The Maltese Zebra: An Investigation of Drug-Induced Immune Thrombocytopenia

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2026 ICHP Annual Meeting

Disclosures

I have no conflicts of interest with ineligible companies to disclose

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Learning Objectives

- Describe the presentation and pathophysiology of immune thrombocytopenias (ITP)
- Discuss the initial management of new onset ITP
- Discuss the investigation and management of suspect drug-induced ITP

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Abbreviations

- AERS: Adverse event reporting system
- BBW: Black Box Warning
- DIC: Disseminated intravascular coagulation
- DITP: Drug-induced immune thrombocytopenia
- ED: Emergency department
- EHR: Electronic heath record
- HIT: Heparin-induced thrombocytopenia
- ITP: Immune thrombocytopenia
- IVIG: Intravenous immune globulin
- PLT: Platelets
- TMP/SMX: Trimethoprim/sulfamethoxazole
- UTI: Urinary tract infection
- WNL: Within normal limits

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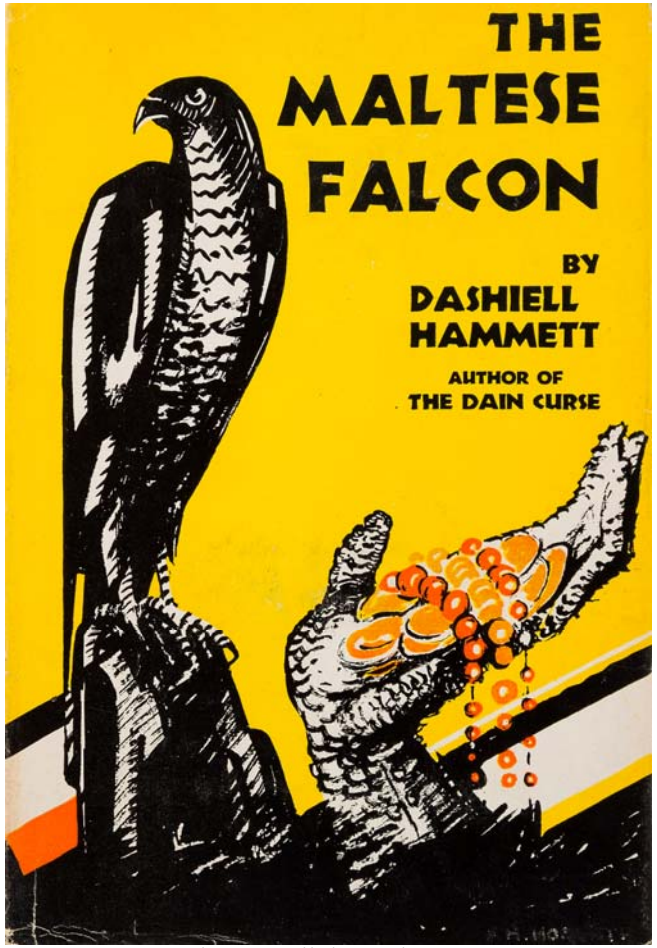
The Maltese Zebra



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GNT Presents to the ED

- 34-year-old woman
- Purpuric rash on lower legs
- History of depression, recent UTI
- No known drug allergies
- Vitals WNL
- Platelets = $7*10^3/\mu L$
- CBC and BMP otherwise WNL
- Coagulation studies and peripheral blood smear WNL

George Henry Fox. "Purpura". Marked as public domain. https://commons.wikimedia.org/wiki/File:Fox_Plate_LXIX.jpg

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Sepsis

Liver Dysfunction

Vitamin B Deficiency

Folate Deficiency

Drug Toxicity

HIT

Disseminated Intravascular Coagulation

Pseudo-thrombocytopenia

Inherited Platelet Disorders

Thrombotic Microangiopathies (TTP, HUS, DITMA)

Immune Thrombocytopenia

1. Devalia V, et al; *Br J Haematol*. 2014;166(4):496-513
2. Adamski J. *Hematology Am Soc Hematol Educ Program*. 2014;2014(1):444-449.
3. Sánchez-Fuentes A, et al. *Biomolecules*. 2025;15(6):846.
4. Toh CH and Hoots WK. *J Thromb Haemost*. 2007;5(3):604-606.

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Immune Thrombocytopenia

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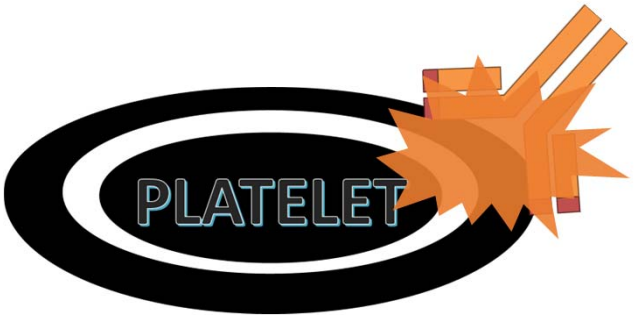
Immune Thrombocytopenia (ITP)

- Acquired thrombocytopenia
- Epidemiology: 2-5 per 100,000
- Autoantibody mediated platelet destruction
- Diagnosis of exclusion
- Variable
  - Symptoms/severity
  - Chronicity
  - Management



5. Neunert C, et al. *Blood Adv*. 2019;3(23):3829-3866.
6. Cines DB, et al. Blood. 2009;113(26):6511-6521.

ITP Presentation

- Platelets < $100*10^3/\mu L$
- Asymptomatic
- Mild-moderate bleeding
  - Petechiae and purpura
  - Mucocutaneous bleeding

5. Neunert C, et al. Blood Adv. 2019;3(23):3829-3866
6. Cines DB,et al. *Blood*. 2009;113(26):6511-6521

ITP Presentation

- Platele
- Asymp
- Mild-n
  - Pet
  - Mu

"Purpura", George Henry Fox. https://commons.wikimedia.org/wiki/File:Fox_Plate_LXIX.jpg Marked as public domain.

" Petechia of the lower leg in a person with platelets of 3 due to ITP". James Heilman, MD. https://commons.wikimedia.org/wiki/File:Petechia_lower_leg.jpg Licensed for use CC BY-SA-4.0.

5. Neunert C, et al. Blood Adv. 2019;3(23):3829-3866.
6. Cines DB,et al. Blood. 2009;113(26):6511-6521

ITP Presentation

- Platelets < $100*10^3/\mu L$
- Asymptomatic
- Mild-moderate bleeding
  - Petechiae and purpura
  - Mucocutaneous bleeding
- Severe bleeding
  - Gastrointestinal bleed
  - Intracranial hemorrhage

5. Neunert C, et al. Blood Adv. 2019;3(23):3829-3866.
6. Cines DB,et al. Blood. 2009;113(26):6511-6521

Types of ITP

Primary

- ITP without apparent trigger
- Most prevalent: ~80% of ITP
- Deepest diagnosis of exclusion

Secondary

- Predisposing condition
  - Autoimmune syndromes
  - Immunodeficiency syndromes
  - Infections
  - Lymphoid malignancies
  - Drugs
- Less prevalent
- Under recognized

6. Cines DB,et al. Blood. 2009;113(26):6511-6521
7. Kashiwagi H et al. *Int J Hematol.* 2024;119(1):1-13
8. Provan D, et al. *Blood Adv*. 2019;3(22):3780-3817

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ITP Initial Management

ITP: Initial Management

- Indications for inpatient management
  - PLT < 20 *10^3/µL
  - Severe bleeding
  - Child with minor mucocutaneous bleeding
- Observation only
  - Adult: PLT ≥30*10^3/µL with only minor or absent bleeding
  - Children: minor or absent bleeding
- Corticosteroids
- IV immune globulin (IVIG) and anti-D immunoglobulin
- Platelet transfusion

5. Neunert C, et al. Blood Adv. 2019;3(23):3829-3866.
9. Provan D, et al. *Blood Adv*. 2019;3(22):3780-3817.

ITP: Corticosteroids

- First line pharmacotherapy
- Suppress of phagocytic cell function
- Reduce autoantibody production
- Pulse doses preferred when rapid recovery is required
- Non-pulsed doses preferred for children without severe bleed

5. Neunert C, et al. Blood Adv. 2019;3(23):3829-3866.
9. Provan D, et al. Blood Adv. 2019;3(22):3780-3817.
10. Mizutani H, et al. *Blood*. 1992;79(4):942-947.

ITP: Corticosteroid Options

	Non-Pulse	**Pulse**	
	Prednisone* / Prednisolone	Dexamethasone*	Methylprednisolone
Adult Dosing	0.5-2.0 mg/kg/day (max 80 mg daily)	40 mg daily	1 g daily
Adult Duration	2-3 weeks + taper **(max 6 weeks total)**	4 days	3 days
Pediatric Dosing	2-4 mg/kg/day (max 120 mg daily)	0.6 mg/kg per day (max 40 mg daily)	30 mg/kg/dose daily
Pediatric Duration	5-7 days **(max 7 days)**	4 days	1-3 days

*Corticosteroids specifically named in guidelines

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11. Prednisolone. Lexi-Drugs. UpToDate Lexidrug
12. Prednisone. Lexi-Drugs. UpToDate Lexidrug.
13. Dexamethasone. Lexi-Drugs. UpToDate Lexidrug
14. Methylprednisolone. Lexi-Drugs. UpToDate Lexidrug.

ITP: IVIG & Anti-D Place in Therapy

- Alternative when corticosteroids are contraindicated
- Addition to corticosteroid
  - Severe/critical bleed (IVIG only)
  - Urgent recovery required
  - Refractory to corticosteroid

9. Provan D, et al. Blood Adv. 2019;3(22):3780-3817.
5. Neunert C, et al. Blood Adv. 2019;3(23):3829-3866.

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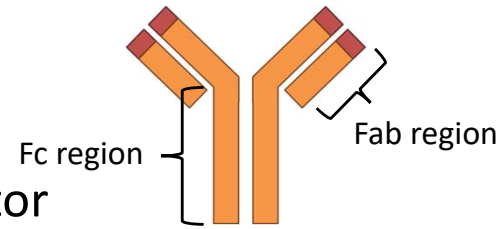
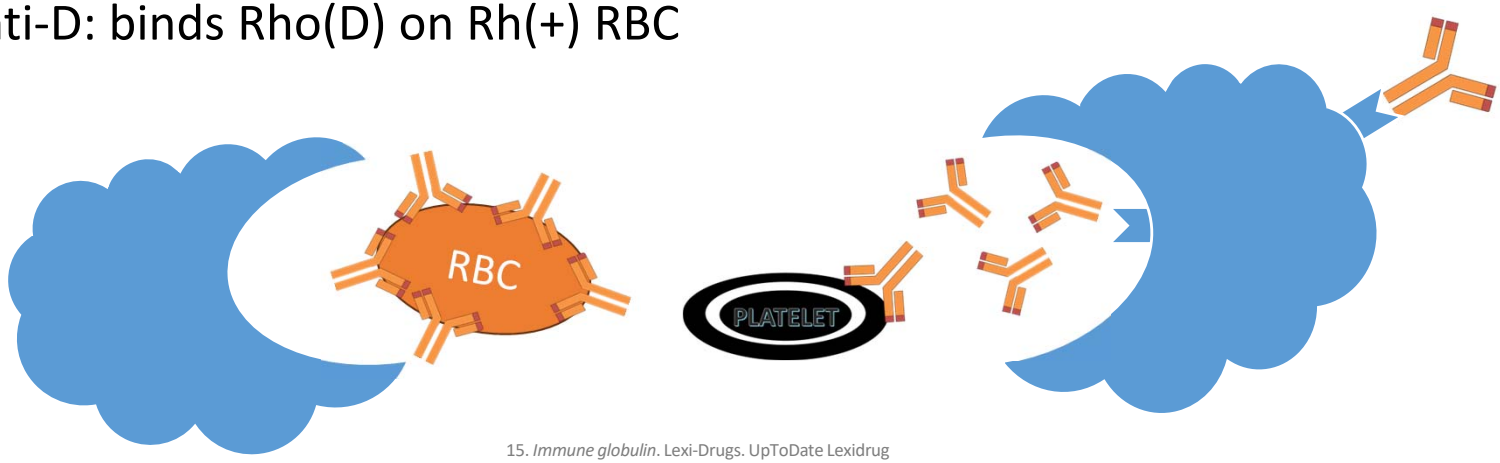
ITP: IVIG & Anti-D Mechanisms

- Concentrated immunoglobulin infusion
- Competes with antiplatelet antibody for Fcγ receptor
- Stimulate inhibitory receptor (FcγRIIB)
- Anti-D: binds Rho(D) on Rh(+) RBC





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ITP: IVIG Dose & Pearls

- Dose: 1 g/kg IV
- May repeat dose after 24 hours
- Preferred over anti-D for severe/critical bleed
- BBW: thrombosis & acute renal dysfunction

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18. Lioger B, et al. J Pediatr. 2019;204:225-233.e8
19. Kane I, et al. *Br J Haematol*. 2010;149(1):79-83.

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ITP: Anti-D Dose & Pearls

- Rhophylac®: 50 mcg/kg
- WinRho SDF®: 25-50 mcg/kg
- IV administration only
- Rh(+) patients only
- BBW: intravascular hemolysis
  - Anemia, DIC, multisystem organ failure, etc
  - Monitor with serial urinalyses
  - Transfuse Rh(-) blood only

5. Neunert C, et al. Blood Adv. 2019;3(23):3829-3866.
17. *Anti-D immune globulin*. Lexi-Drugs. UpToDate Lexidrug.
18. Lioger B, et al. J Pediatr. 2019;204:225-233.e8
19. Kane I, et al. *Br J Haematol*. 2010;149(1):79-83.

ITP: Platelet Transfusion

- Pharmacotherapy only prevents platelet destruction
- Only treatment that can increase platelets within 24 hours
  - Life threatening bleed
  - Severe, refractory bleed
  - Urgent surgical procedure
- Priority: platelets → IVIG → corticosteroids

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5. Neunert C, et al. Blood Adv. 2019;3(23):3829-3866.
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Back to GNT

Q1: Initial treatment of GNT

- 34-year-old woman
- Purpuric rash
- No mucosal bleed
- No GIB or ICH
- PLT = $7*10^3/\mu L$
- Blood counts WNL otherwise
- Blood type: AB-
- No known drug allergy

Which treatment is most appropriate for GNT?

a) Outpatient prescription for prednisone for 14 days

b) Initiate methylprednisolone

c) Initiate dexamethasone and anti-D

d) Initiate STAT platelet transfusion, IVIG, and dexamethasone

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Drug-induced Immune Thrombocytopenia (DITP)

Drug-induced Immune Thrombocytopenia

- Suspect whenever PLT < 20 *10^3/µL
- Epidemiology
  - General population: 10 per 1 million
  - TMP/SMX: 26 per 1 million
  - Quinine/quinidine: 38 per 1 million
- Likely underreported

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23. Reese JA, et al. *Pediatr Blood Cancer*. 2013;60(12):1975-1981.

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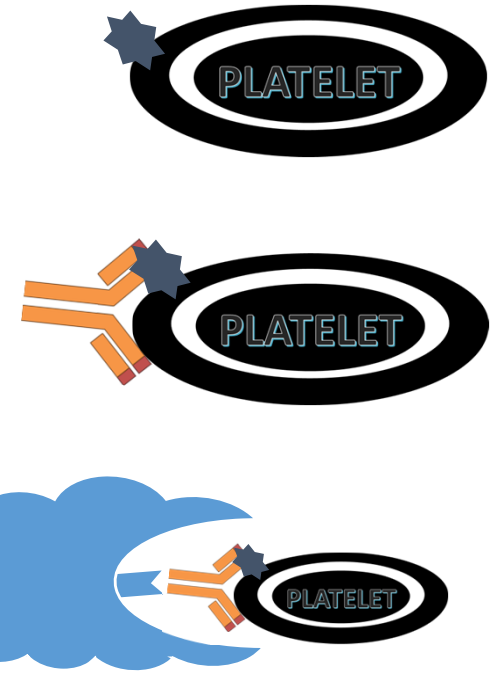
DITP Pathophysiology

- Drug binds to platelet
- Alters surface protein
- Drug/platelet complex recognized as non-self
- Antiplatelet antibody is drug dependent



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- 24. Arnold DM, et al. *Transfus Med Rev*. 2013;27(3):137-145.

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DITP vs ITP

	DITP	ITP
Antiplatelet antibodies	**Drug dependent**	Not drug dependent
Thrombocytopenia	Severe, PLT < 20 *10^3/µL	Variable, PLT < 100 *10^3/µL
Asymptomatic	Rarely asymptomatic	Often asymptomatic
Severe bleed risk	Major bleed: 19%	Variable Correlated with platelet counts

9. Provan D, et al. *Blood Adv*. 2019;3(22):3780-3817.
21. Bakchoul T, Marini I. *Hematology Am Soc Hematol Educ Program*. 2018;2018(1):576-583.
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26. George JN, et al. *Ann Intern Med*. 1998;129(11):886-890.
27. Pedersen-Bjergaard, et al. *Eur J Clin Pharmacol*. 1997;52(3):183-189.

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DITP vs ITP

	DITP	ITP
Antiplatelet antibodies	**Drug dependent**	Not drug dependent
Thrombocytopenia	Severe, PLT < 20 *10^3/µL	Variable, PLT < 100 *10^3/µL
Asymptomatic	Rarely asymptomatic	Often asymptomatic
Severe bleed risk	Major bleed: 19%	Variable Correlated with platelet counts
Platelet trend	Distinct nadir then recovery	Fluctuates
Duration	1 – 2 weeks	Weeks to years

9. Provan D, et al. *Blood Adv*. 2019;3(22):3780-3817.
21. Bakchoul T, Marini I. *Hematology Am Soc Hematol Educ Program*. 2018;2018(1):576-583.
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26. George JN, et al. *Ann Intern Med*. 1998;129(11):886-890.
27. Pedersen-Bjergaard, et al. *Eur J Clin Pharmacol*. 1997;52(3):183-189.

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Back to GNT

Q2: Red Herring or Red Handed?

- 34-year-old woman
- Purpuric rash
- No mucosal bleed
- No GIB or ICH
- PLT = $7*10^3/\mu L$
- Blood counts WNL otherwise
- Blood type: AB-
- No known drug allergy

Is DITP a suspect cause of GNT's thrombocytopenia? Why/why not?

a) No, GNT is not actively bleeding

b) No, GNT has no known drug allergies

c) Yes, GNT's PLT < $20*10^3/\mu L$

d) Yes, DITP should be suspected for anyone taking medications

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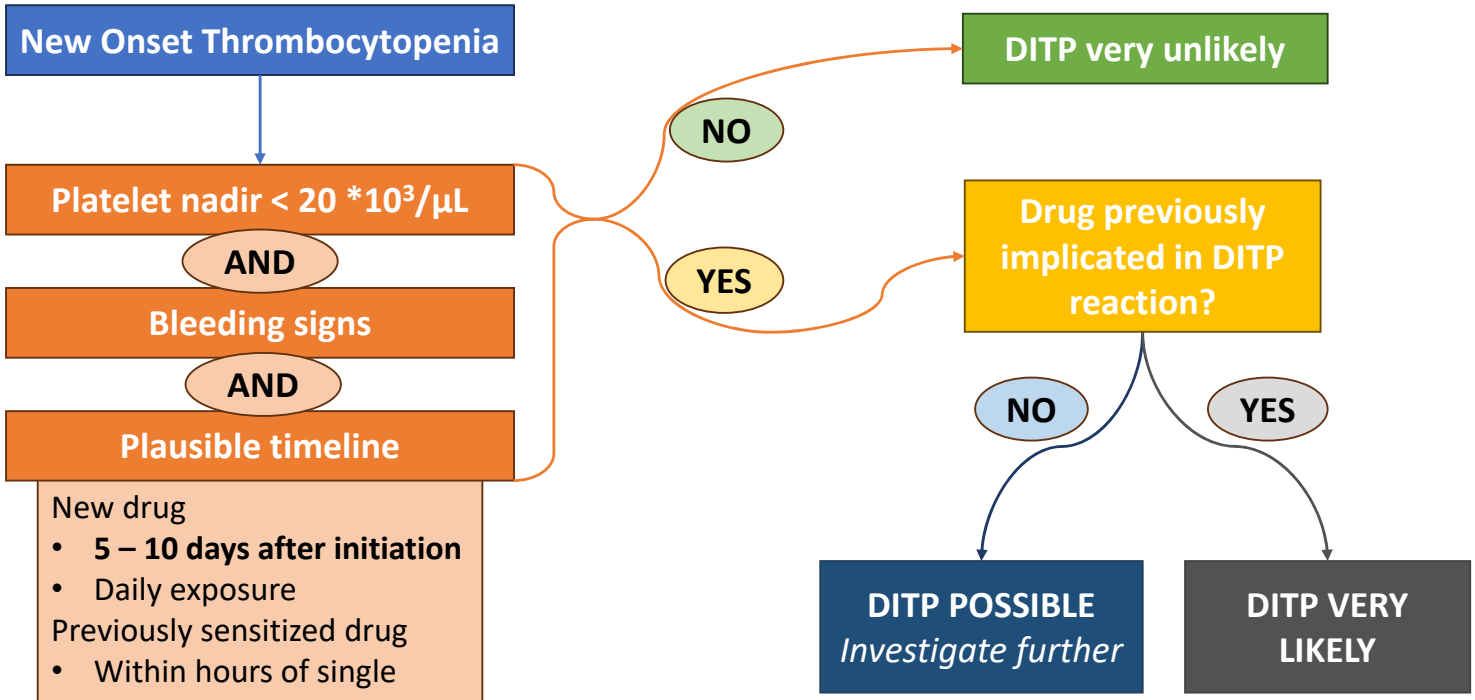
Investigating DITP

Investigating DITP



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33. George JN, Aster RH. *Hematology Am Soc Hematol Educ Program*. 2009;153-158.

Unique DITP Presentations

GP IIb/IIIa Inhibitors

- Tirofiban, eptifibatide, abciximab
- Intended to bind to platelets
- Elicit DITP reaction in hours

Drug Independent Antibodies

- Gold, levodopa, procainamide
- Mechanism largely unknown

- 24. Arnold DM, et al. *Transfus Med Rev*. 2013;27(3):137-145.
- 21. Bakchoul T, Marini I. *Hematology Am Soc Hematol Educ Program*. 2018;2018(1):576-583.

Unique DITP Presentations

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Immune Checkpoint Inhibitors (ICIs)

- Atezolizumab, durvalumab, ipilimumab
- Unclear mechanism
  - Immune dysregulation
  - Possible drug-dependent antibody involvement
- 70% tolerate rechallenge

HIT Type-II

- Heparin, enoxaparin, protamine
- HIT-antibodies bind platelets
- Mark for destruction → thrombocytopenia
- Activate platelets → thrombosis
- Mean platelets ~60 *10^3/µL

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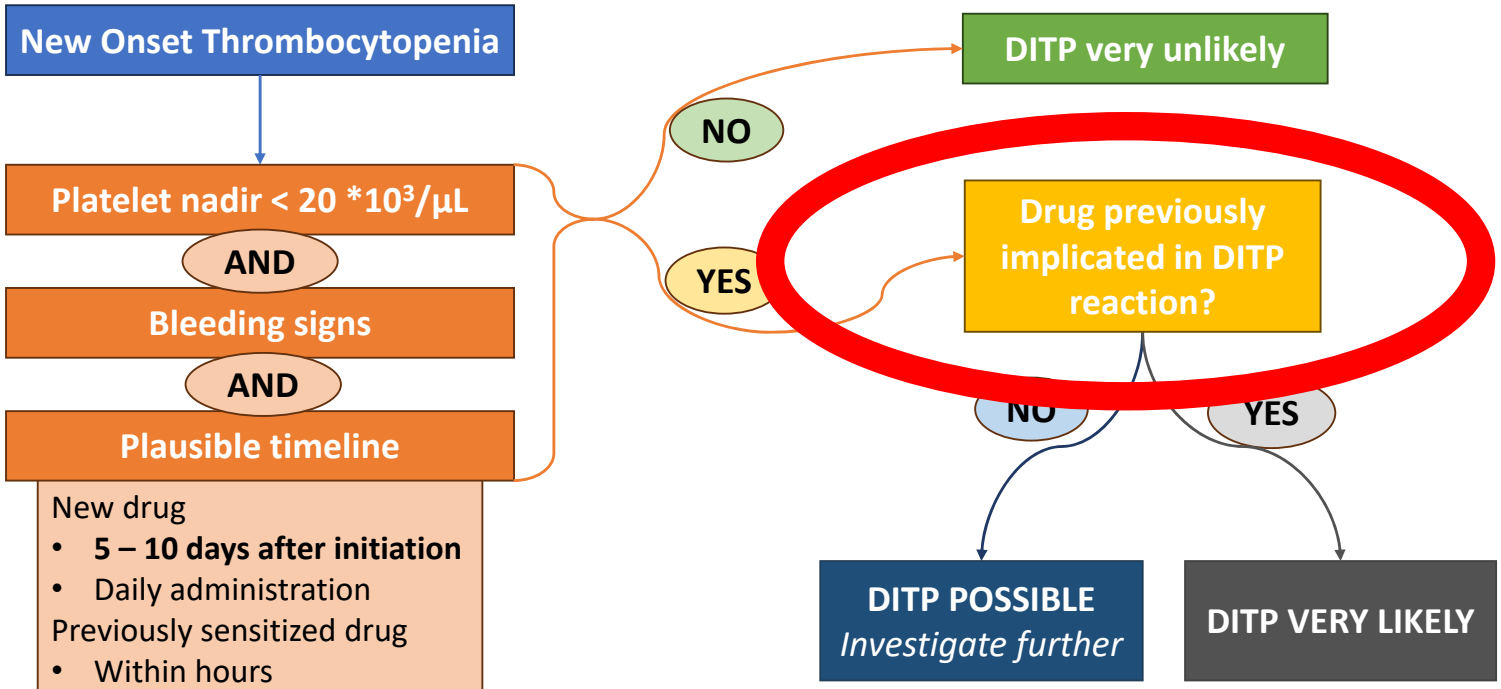
Investigating DITP



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33. George JN, Aster RH. *Hematology Am Soc Hematol Educ Program*. 2009;153-158.

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"Identifying Drugs That Cause Acute Thrombocytopenia: an Analysis Using 3 Distinct Methods"

Reese JA, et al. *Blood*. 2010;116(12):2127-2133.

Design

Clinical	Lab	Data Mining
• Systemic review of case reports • Establishment of causal relationship	• Data from BloodCenter of Wisconsin • Drug-dependent, platelet reactive antibodies	• Data mining FDA's AERS database • Statistical association with thrombocytopenia

Excluded

- Marrow-suppressive thrombocytopenias
- Heparin + heparin analogues

34. Reese JA, et al. *Blood*. 2010;116(12):2127-2133.

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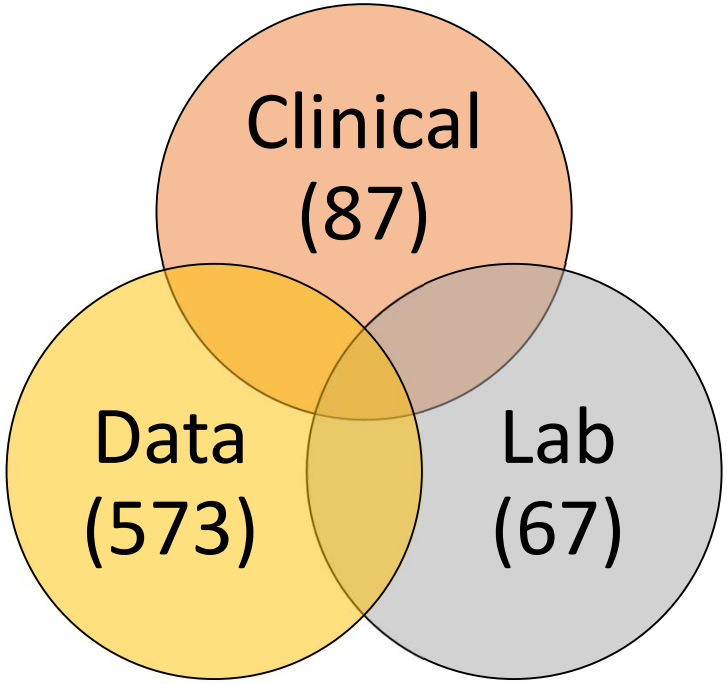
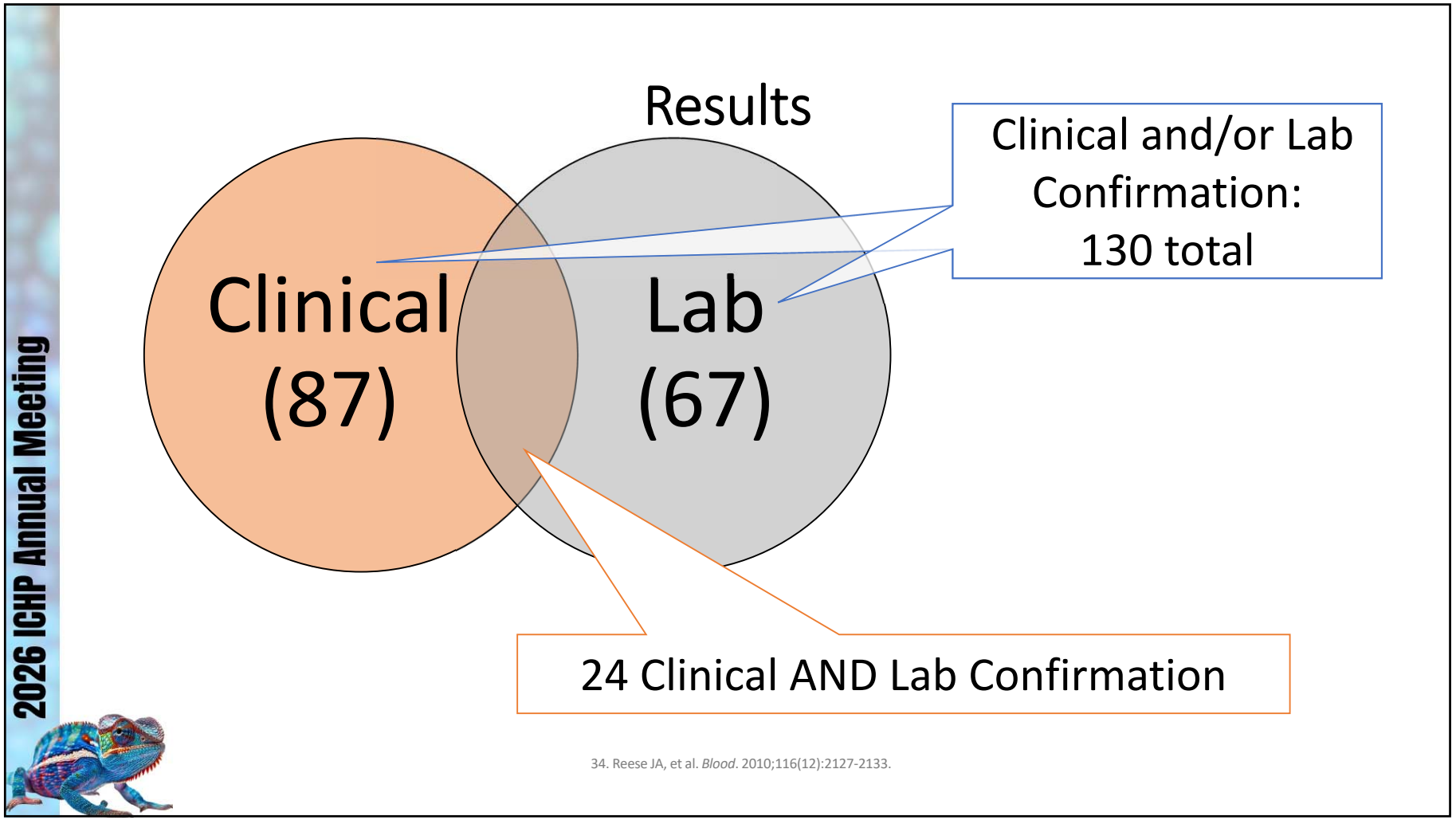
Results



34. Reese JA, et al. *Blood*. 2010;116(12):2127-2133.



34. Reese JA, et al. *Blood*. 2010;116(12):2127-2133.

DITP: Most Wanted

Both Clinical and Lab Confirmation	
Abciximab	Phenytoin
Acetaminophen	Piperacillin
Amiodarone	Quinidine
Ampicillin	Quinine
Carbamazepine	Ranitidine
Eptifibatide	Rifampin
Ethambutol	Simvastatin
Haloperidol	Sulfisoxazole
Ibuprofen	SMX-TMP
Irinotecan	Tirofiban
Naproxen	Valproic acid
Oxaliplatin	Vancomycin

≥10 Lab Reports + Clinical Confirmation	
Abciximab	Quinine
Carbamazepine	Rifampin
Eptifibatide	SMX-TMP
Phenytoin	Tirofiban
Piperacillin	Vancomycin
Quinidine	

≥10 Lab Reports + ≥10 Case Reports
Abciximab
Carbamazepine
Quinidine
Quinine
Rifampin
SMX-TMP

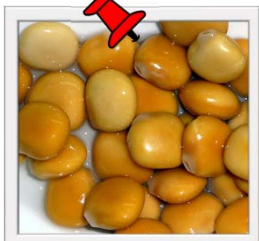
DITP: Quinine

- BBW: Thrombocytopenia
- Known cause of purpura for >150 years
- Non-drug sources
  - Tonic water, gin and tonics, bitter lemon
  - Fluorescent cocktails aka “Shocktails”
  - Natural leg cramp remedies

17. Vipan, W. H. "Quinine as a cause of purpura." The Lancet 86.2184 (1865): 37.
35. *Quinine*. Lexi-Drugs. UpToDate Lexidrug.

DITP: Food, Alternative Meds, etc.


Walnuts

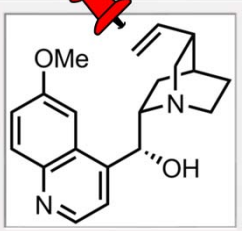

Lupin Beans


Tahini


Cranberry Juice


Cow's Milk


Jui, Herbal Tea



Adulterants

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GNT Medication History

Q3: Ms GNT, Just One More Thing…

- **Citalopram daily for 7 years. Last taken last night**
- **Cephalexin daily for 10 days. Last taken ~2 weeks ago**
- **Acetaminophen prn. Typically, every few months. Single dose 4 days ago.**
- **"Vertigo Glowing Vodka Tonic" past 6 evenings**

Which of the following is the most likely cause of suspect DITP?

a) Citalopram

b) Cephalexin

c) Acetaminophen

d) Quinine

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DITP Treatment and Recovery

DITP Treatment and Recovery

- Definitive treatment: **stop offending agent**
- Treat ITP as appropriate
- Stop all drugs started in past 2 weeks
- Investigate possible offending agent
- Expected platelet recovery
  - Starts after 4-5 half-lives of offending drug
  - Complete ~1 week

24. Arnold DM, et al. *Transfus Med Rev*. 2013;27(3):137-145.
21. Bakchoul T, Marini I. *Hematology Am Soc Hematol Educ Program*. 2018;2018(1):576-583.
33. George JN, Aster RH. *Hematology Am Soc Hematol Educ Program*. 2009;153-158.

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DITP Treatment and Recovery

- Drug-dependent antibodies linger for years
  - Counsel on avoidance
  - Non-drug sources
- Case report of a definite or probable reaction
  - If few exist for offending drug
  - Management relies on historical association

34. Reese JA, et al. *Blood*. 2010;116(12):2127-2133.

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2026 ICHP Annual Meeting

The Maltese Zebra: An Investigation of Drug-Induced Immune Thrombocytopenia

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