <20,000/microL**).

The risk of clinically significant bleeding with ibuprofen is low.

Nevertheless, because of the potential for severe bleeding with its use, we advise avoiding ibuprofen unless it is truly necessary.

Antiplatelet & anticoagulants in ITP

If these medications are necessary,

pharmacologic treatment of the ITP may be warranted

to increase the platelet count to a safe level

(eg, for patients requiring ongoing anticoagulant therapy,

the platelet count usually is kept >50,000/microL).

Antipyretic or Analgesic therapy in ITP

For children with ITP who require antipyretic or analgesic therapy, we suggest starting with acetaminophen.

If the child does not have adequate symptom relief with acetaminophen, other agents can be tried such as a cyclooxygenase-2 selective NSAID (eg, **celecoxib**) since these agents have less antiplatelet activity compared with ibuprofen and aspirin.

Vaccination and ITP

There is a very small increased risk of developing ITP in the six weeks following a (MMR) vaccination.

MMR-associated ITP is rare, occurring in approximately 2.6 cases per 100,000 doses of vaccine

Risk factors for chronic ITP

- Age at Onset(<2y Vs >10Y)
- Gender(females, particularly those in their teenage years,)
- Presence of Autoimmune Diseases(SLE, rheumatoid arthritis, or Hashimoto's thyroiditis)
- Response to Initial Treatment
- Need for Multiple Therapies

Risk factors for chronic ITP

- Delayed Intervention
- The persistence of immune dysregulation, where the immune syste fails to recognize platelets as “self,” can contribute to chronic ITP.
- Less severe thrombocytopenia at the initial diagnosis
- Insidious onset of symptoms
- Lack of preceding infection or vaccination prior to development of ITP
- Lack of mucosal bleeding at diagnosis
- Genetic Predisposition

Splenectomy in Children with ITP :

Splenectomy is considered a treatment option in chronic ITP in children,
particularly when other treatments have not been successful.

and the risk of bleeding remains significant.

Splenectomy in Children with ITP :

Main indications for splenectomy in children with ITP:

1. Failure of First-Line and Second-Line Treatments If a child with chronic ITP does not respond to or has relapses after first-line treatments

2. Severe Bleeding Risk Despite Medical Treatment(plt< 10000)

Splenectomy in Children with ITP :

3. Significant Impact on Quality of Life(hospitalizations, treatment side effects, emotional, and psychological stress)

4. Desire for a Permanent Solution (Parental Choice)

Splenectomy in Children with ITP :

Benefits of Splenectomy in ITP:

Increase in Platelet Count: Approximately 60–80%

Reduced Need for Ongoing Medication

Improve the quality of life.

Risks of Splenectomy:

Infection Risk

Relapse of ITP

Surgical Risks

Role of Thrombopoietin Receptor Agonists (TPO Agonists)

Some specific situations where TPO agonists are indicated include:

- 1. Chronic ITP (lasting >12 months)
- 2. Failure to Respond to Other Treatments
- 3. Platelet Counts Below Safe Levels <30000
- 4. **Alternatives to Splenectomy**

Role of Thrombopoietin Receptor Agonists (TPO Agonists)

- **Benefits of TPO Agonists**
- 1. Improved Quality of Life
- 2. Avoidance of Splenectomy
- 3. Reduced Need for Steroids and Immunosuppressive Therapies

- **Risks and Side Effects of TPO Agonists**
- Long-term use of TPO agonists may lead to bone marrow fibrosis
- Thrombosis .
- Liver Enzyme Elevations (for Eltrombopag)

Role of Thrombopoietin Receptor Agonists (TPO Agonists)

- **Risks and Side Effects of TPO Agonists**
- Injection Site Reactions (for Romiplostim)
- Development of Antibodies

- In some cases, children may develop antibodies against the TPO agonists, leading to treatment resistance.
- This is more common with Romiplostim.

Role of Sirolimus in the Treatment of ITP :

Sirolimus is an immunosuppressive medication
it has also been explored as a potential treatment for (ITP),
particularly in cases that are chronic or refractory to
standard therapies like corticosteroids, IV immunoglobulin (IVIg),
or splenectomy.

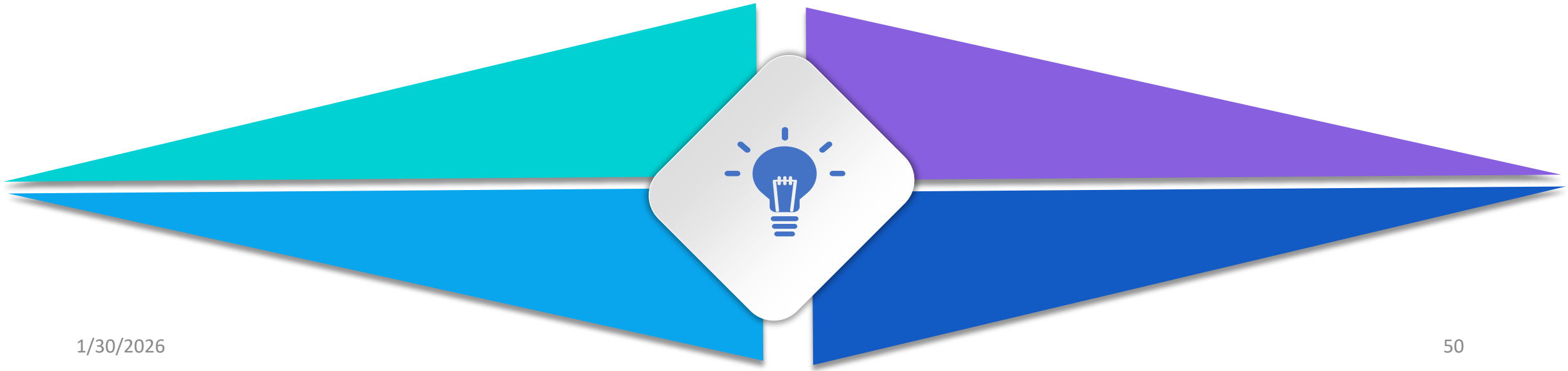
Role of Sirolimus in the Treatment of ITP :

Mechanism of action:

1. Inhibition of mTOR Pathway.
2. Reduction of Autoimmune Response
3. Possible Direct Effects on Platelet Production

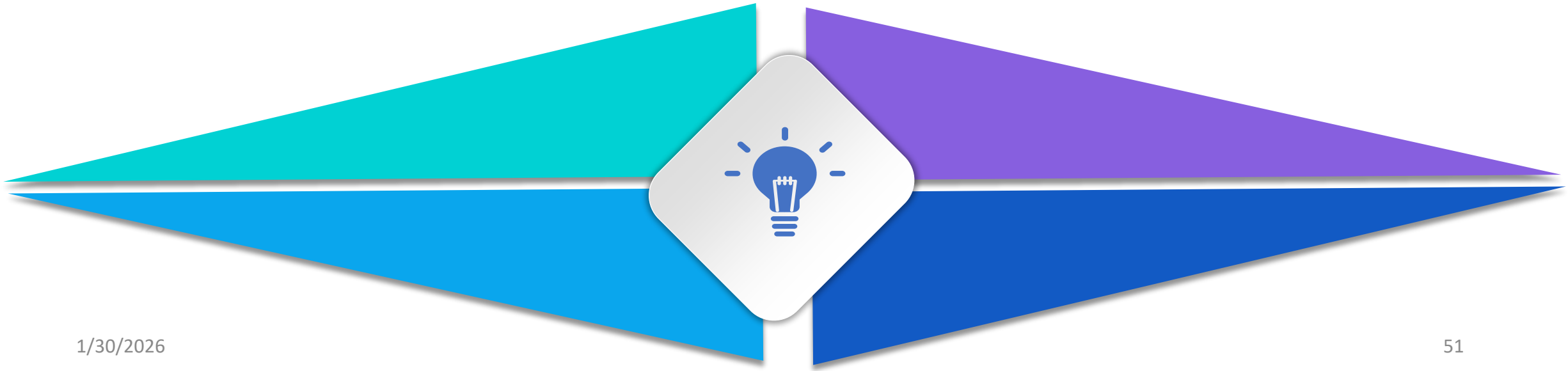
Novel Therapies: FcRn Inhibitors

- Block IgG recycling
- Rapid reduction of pathogenic autoantibodies
- Example: **Efgartigimod**



Novel Therapies:
BTK (Bruton's Tyrosin kinase) Inhibitors

- Target B-cell and macrophage signaling
- Rilzabrutinib preserves platelet function
- Rapid onset of response



Targeting Plasma Cells

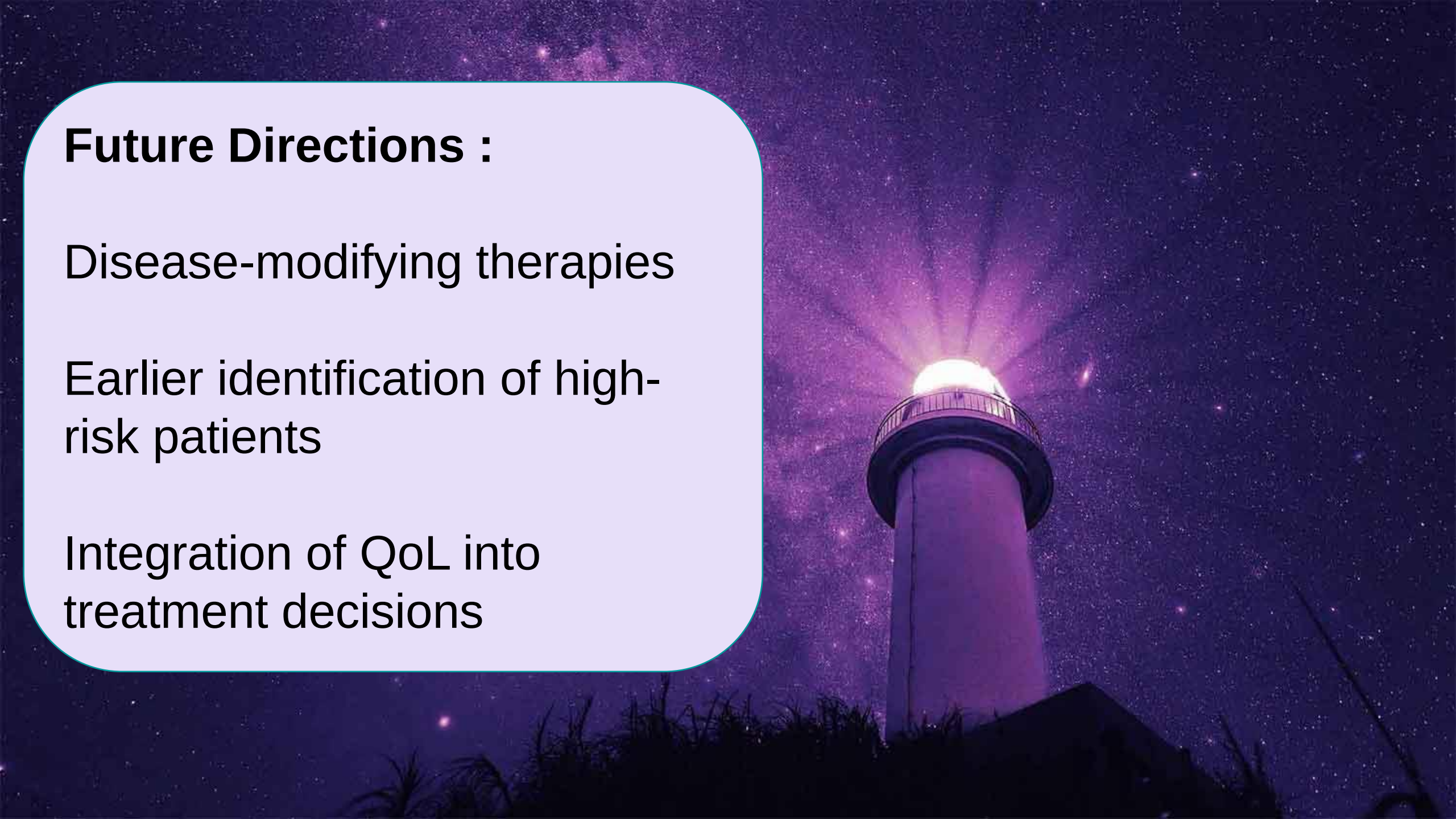
- Long-lived plasma cells resist rituximab
- Anti-CD38 therapy (daratumumab)
- Promising in severe refractory cases

Complement Inhibition

- Complement-mediated platelet destruction
- Sutimlimab (anti-C1s)
- Potential role in emergency rescue

Precision Medicine in ITP

- Identify underlying immune dysregulation
- Targeted therapy based on genetics
- Shift from empiric to individualized treatment



Future Directions :

Disease-modifying therapies

Earlier identification of high-risk patients

Integration of QoL into treatment decisions

Take-Home Messages

ITP is heterogeneous and complex

Diagnosis is the first major challenge

Platelet count alone is insufficient

Future management will be precision-based

Treat the Patient, Not the Platelet

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Thanks For Your attention