Mechanisms of Thrombocytopenia

Donald M. Arnold MD MSc
Director, McMaster Centre for Transfusion Research
John G. Kelton Chair in Translational Research
McMaster University

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Faculty/Presenter Disclosure

- **Faculty:** Donald M. Arnold

- **Relationships with commercial interests:**
  - **None**
  - **Other:** Employee of Hamilton Health Sciences, CBS Medical Consultant

Disclosure of Commercial Support

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- **<u>Potential for conflict(s) of interest</u>:**
  - None

Mitigating Potential Bias

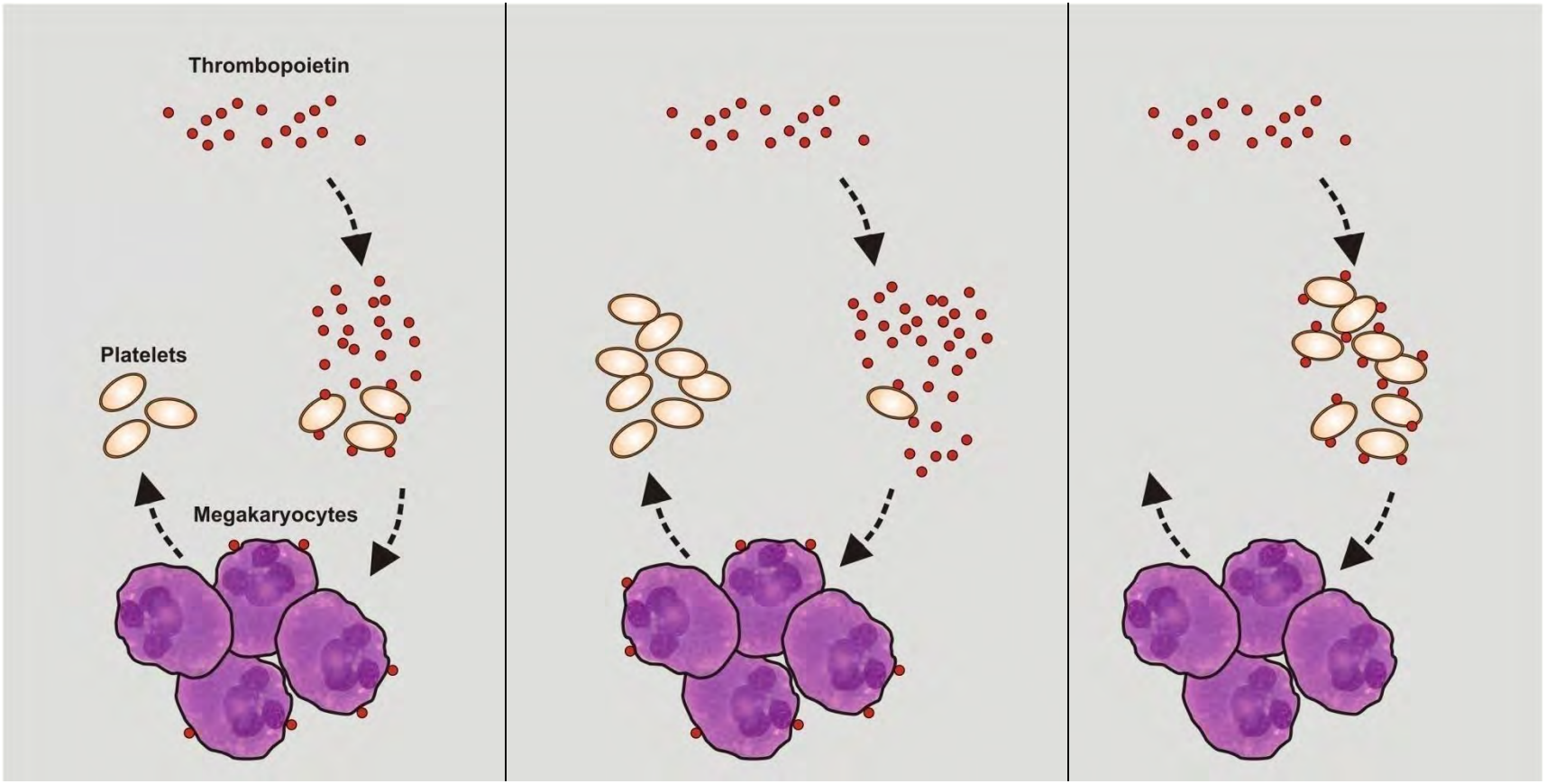
- N/A

Objectives

1. How is the platelet count regulated?
2. Platelet diagnoses you don't want to miss
3. When you should/ should not transfuse

1. Regulation of Platelet Number

Steady State *LOW platelets* *HIGH platelets*



Platelet count is stable over time

NHANES III (N= 12,142). Mean platelet counts (95% CI), models controlled for nutrition and inflammation.

	Unadjusted	Model 1	Model 2	Model 3
Non-Hispanic white				
17–19	260 (254–266)	258 (252–264)	259 (254–264)	258 (253–264)
20–29	251 (245–257)	250 (244–256)	253 (247–258)	252 (246–257)
30–39	252 (245–258)	251 (244–257)	254 (247–261)	253 (247–260)
40–49	249 (245–255)	249 (243–254)	252 (247–257)	251 (243–256)
50–59	253 (245–260)	254 (247–261)	256 (250–263)	256 (249–262)
60–69	242 (235–249)	243 (237–250)	245 (239–252)	245 (239–251)
>70	232 (226–239)	235 (228–241)	235 (229–242)	235 (228–241)

Segal, Ann Epidemiol 2006

Platelet-type bleeding


[A]
[P]

Thrombocytopenia in hospital

Very common

- 1 in 20 people attending for pre-op assessments
- 1 in 4 patients admitted to hospital
- 1 in 2 patients in ICU

Glance LG et al. Anesthesiology. 2014; Hui P et al. Chest. 2011 Feb;139(2):271–8.

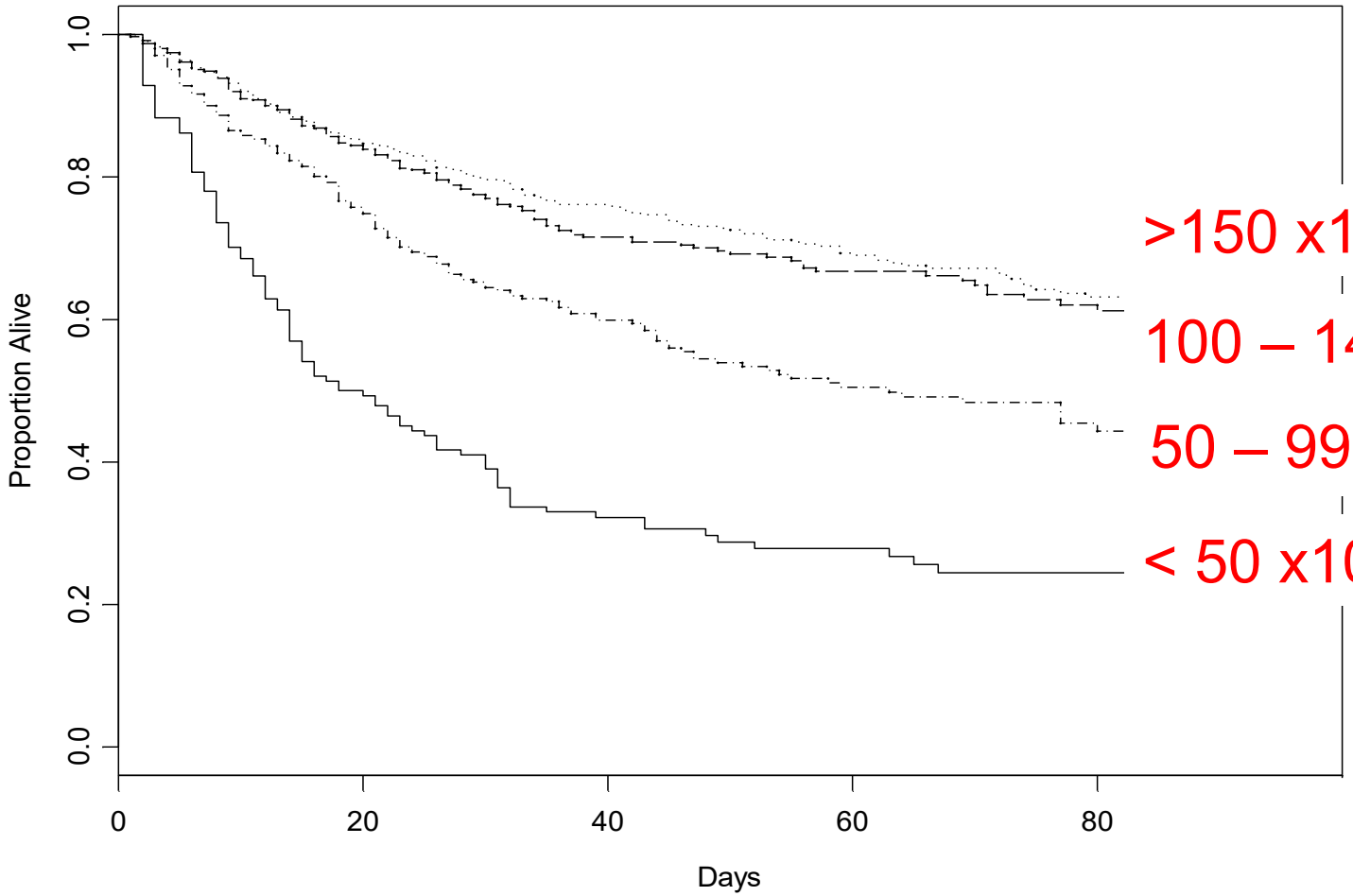
Almost always secondary

- Inflammation, consumption, dilution, etc

Poor prognostic sign

- Morbidity is rarely from bleeding
- Underlying illness, omission of treatments

Mortality



risk					
10⁹/L	2769	922	385	240	119
9 x10⁹/L	705	456	210	124	77
x10⁹/L	241	256	131	80	41

N= 3,746 critically ill patients from the PROTECT trial

Williamson DR et al, CHEST 2013

2. Approach to thrombocytopenia

1	2	3	4	5	6
Life-threatening causes	Examine the blood film	Determine clinical context	Assess the severity	Assess timing of onset	Assess for bleeding signs

Arnold DM, Lim W. *Semin Hematol.* 2011 Oct;48(4):251-8.

Diagnoses you don't want to miss

1	2	3	4	5	6
life-threatening causes	Examine the blood film	Determine clinical context	Assess the severity	Assess timing of onset	Assess for bleeding signs

- **Acute leukemia (AML)**
- **Thrombotic thrombocytopenic purpura (TTP)**
- **Disseminated intravascular coagulation (DIC)**
- **Heparin - induced thrombocytopenia (HIT)**
- **Drug-induced immune thrombocytopenia (D-ITP)**

1	2	3	4	5	6
Life-threatening causes	Examine the blood film	Determine clinical context	**Assess the severity**	**Assess timing of onset**	Assess for bleeding signs

Arnold DM, Lim W. *Semin Hematol.* 2011 Oct;48(4):251-8.

Thrombocytopenia

SEVERITY	Think about:
PLTs < 30	ITP (primary or secondary)
PLTs 30 – 80	HIT
PLTs 80 – 130	Hypersplenism

TIMING	Think about:
1 – 2 days	Dilution (post-op)
5 – 10 days	Drug-induced ITP , HIT
Weeks - months	Bone marrow failure, other

3. Management

1. Hematology oncology
2. Cardiac surgery
3. Acute thrombocytopenic disorders

Question #1:

Chemotherapy-induced thrombocytopenia

37F with AML. Admitted for consolidation chemotherapy. Baseline PLT = 110 $x10^9$/L. Day 8 post chemo: PLT = 16 $x10^9$/L. No bleeding.

Should you transfuse platelets?

Answers for Question #1

1. YES

2. NO

(Correct answer: 2)

PLT transfusion strategies: Heme-Onc

(n=2331 participants)

- *High vs. low PLT count threshold (N=3)*
  - No difference in bleeding (RR 1.35; 95% CI 0.95 to 1.9)
- *High vs. low platelet dose (n=6)*
  - No different in bleeding
- *Prophylactic vs. therapeutic-only (N=3)*
  - No difference in bleeding (RR= 1.66; 95% CI 0.9 to 3.04)

Estcourt L et al. Cochrane Database Syst Rev. 2012

TOPPS trial

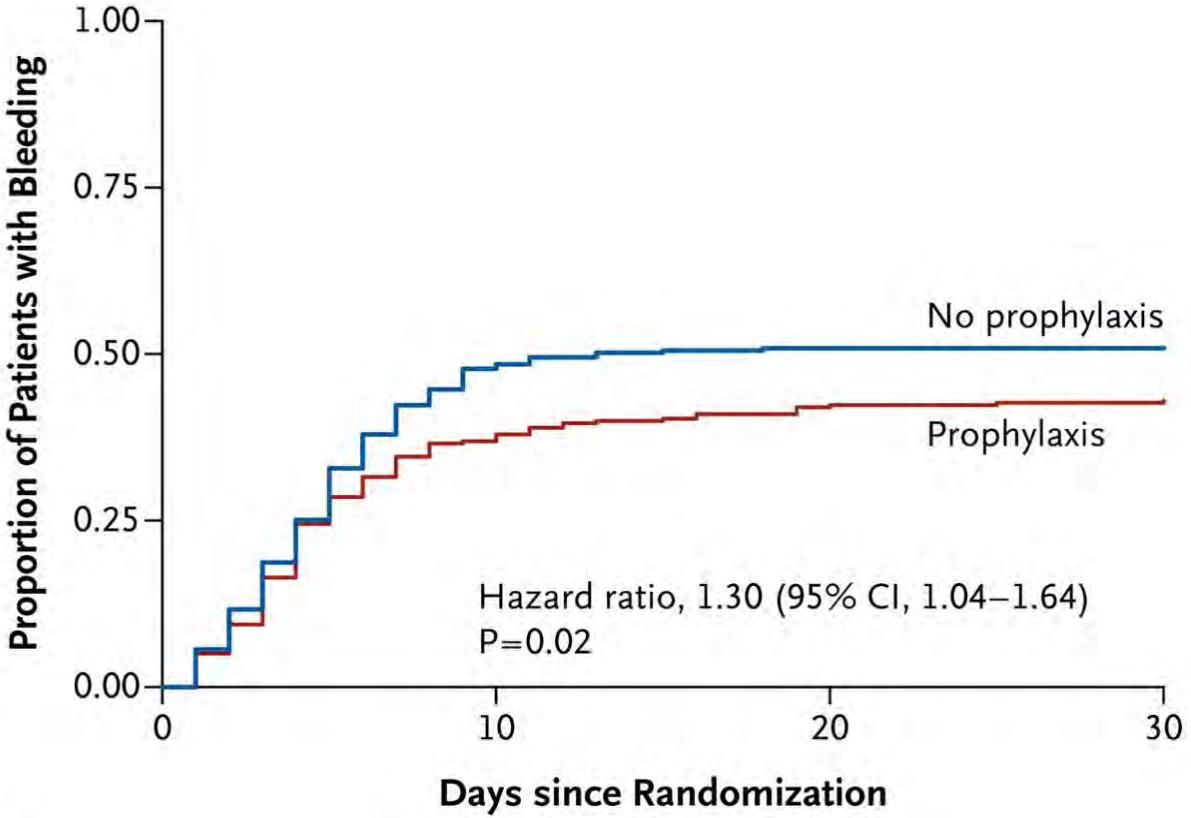
(Stanworth et al, *NEJM* 2013)

Multicenter, non-inferiority RCT (N=600): therapeutic (no prophylaxis) vs. prophylactic PLT transfusions for PLT <10 $x10^9$/L.

- Bleeding events (WHO Grade 2, 3, or 4):
  - 50% vs 43% (P=0.06 for non-inferiority)

- A 'no-prophylaxis' strategy was not non-inferior to a prophylaxis strategy (e.g. it might be worse).

Time to Bleeding



No. at Risk				
Prophylaxis	298	188	170	165
No prophylaxis	300	152	140	139

Stanworth SJ et al. N Engl J Med 2013

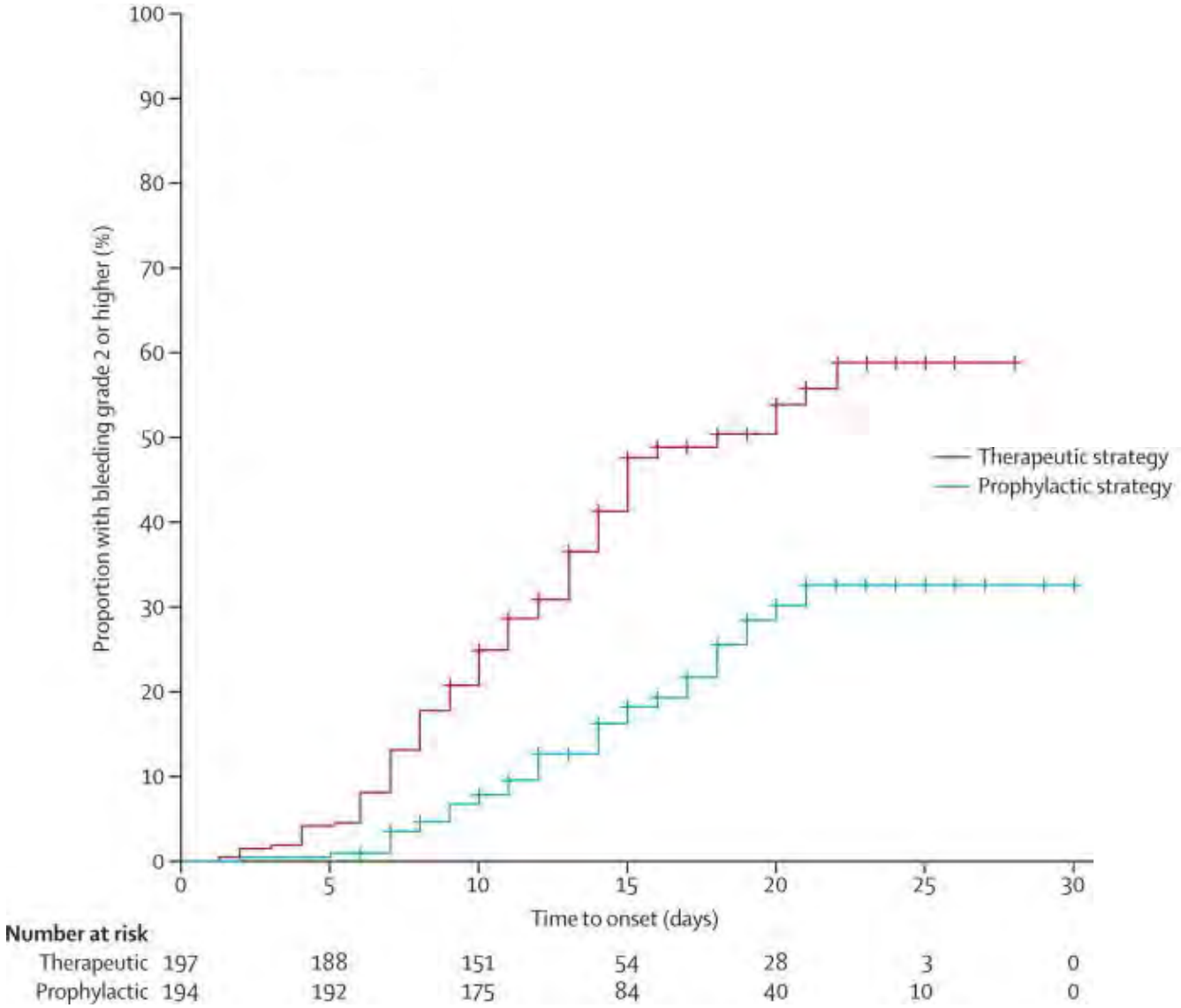
Wandt et al (Lancet 2012)

Multicenter, RCT N=391 patients therapeutic (e.g. wait until bleeding occurs) vs. prophylactic PLT transfusion strategy (for PLT ≤ 10 $x10^9$/L)

- Increased risk of bleeding in patients with AML
- No increased risk of major bleeding in autologous transplantation.

Proportion with Bleeding

(Wandt, Lancet 2012)



Question #2:

Cardiac surgery

76M, diabetes. Platelet count at baseline 175 x10^9/L. He underwent coronary artery bypass graft surgery (prolonged bypass). Uncomplicated post operative course. On day 8, the PLT count is = 70 x 10^9/L.

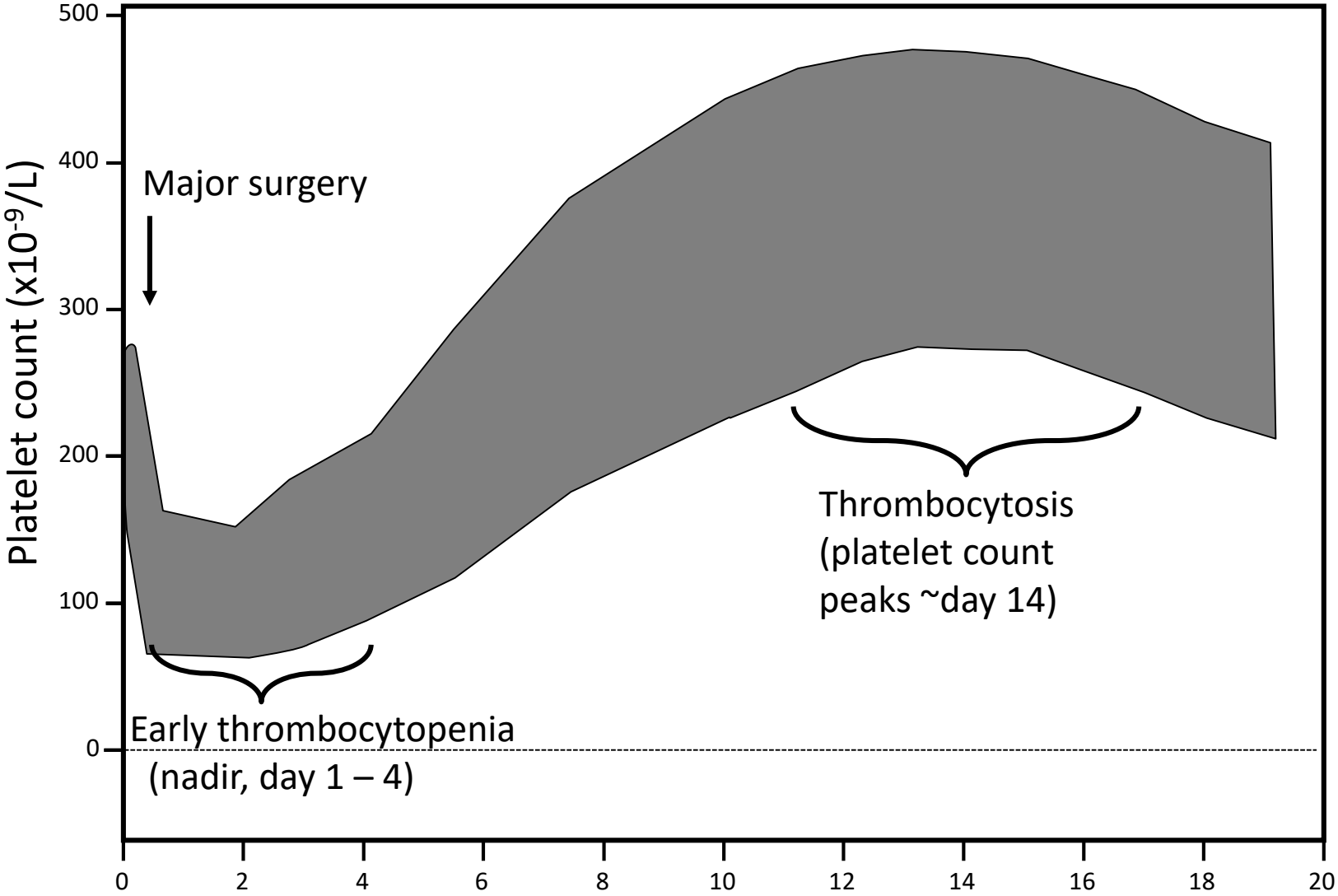
What is the most likely diagnosis?

Answers for Question #2

1. Post operative dilutional thrombocytopenia
2. Heparin-induced thrombocytopenia
3. Sepsis
4. Myelodysplastic syndrome

(correct answer: 2)

Natural History of Postoperative Thrombocytopenia



Modified from Warkentin, Mithoowani & Arnold. In: Schmaier & Lazarus, eds. Springer Int'l, 2019.

HIT

Clinical Presentation:

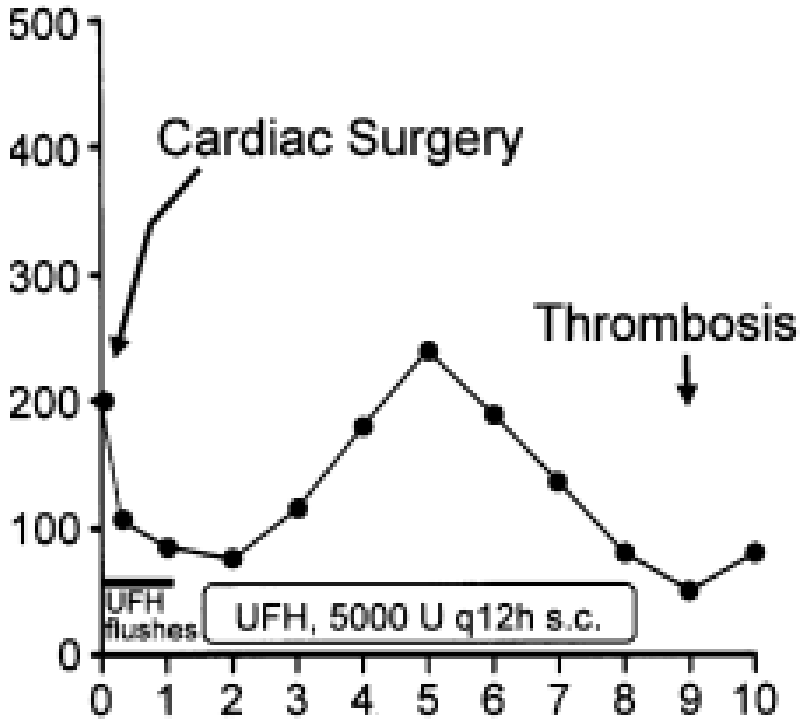
- 50% drop in PLT
- 5 – 10 after heparin
- High risk of thrombosis (50%), limb loss, death (5 – 10%)

Treatment:

- Anticoagulation (non-heparin): argatroban, fondaparinux
- IVIG?

Warkentin, Ann Int Med 1997

Typical-Onset HIT



Warkentin, Theodore E.
Heparin-induced thrombocytopenia: pathogenesis and management.
British Journal of Haematology **121** (4), 535-555.

Question #3:
Immune thrombocytopenia (ITP)

28F presents to the Emergency Department with a 1-week of bruising and 1-day of diffuse petechial rash. She has blood blisters in her mouth.

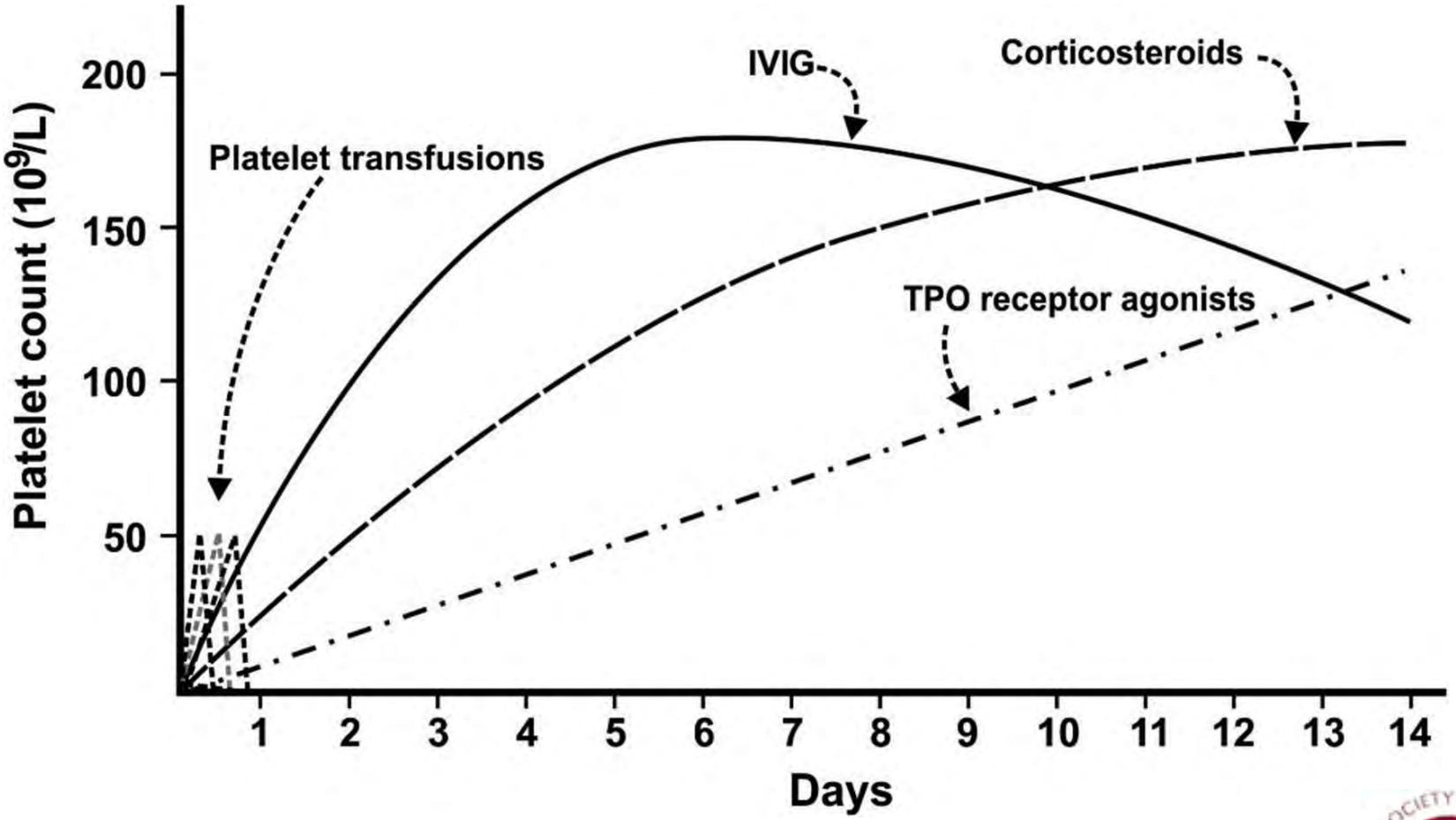
What is the best treatment?

Answers for Question #3

1. Intravenous immune globulin (IVIG)
2. Platelet transfusion
3. IVIG and corticosteroids
4. Careful observation

(correct answer: 3)

Emergency Management of ITP



Arnold, Hematology 2015;2015:237-242

Take home messages

1. Thrombocytopenia is a poor prognostic indicator.

2. PLT < 10 x10^9/L for transfusion for chemotherapy.

3. Think about HIT (surgical > medical).

4. For acute ITP, IVIG and corticosteroids are first-line.

"Sometimes we doctors, despite all our years of training and experience, can only marvel at how little we really know."

-Jeff Brown

Thank you.