SELF-SABOTAGE: AUTOIMMUNE DISORDERS IN PEDIATRIC HEMATOLOGY

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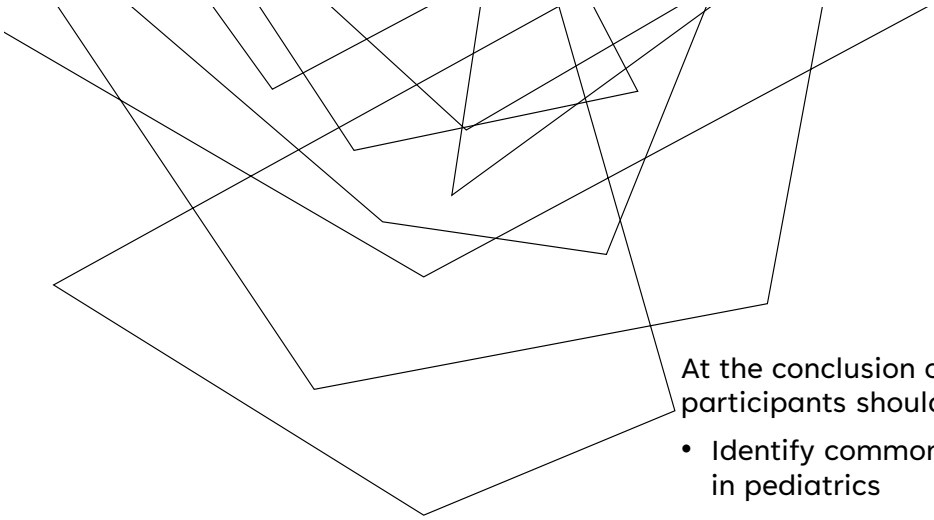


OBJECTIVES

At the conclusion of this session, participants should be able to

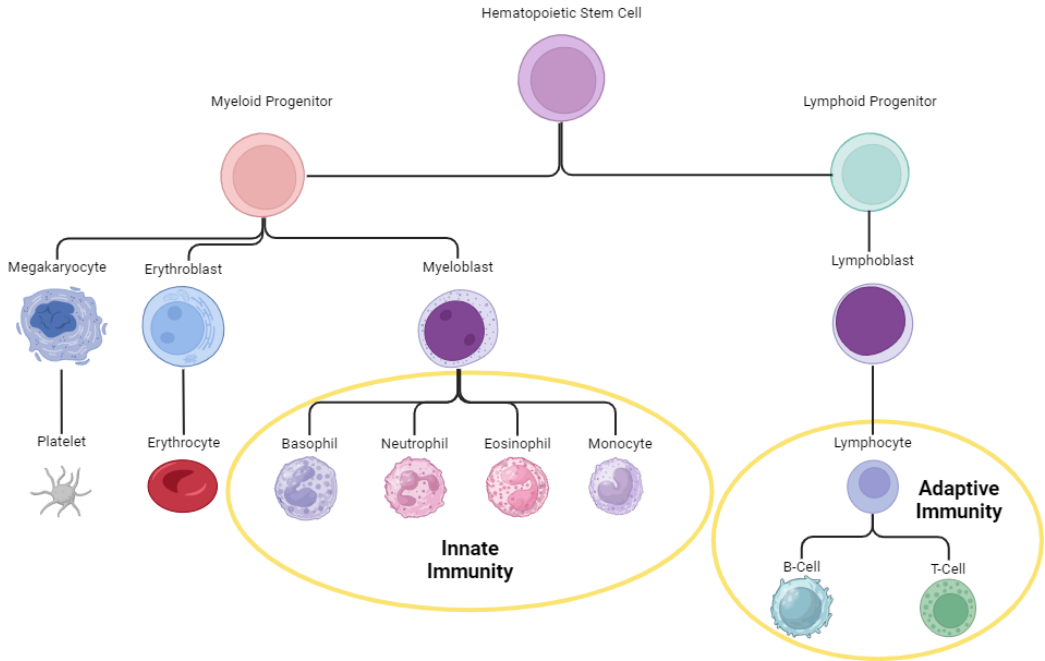
- Identify common autoimmune disorders in pediatrics
- Review hematologic manifestations of common pediatric autoimmune disorders
- Discuss management of autoimmune disorders in pediatric hematology

OUTLINE

- Autoimmunity overview
- Hematology overview
- General therapeutic strategies
- Case studies: Autoimmune disorders impacting
  - RBC
  - WBC
  - Platelets
  - Bleeding/Clotting
- Conclusion

WHAT IS AUTOIMMUNITY?

- Autoimmune processes are set in motion by B cell and T cell reactions to self.
- Other cell types as well as cytokines also interact to produce an immune response.
- Etiologies for autoimmunity are not fully understood but are thought to be a result of both environmental and genetic factors.

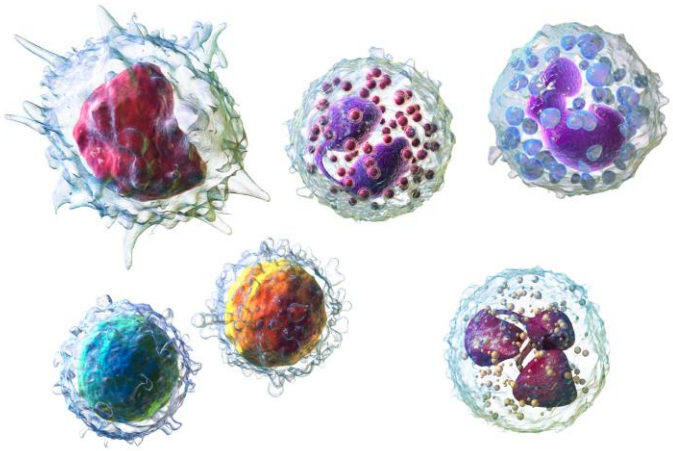

Hematopoietic Stem Cell
Myeloid Progenitor
Lymphoid Progenitor
Megakaryocyte
Erythroblast
Myeloblast
Lymphoblast
Platelet
Erythrocyte
Basophil
Neutrophil
Eosinophil
Monocyte
Lymphocyte
Innate Immunity
Adaptive Immunity
B-Cell
T-Cell

ADAPTIVE IMMUNE SYSTEM

B-cells
- Plasma cells
- Memory cells

T-cells
- Cytotoxic (CD8+)
- Helper (CD4+)

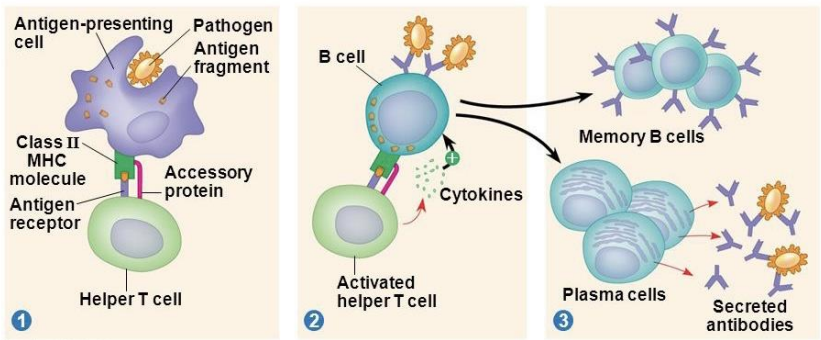
Immunoglobulins
IgG
IgA
IgM



1. B cells: Types and function. Cleveland Clinic. February 1, 2023. Accessed March 11, 2024. https://my.clevelandclinic.org/health/body/24669-b-cells.
2. T cells: Types and function. Cleveland Clinic. January 17, 2023. Accessed March 11, 2024. https://my.clevelandclinic.org/health/body/24630-t-cells.

MECHANISM OF IMMUNITY

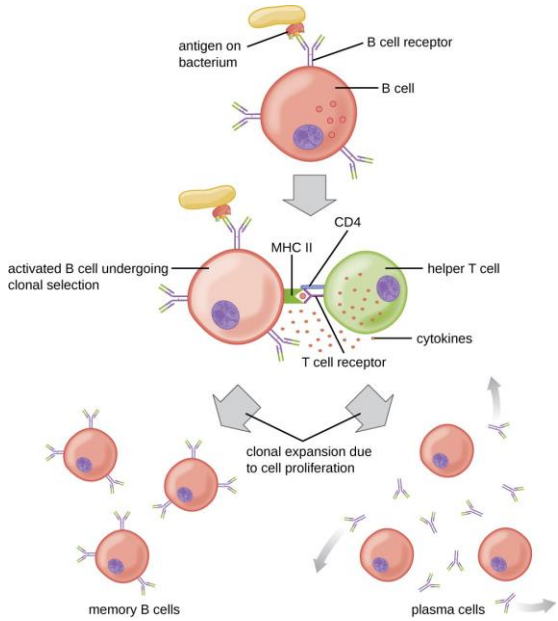
1. Antigen-presenting cell binds antigen to an MHC-II complex
2. Activated Helper T-cells
   → Bind to MHC-II/Ag complex
   → Cause B-cells to activate
3. B cells produce antibodies which bind to the specific antigen in question



Reece JB, Campbell NA. *Campbell Biology*. Pearson; 2011.

MECHANISM OF AUTOIMMUNITY

- B cell/T cell response to an autoantigen
- May be tissue-specific, organ-specific, or generalized
- May be acute or chronic



INBORN ERRORS OF IMMUNITY (IEI)

- Caused by genetic point mutations
- Associated with immune dysregulation (e.g. autoimmunity or autoinflammation) and infections
- Range in severity
- IEI with associated hematologic effects include severe combined immunodeficiency and Wiskott-Aldrich syndrome

IMMUNE DISORDERS WITH ASSOCIATED HEMATOLOGIC ABNORMALITIES

- Autoimmune hemolytic anemia
- Hemolytic disease of the fetus and newborn
- Autoimmune neutropenia
- Autoimmune lymphoproliferative syndrome
- Immune thrombocytopenia
- Neonatal autoimmune thrombocytopenia
- Neonatal alloimmune thrombocytopenia
- Evans syndrome
- Antiphospholipid antibody syndrome
- Systemic lupus erythematosus
- Immune thrombotic thrombocytopenia purpura
- *And more*

HEMATOLOGY WORKUP FOR AUTOIMMUNE DISORDERS

Select associated laboratory parameters:

- Erythrocytes
- CBC
- Reticulocyte count
- Direct Antiglobulin Test (DAT)

- Leukocytes
- Differential
- Flow cytometry immunofluorescence for antineutrophil antibodies

Platelets
- (CBC)
- MPV
- Platelet antigen genotyping
- Platelet antibody identification

Miscellaneous
- PT/PTT
- IgG/IgM
- Antinuclear antibody (ANA)

SECOND-LINE TESTING

Direct Antiglobulin Test (DAT):

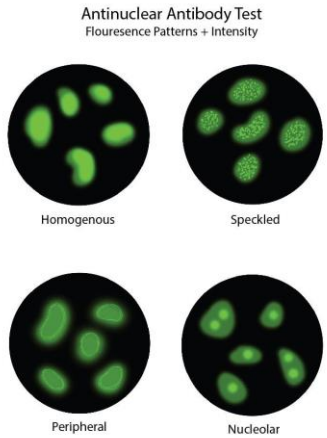
- Ordered when erythrocyte antibody-induced hemolysis is suspected (e.g. AIHA, hemolytic disease of the newborn)

Theis SR, Hashmi MF. Coombs test. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK547707/. Published September 12, 2022.

SECOND-LINE TESTING

Antinuclear antibodies (ANA):

- Ordered when a systemic autoimmune disorder is suspected
- Testing detects antibodies to nuclear components (e.g. DNA, RNA)
- Reported as a titer
- Nonspecific
  - May be targeted to detect specific autoantibodies

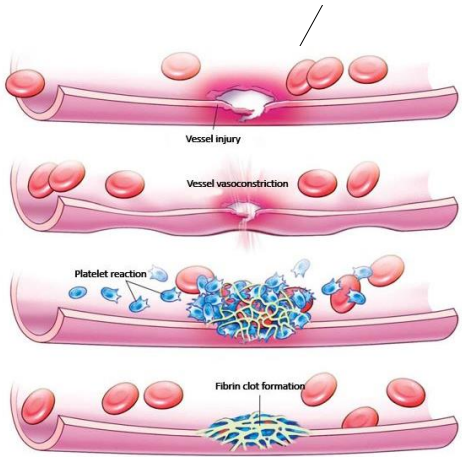


Nosal RS, Superville SS, Amraei R, et al. Biochemistry, Antinuclear Antibodies (ANA) . StatPearls – NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK537071. Published December 29, 2022.

Xavier B, De LE, Borghi MO, Meroni PL. Understandindg and interpreting antinuclear antibody tests in systemic rheumatic diseases. *Nature Reviews. Rheumatology*. 2020;16(12):715-726.

HEMOSTASIS REVIEW

- Vessel injury
- Vasoconstriction
  - Restricts blood flow
- Platelet reaction
  - Adhesion
  - Release of granules and lysosomes
  - Aggregation
- Procoagulant activation
- Fibrin clot formation

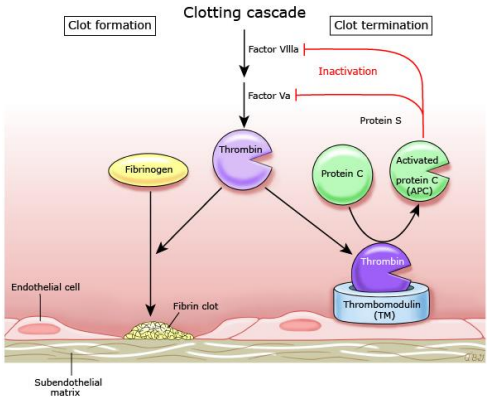


Fritsma MC, Fritsma GA. Normal hemostasis and coagulation. In: Rodak BF, Fritsma GA, Keohane E, eds. Hematology: Clinical Principles and Applications. 4th ed. St. Louis, MO: Elsevier Saunders; 2013:626-46.

HEMOSTASIS REVIEW

Coagulation Inhibitors

- Antithrombin
- Protein S
- Protein C
- Tissue factor pathway inhibitor
- C1 esterase inhibitor



	Procoagulants	Coagulation Inhibitors	Fibrinolysis
Hemorrhage	↓		↑
Thrombosis	↑	↓	↓

GENERAL TREATMENT STRATEGIES

Immunosuppressants – reduce the degree of an immune response

Glucocorticoids

- Restrict production of inflammatory cytokines, T cells, and B cells
- Suppress adhesion molecules

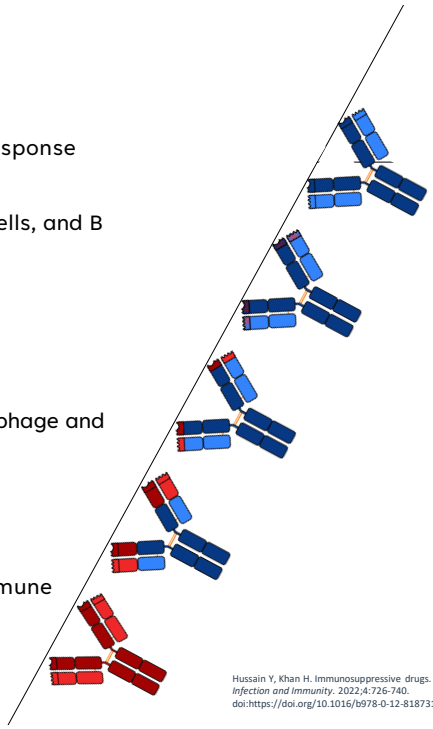
Immunoglobulins

- Pooled donor product administered intravenously
- IgG-dominant
- Reduce proinflammatory factors as well as macrophage and monocyte activation

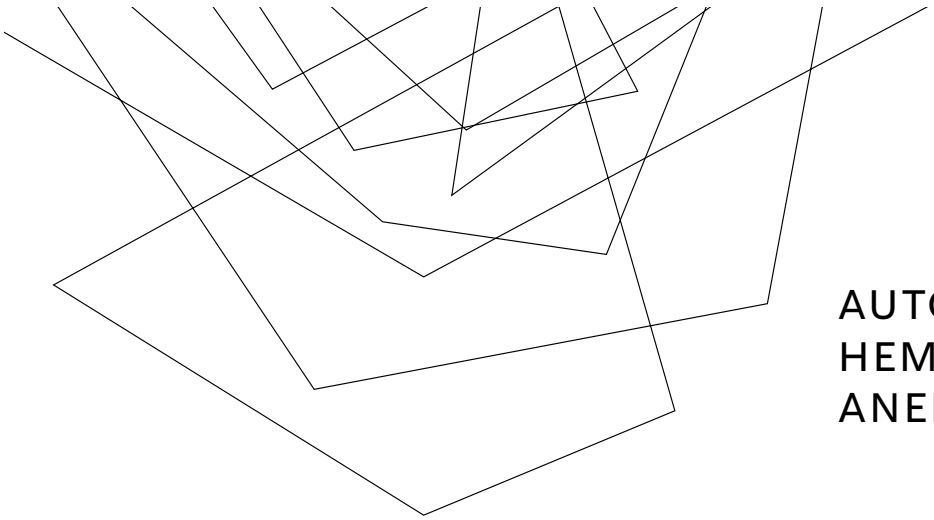
Monoclonal antibodies

- Bind to specific antigens
- Inhibit cytokines, complement, T cells, B cells

Anti-inflammatories – used in the management of autoimmune diseases with an associated inflammatory component.



Hussain Y, Khan H. Immunosuppressive drugs. *Encyclopedia of Infection and Immunity.* 2022;4:726-740. doi:https://doi.org/10.1016/b978-0-12-818731-9.00068-9



AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA)

AIHA

- 50-60% of cases are secondary to another condition.
- Anemia may be acute and severe (Hb ~2-3 g/dL)
- Autoantibodies bind to antigens on erythrocytes, resulting in hemolysis.
- Associated autoimmune disorders: SLE, JIA, scleroderma, UC
- Lab findings: +DAT; decreased Hb; elevated reticulocyte count, bilirubin, AST, and LDH; high titer cold agglutinin (cold agglutinin disease); hemoglobinuria (PCH); Donath-Landsteiner autoantibodies (PCH)

Warm-reactive AIHA

- Most common form of AIHA in children (60-90%)
- IgG involvement
- Extravascular hemolysis

Cold agglutinin disease

- IgM involvement
- Typically occurs post-infection (M. pneumoniae, EBV)
- Less common in children (~10% of diagnoses)

Paroxysmal cold hemoglobinuria

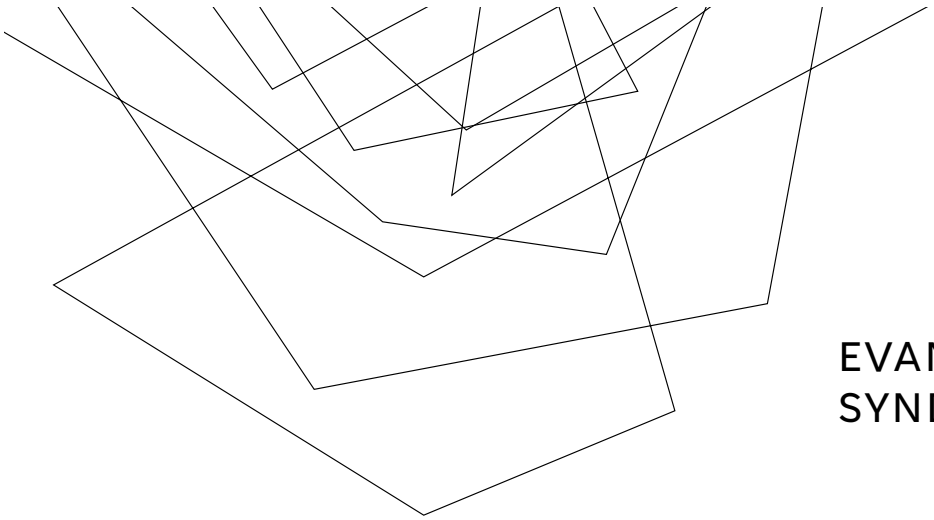
- Typically diagnosed in young children, post-viral
- IgG binds to the P antigen on RBC
- Intravascular hemolysis and hemoglobinuria

AIHA - MANAGEMENT

Treatment choices are dictated by degree of anemia

If severe, urgently transfuse with compatible pRBC

- **Warm-reactive AIHA**
  - Glucocorticoids (IV methylprednisolone, oral prednisone)
  - Frequent laboratory monitoring of hematologic parameters, slow steroid taper until values have normalized
  - Rituximab
  - IVIG may be indicated in the setting of severe hypogammagobulinemia
  - Splenectomy
- **Cold-agglutinin disease** and **paroxysmal cold hemoglobinuria**
  - Keep patient warm and warm donor pRBC. Transfuse slowly to reduce risk of transfusion reaction.
- Workup for secondary causes of AIHA (initially, then annually)



EVANS SYNDROME

EVANS SYNDROME

Autoimmune hemolytic anemia and immune thrombocytopenia and/or autoimmune neutropenia

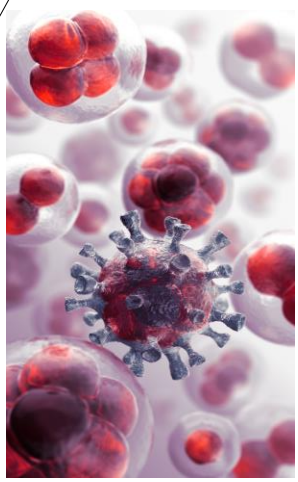
Frequently (~50%) associated with autoimmune lymphoproliferative syndrome, systemic lupus erythematosus, malignancy, etc. (Secondary Evans syndrome)

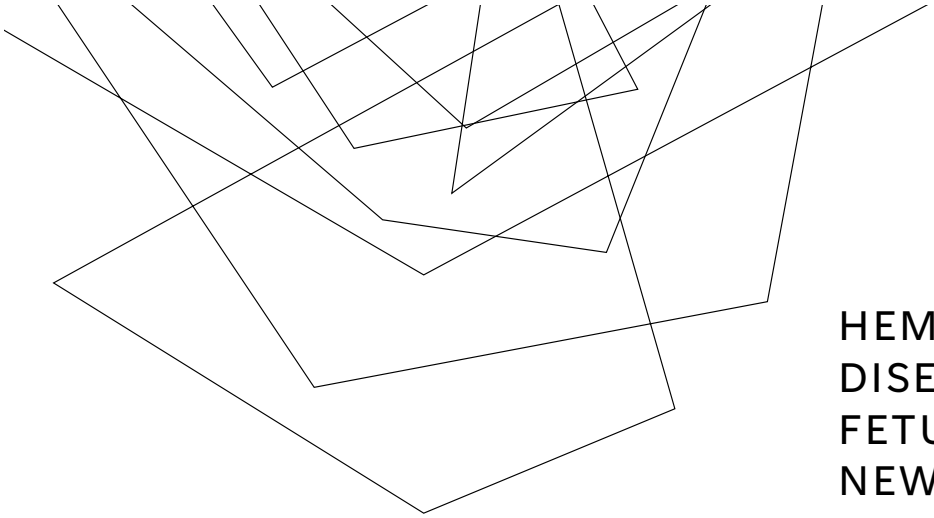
Genetic testing may be indicated

EVANS SYNDROME - MANAGEMENT

- Glucocorticoids
- IVIG (for concomitant ITP)
- Rituximab
- Splenectomy
- Hematopoietic stem cell transplantation

- ➢ May require long-term immunosuppression, often refractory to treatment
- ➢ Joint management with Hematology and Rheumatology





HEMOLYTIC DISEASE OF THE FETUS AND NEWBORN

HEMOLYTIC DISEASE OF THE FETUS AND NEWBORN

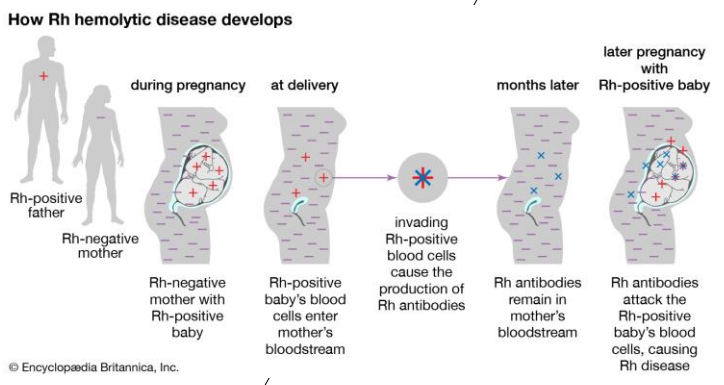
Mismatch between maternal and fetal antigens

- Rh incompatibility: Mother Rh antigen negative, baby Rh antigen positive

Also: anti-K, anti-c, anti-E

Maternal IgG antibodies cross the placenta and enter fetal circulation.

- Clinically significant anemia due to ABO incompatibility is much less common.



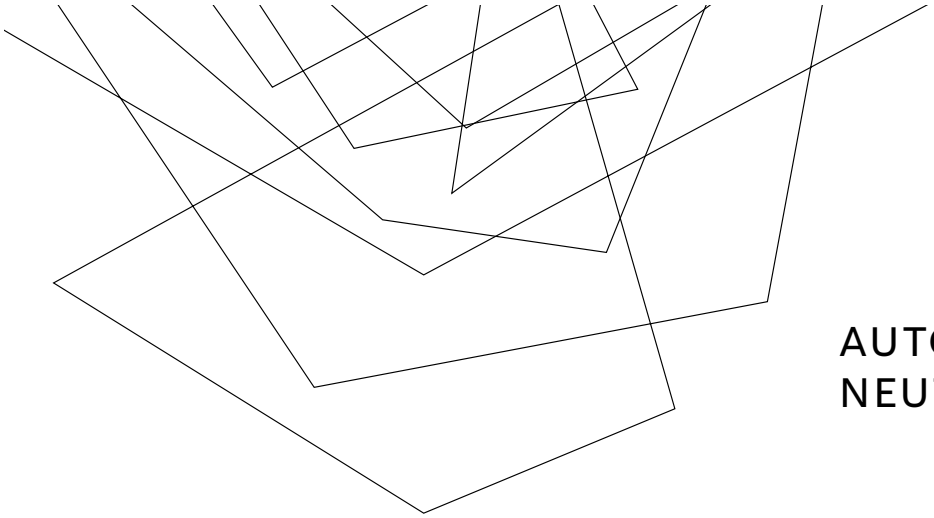
HEMOLYTIC DISEASE OF THE FETUS AND NEWBORN – MANAGEMENT

Antenatal

- Maternal alloantibody screening and quantification
- If positive,
  - paternal antigen testing
  - Anti-D immune globulin (RhoGAM)
  - If necessary, cell-free fetal DNA testing or amniocentesis for fetal antigen status
- Degree of fetal anemia determined by
  - Fetal middle cerebral artery Doppler scan
    - If elevated, percutaneous umbilical cord blood sampling
    - If anemia is severe, intrauterine transfusions may be indicated

Postnatal

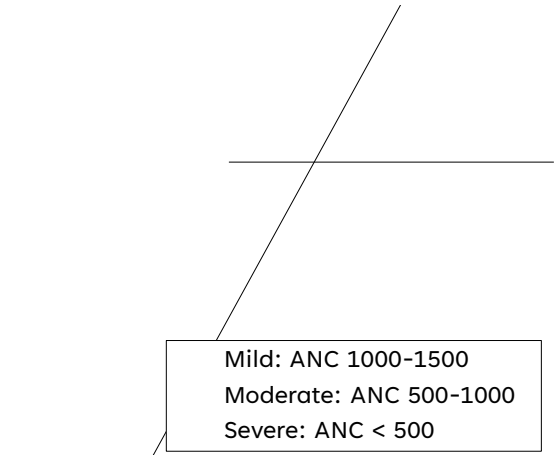
- If anemia is severe, transfuse with Group O, RhD-negative pRBC (or IVIG) followed by exchange transfusion
- If anemia is moderate, perform a simple transfusion and manage hyperbilirubinemia
- Mild anemia typically does not require correction with transfusion



AUTOIMMUNE NEUTROPENIA

PRIMARY AUTOIMMUNE NEUTROPENIA

- Development of antibodies to human neutrophil antigens (HNAs) on granulocytes
- Often preceded by a viral infection.
- May be an incidental finding. Not typically associated with severe infections.
- No evidence of significant underlying disorders
  - Important to rule out other causes of neutropenia
- Typically occurs between 4-28 months old



Callejas Caballero I, Illán Ramos M, Berzosa Sánchez A, Anguita E, Ramos Amador JT. Autoimmune neutropenia associated with influenza virus infection in childhood: a case report. BMC Infect Dis. 2021;21(1):830. Published 2021 Aug 18. doi:10.1186/s12879-021-06506-9

AUTOIMMUNE NEUTROPENIA - MANAGEMENT

- Fever precautions
- Exhaustive personal and family history to investigate possibility of congenital neutropenia
- Unclear role for prophylactic antibiotics
- Monitor until resolution to rule out malignancy, immunodeficiency, or systemic autoimmune conditions
- Remission is typically spontaneous after 1-2 years
- In rare cases, granulocyte colony stimulating factor (G-CSF) may be indicated

AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS)

AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS)

- Inadequate lymphocyte apoptosis leads to lymphoproliferation
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Cytopenias (associated with Evans syndrome)
  - Increased risk of malignancy
- Autosomal dominant autoimmune condition associated with *FAS* genetic mutations
- Increased risk of lymphoma due to defective lymphocyte apoptosis
- Associated with inborn errors of immunity (e.g. *FAS, CASP10, NRAS, KRAS*)
- Initial presentation in early childhood. Males > females.

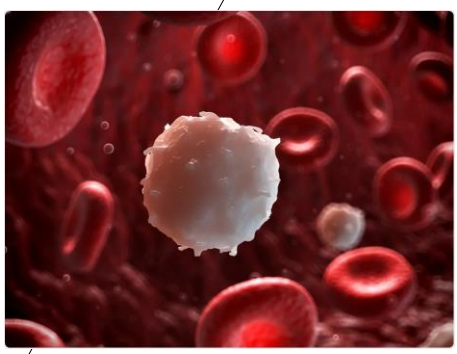
Workup:
- Flow cytometry for alpha beta double-negative (CD4 and CD8) T cells
- Lymph node biopsy
- Immunoglobulins (increased IgG, IgA, IgE)
- DAT
- Antiplatelet/antineutrophil/ antiphospholipid/antinuclear antibodies
- Rheumatoid factor

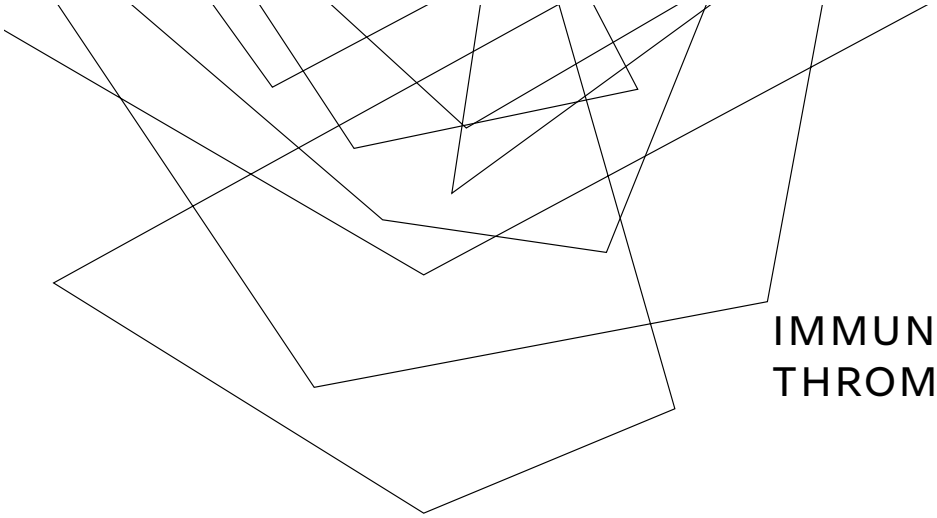
Sogkas G, Witte T. The link between rheumatic disorders and inborn errors of immunity. *EBioMedicine*. 2023;90:104501. doi:10.1016/j.ebiom.2023.104501

ALPS - MANAGEMENT

Treatment strategies differ based upon lymphoproliferative effects vs. autoimmune cytopenias and include immunosuppressants and immunomodulators.

- Sirolimus or mycophenolate mofetil/MMF (immunosuppressants)
- IVIG
- Glucocorticoids
- Rituximab
- Hematopoietic stem cell transplantation
- Splenectomy is not recommended.

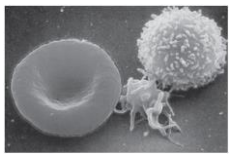




IMMUNE THROMBOCYTOPENIA

IMMUNE THROMBOCYTOPENIA

- May be primary or secondary
- Autoantibodies targeting antigens on the platelet membrane
  - Shortened platelet half life
  - Cleared by macrophages (spleen-predominant)
  - Isolated thrombocytopenia, typically with elevated MPV
  - Rarely, microcytic anemia may be present if bleeding has been significant/prolonged
  - Normocytic anemia should prompt additional workup



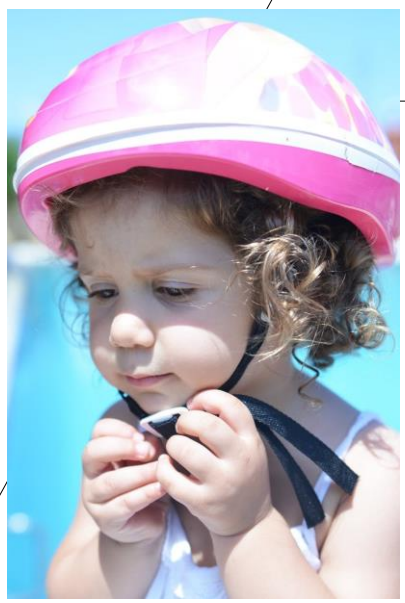
- Typical presentation is sudden mucocutaneous bleeding in a young child with a recent history of viral illness
  - Peak age 2-5 years
  - ~60% post-infectious
- Normal or increased number of megakaryocytes on bone marrow biopsy
- Rule out other possible etiologies of thrombocytopenia
  - Malignancy
  - Bone marrow failure
  - Congenital thrombocytopenia
  - Medication-induced thrombocytopenia

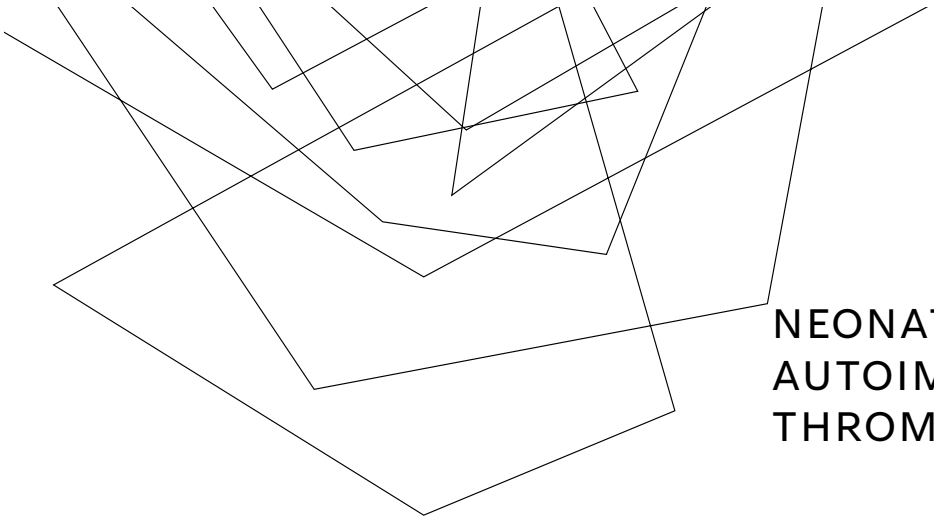
SECONDARY ITP

- SLE
- ALPS
- APAS
- CVID

IMMUNE THROMBOCYTOPENIA – MANAGEMENT

- Frequent laboratory monitoring to trend platelet counts
- Safety precautions and restriction of contact activities
- Avoidance of medications with antiplatelet/anticoagulant effects
- Therapeutic options are selected based upon severity of bleeding symptoms (e.g. mucocutaneous bleeding) and desired activity.
  - IVIG
  - Anti-D immune globulin
  - Oral glucocorticoids
- Management of refractory/chronic ITP may include
  - Rituximab
  - Thrombopoietin receptor agonists
  - Immunosuppressants (e.g. MMF, sirolimus, cyclosporine)

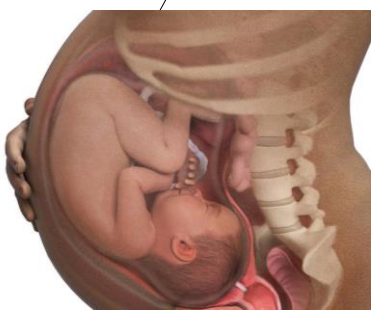




NEONATAL AUTOIMMUNE THROMBOCYTOPENIA

NEONATAL AUTOIMMUNE THROMBOCYTOPENIA

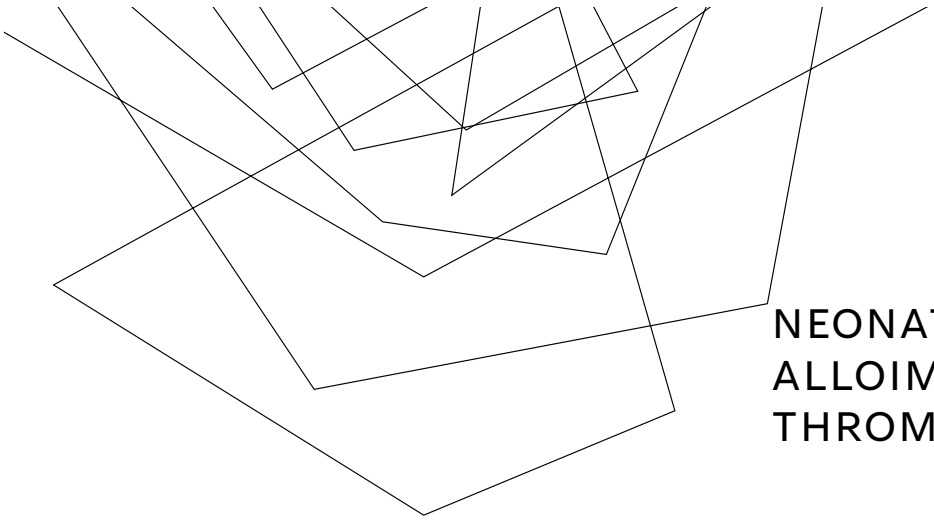
- Maternal history of ITP during pregnancy
- Possible risk factors for increased severity of neonatal autoimmune thrombocytopenia
  - Maternal splenectomy
  - Maternal platelet count < 50,000 at any point during pregnancy
  - Older sibling with history of neonatal ITP
- The minority of affected infants develop severe thrombocytopenia (10-25%)
- Clinically significant bleeding is rare



NEONATAL AUTOIMMUNE THROMBOCYTOPENIA - MANAGEMENT

- Close monitoring of the neonate's platelet count is required
  - Platelet count should be > 30,000 and stable before discharge
- Cranial ultrasound is indicated for platelet counts <50,000
- IVIG is indicated for significant bleeding and/or platelet counts <30,000
- Counsel parents that maternal IgA can be present in breastmilk and transferred to baby, leading to thrombocytopenia

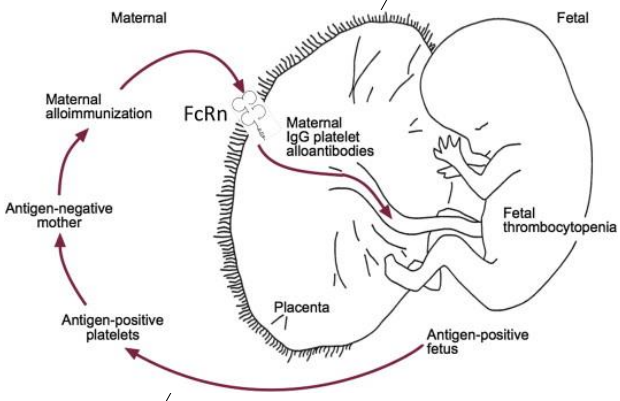
https://www.sciencedirect.com/topics/medicine-and-dentistry/neonatal-thrombocytopenia



NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

(FETAL AND) NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

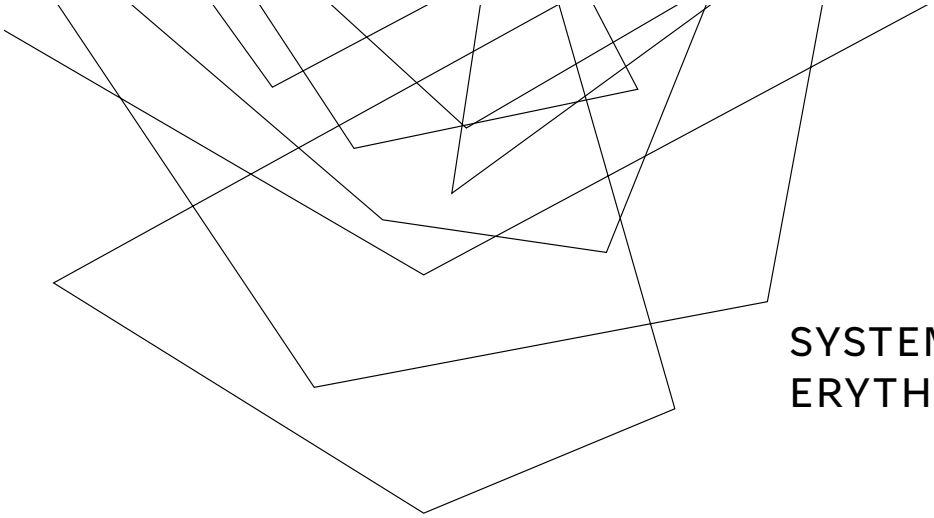
- Resembles HDFN
- Fetus has HPA-1a antigen (most commonly) not shared by mother
- Mother develops IgG antiplatelet antibodies which cross the placenta
  - Mother's platelet count is normal.
- Infant bleeding manifestations may range from asymptomatic (~30%) to intracranial hemorrhage (~10-25%)
- Workup includes maternal and paternal platelet antigen typing as well as maternal platelet HPA antibody testing



Vadasz B, et al. Platelets and platelet alloantigens: Lessons from human patients and animal models of fetal and neonatal alloimmune thrombocytopenia. Genes & Diseases (2015) 2: 173-185

NEONATAL ALLOIMMUNE THROMBOCYTOPENIA – MANAGEMENT

- Closely monitor platelet count
- Cranial ultrasound after birth to rule out intracranial hemorrhage
- Transfuse with ABO-matched, irradiated, leukoreduced, CMV-negative platelets if platelet count is <30,000 or in the event of major bleeding
- Preference is for maternal platelets, but donor platelets may be used if maternal platelets are not readily available
  - May temporarily raise platelet count and help to prevent bleeding
- IVIG may be used as well.



SYSTEMIC LUPUS ERYTHEMATOSUS

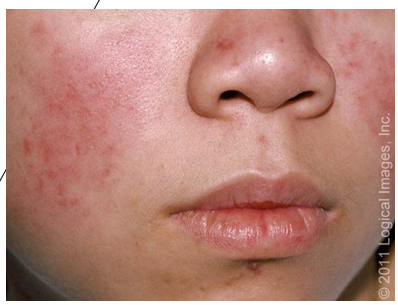
SYSTEMIC LUPUS ERYTHEMATOSUS

Characterized by the development of autoantibodies affecting multiple organ systems

Diagnosis is typically made based on clinical and immunologic classification criteria

Clinical and laboratory findings are extensive and may include

- Fatigue, anorexia, arthralgia, arthritis, rash, photosensitivity, lymphadenopathy
- Anemia, leukopenia/lymphopenia, thrombocytopenia, hematuria/proteinuria, +autoantibodies (ANA, anti-dsDNA, lupus anticoagulant, anti-Smith, anti-RNP, etc.), low C3/C4



SYSTEMIC LUPUS ERYTHEMATOSUS - MANAGEMENT

Nonimmunosuppressants

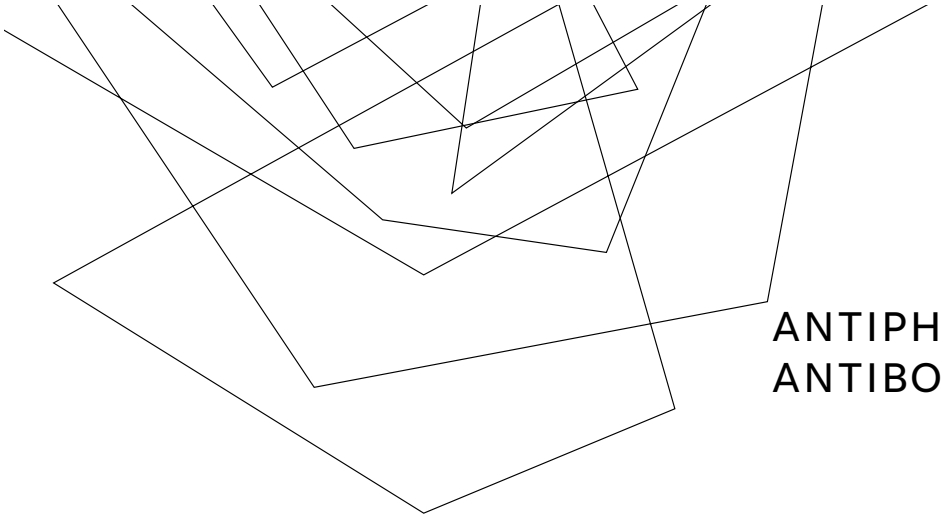
- Hydroxychloroquine
- NSAIDs for musculoskeletal involvement

Immunosuppressants

- Glucocorticoids (use caution with dosing/duration in children)
- DMARDs (e.g. methotrexate, MMF)

➢ G-CSF, IVIG, iron supplementation, aspirin, Rituximab as needed to manage hematologic complications

➢ Co-management with Rheumatology and Ophthalmology in addition to other subspecialists as indicated by organ systems affected.



ANTIPHOSPHOLIPID ANTIBODY SYNDROME

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

Diagnosis

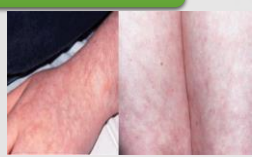
- Cellular activation via antibodies to phospholipid binding proteins (e.g. prothrombin, β2GPI)
- May be primary or secondary (co-occurring autoimmune disorder)

Antiphospholipid Antibodies

- Lupus anticoagulant
- Anti-cardiolipin IgG or IgM
- Anti-β2 glycoprotein I IgG or IgM

Complications (Thrombotic/Non-Thrombotic)

- DVT, PE, arterial thrombosis, ischemic stroke, CSVT
- Anemia, thrombocytopenia, cardiac valvular abnormalities, livedo reticularis



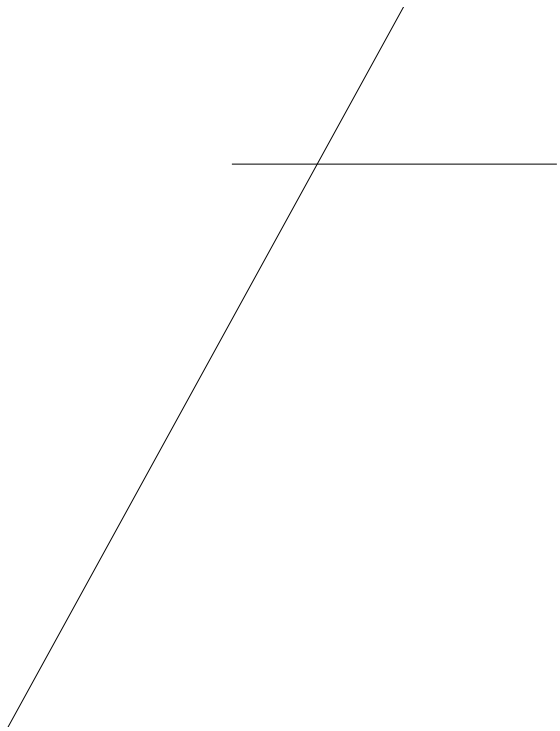
Barry L Myones, M. (2023) Pediatric antiphospholipid antibody syndrome, Practice Essentials, Background, Pathophysiology. Available at: https://emedicine.medscape.com/article/1006128-overview (Accessed: 02 May 2024).

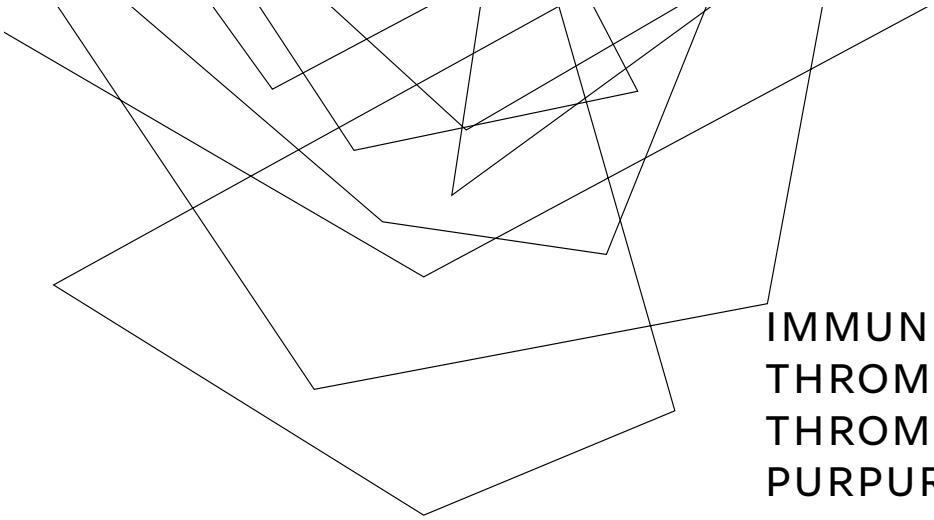
ANTIPHOSPHOLIPID ANTIBODY SYNDROME - MANAGEMENT

Thrombotic prophylaxis

- LMW heparin
- Warfarin
- ± aspirin
- ± immunosuppressants
- Hydroxychloroquine if comorbid SLE

➢ If thrombosis was unprovoked, anticoagulation may be lifelong



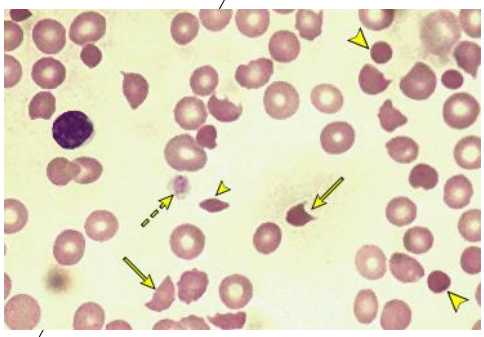


IMMUNE
THROMBOTIC
THROMBOCYTOPENIA
PURPURA

IMMUNE THROMBOTIC THROMBOCYTOPENIA PURPURA

A thrombotic microangiopathic hemolytic anemia

- Arteriole and capillary vessel wall abnormalities → microvascular thrombosis and thrombocytopenia
- Autoantibody develops against ADAMTS13, a von Willebrand factor multimer-cleaving protease
- Activity level drops to <10%
- Clinical presentation may include anemia, thrombocytopenia, TIA, or CVA.
- Elevated LDH, elevated indirect bilirubin. DAT negative.
- Peripheral blood smear will typically show schistocytes and thrombocytopenia

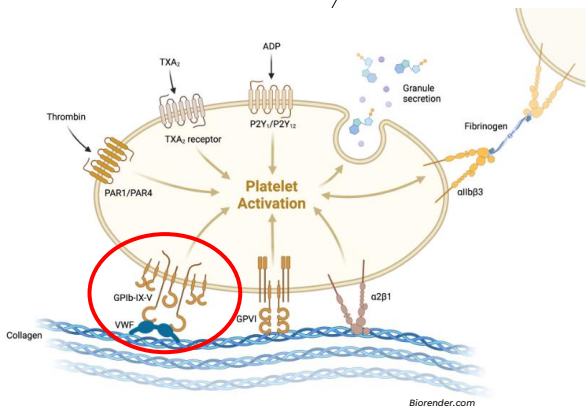


UpToDate, Inc. Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes
Diagnosis of Immune TTP UpToDate. Available at: https://www.uptodate.com/contents/diagnosis-of-immune-ttp?search=immune+thrombotic+thrombocytopenia+purpura&source=search_result&selectedTitle=2~71&usage_type=default&display_rank=2 (Accessed: 02 May 2024).

IMMUNE THROMBOTIC THROMBOCYTOPENIA PURPURA - MANAGEMENT

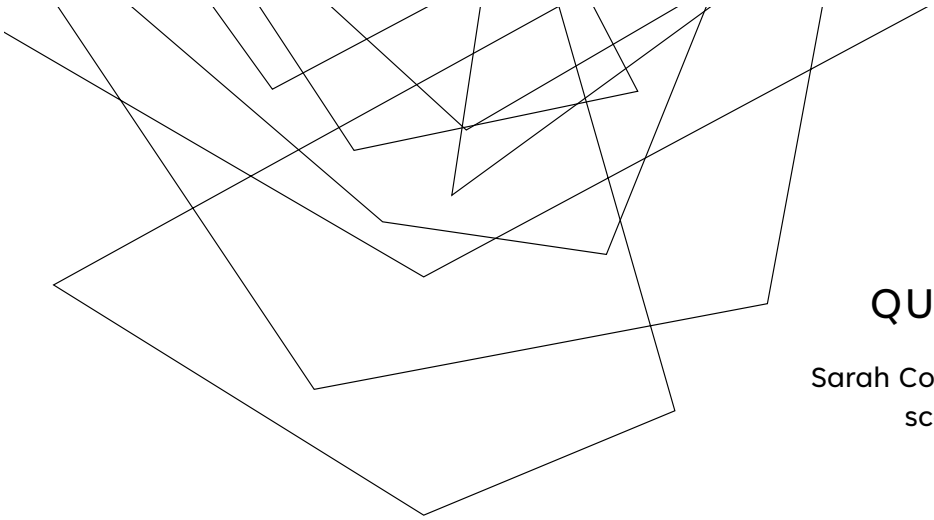
- Immediate therapeutic plasma exchange
- Rituximab
- Glucocorticoids

- ➢ Treatment inhibits the anti-ADAMTS13 antibody
- ➢ Relapse is common.
- ➢ Co-manage with Nephrology



AUTOIMMUNE DISORDERS IN PEDIATRIC HEMATOLOGY
CONCLUSIONS

- Pediatric patients with autoimmune and hematologic abnormalities can be challenging to diagnose and treat
- Early recognition of coexisting autoimmune disorders can aid both clinicians and families in choosing appropriate treatment regimens
- Optimizing management of an underlying autoimmune disorder can help mitigate hematologic abnormalities
- It benefits PAs working in family practice, general pediatrics, and pediatric subspecialities to be well-versed in the associations between autoimmunity and blood dyscrasias and to become familiar with current management guidelines.



QUESTIONS?

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REFERENCES

1. B cells: Types and function. Cleveland Clinic. February 1, 2023. Accessed March 11, 2024. https://my.clevelandclinic.org/health/body/24669-b-cells.
2. Reece JB, Campbell NA. *Campbell Biology*. Pearson; 2011.
3. T cells: Types and function. Cleveland Clinic. January 17, 2023. Accessed March 11, 2024. https://my.clevelandclinic.org/health/body/24630-t-cells.
4. Hussain Y, Khan H. Immunosuppressive drugs. *Encyclopedia of Infection and Immunity*. 2022;4:726-740. doi:https://doi.org/10.1016/b978-0-12-818731-9.00068-9
5. Theis SR, Hashmi MF. Coombs test. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK547707/. Published September 12, 2022.
6. Nosal RS, Superville SS, Amraei R, et al. Biochemistry, Antinuclear Antibodies (ANA) . StatPearls – NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK537071. Published December 29, 2022.
7. Xavier B, De LE, Borghi MO, Meroni PL. Understanding and interpreting antinuclear antibody tests in systemic rheumatic diseases. *Nature Reviews. Rheumatology*. 2020;16(12):715-726.
8. Fritsma MC, Fritsma GA. Normal hemostasis and coagulation. In: Rodak BF, Fritsma GA, Keohane E, eds. Hematology: Clinical Principles and Applications. 4th ed. St. Louis, MO: Elsevier Saunders; 2013:626-46.
9. Hussain Y, Khan H. Immunosuppressive Drugs. *Encyclopedia of Infection and Immunity*. 2022;726-740. doi:10.1016/B978-0-12-818731-9.00068-9
10. Callejas Caballero I, Illán Ramos M, Berzosa Sánchez A, Anguita E, Ramos Amador JT. Autoimmune neutropenia associated with influenza virus infection in childhood: a case report. BMC Infect Dis. 2021;21(1):830. Published 2021 Aug 18. doi:10.1186/s12879-021-06506-9
11. Sogkas G, Witte T. The link between rheumatic disorders and inborn errors of immunity. *EBioMedicine*. 2023;90:104501. doi:10.1016/j.ebiom.2023.104501
12. Neonatal thrombocytopenia (no date) Neonatal Thrombocytopenia - an overview | ScienceDirect Topics. Available at: https://www.sciencedirect.com/topics/medicine-and-dentistry/neonatal-thrombocytopenia (Accessed: 02 May 2024).
13. Vadasz B, et al. Platelets and platelet alloantigens: Lessons from human patients and animal models of fetal and neonatal alloimmune thrombocytopenia. Genes & Diseases (2015) 2: 173-185
14. Barry L Myones, M. (2023) Pediatric antiphospholipid antibody syndrome, Practice Essentials, Background, Pathophysiology. Available at: https://emedicine.medscape.com/article/1006128-overview (Accessed: 02 May 2024).
15. UpToDate, Inc. Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes; Diagnosis of Immune TTP UpToDate. Available at: https://www.uptodate.com/contents/diagnosis-of-immune-ttp?search=immune+thrombotic+thrombocytopenia+purpura&source=search_result&selectedTitle=2~71&usage_type=default&display_rank=2 (Accessed: 02 May 2024).