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HIT, una complicanza life-threatening: epidemiologia, diagnosi, trattamenti

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Agenda:

1. Definizione HIT
2. Epidemiologia e patogenesi
3. Presentazione clinica
4. Diagnosi nel setting dell'urgenza

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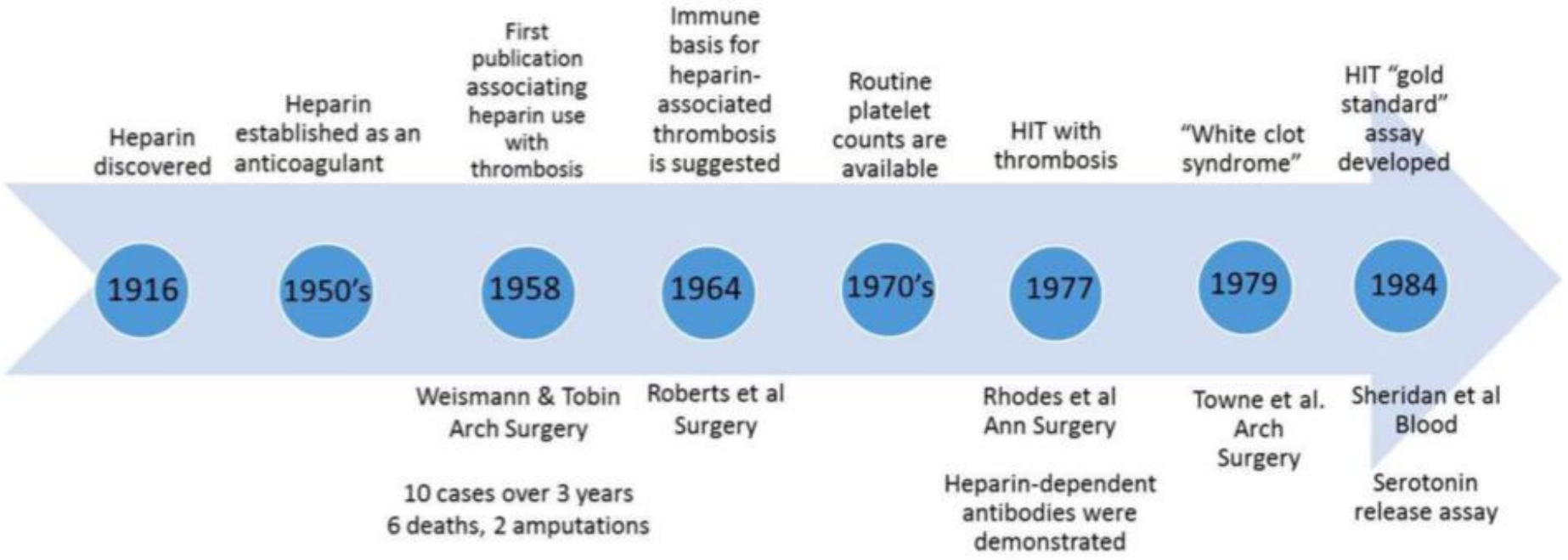
Storia di una scoperta...

HIT



Definizione

HIT

HIT (**H**eparin - **I**nduced **T**hrombocytopenia) è una reazione avversa farmaco indotta - generalmente legata a uso di UFH, meno frequentemente LMWH - pericolosa, potenzialmente fatale, immunologicamente mediata.

HIT: descritta per la prima volta nel 1977, 20 anni dopo il primo report di un caso di eparina associata a trombosi.

Una nomenclatura più vecchia definisce 2 tipi di HIT (*Chong e Berndt, 1989*)

Definizione

HIT

Tipo I:

si osserva nel 10% fino al 30% dei pazienti trattati con eparina; caratterizzata da trombocitopenia benigna. Generalmente si verifica dopo 2 giorni dalla somministrazione di eparina. La conta delle piastrine si normalizza spontaneamente, anche proseguendo la terapia, e non si associa ad aumentato rischio di trombosi.

Tipo II:

Anticorpo-mediata, potenzialmente life-threatening.
Necessaria la sospensione dell'eparina. Richiede una strategia anche anticoagulante per prevenire lo sviluppo di HIT e trombosi (**HITT**).

Epidemiologia e Patogenesi

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Incidenza

The incidence of HIT is variable and is influenced by the heparin formulation and the clinical context in which heparin is administered.

Prospective studies have documented an incidence of HIT among patients treated with unfractionated heparin that was **10 times** the incidence among those receiving LMWH.

HIT develops more frequently in patients being treated with LMWH who have had a recent exposure to unfractionated heparin (within 100 days) than in those who have not had a recent exposure to UFH.

The pentasaccharide fondaparinux is rarely associated with HIT (only few case reports).

The incidence appears particularly high after orthopedic surgery and is higher among surgical patients than medical patients.

Fattori di rischio

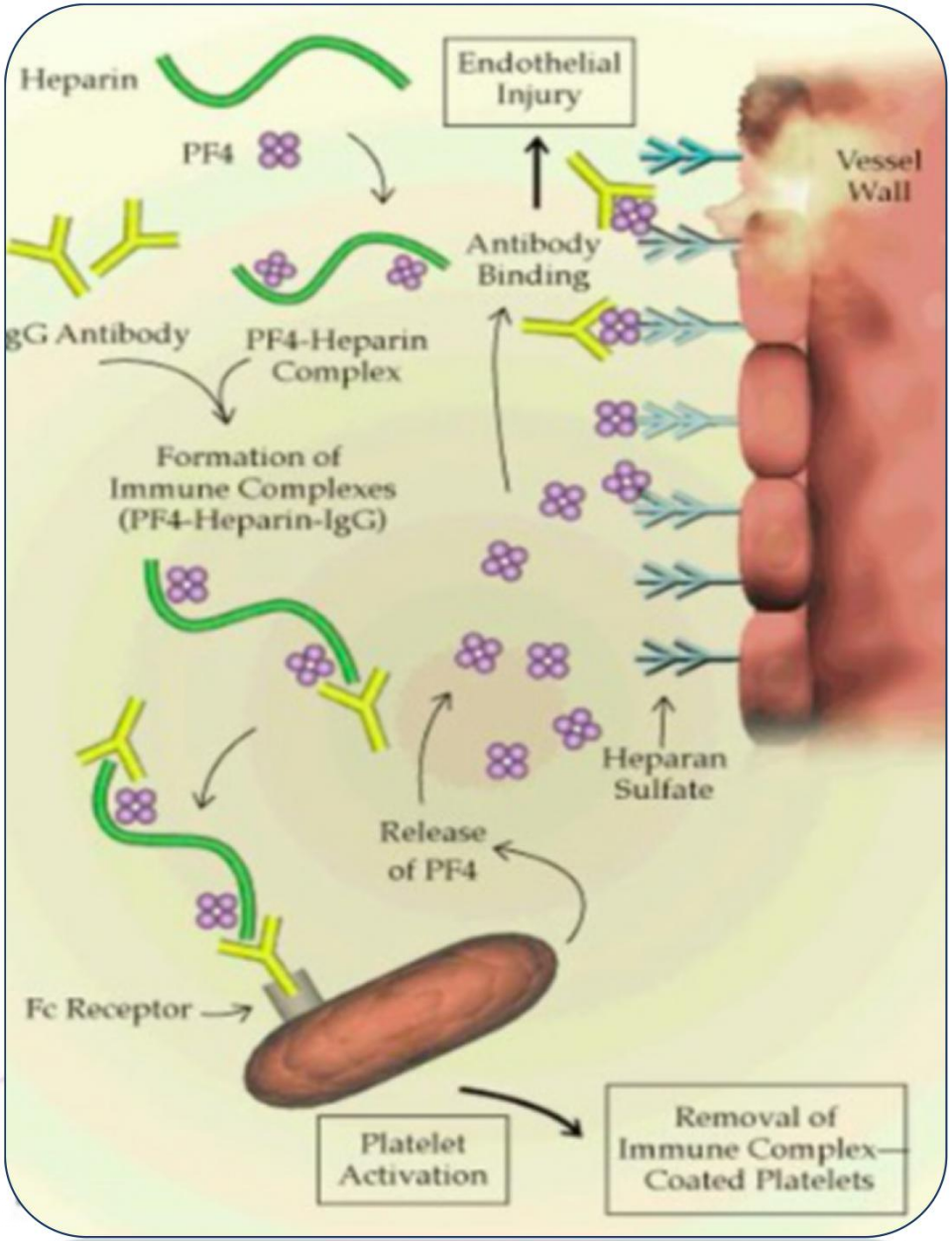
HIT

Il rischio di sviluppare la HIT dipende da numerose variabili, legate in parte alla terapia e in parte alle condizioni del paziente.

- durata della terapia con eparina (un tempo >5 giorni fattore di rischio)
- il tipo (UFH bovina associata a rischio più alto rispetto all'eparina porcina)
- la dose: la dose terapeutica si traduce in una riduzione delle PLT maggiore, ma anche i flush per l'eparinizzazione delle vie venose possono portare alla formazione di anticorpi
- il sesso: le donne hanno circa il doppio della probabilità di sviluppare la HIT rispetto agli uomini, verosimilmente per la loro aumentata risposta immunitaria

Patogenesi

HIT

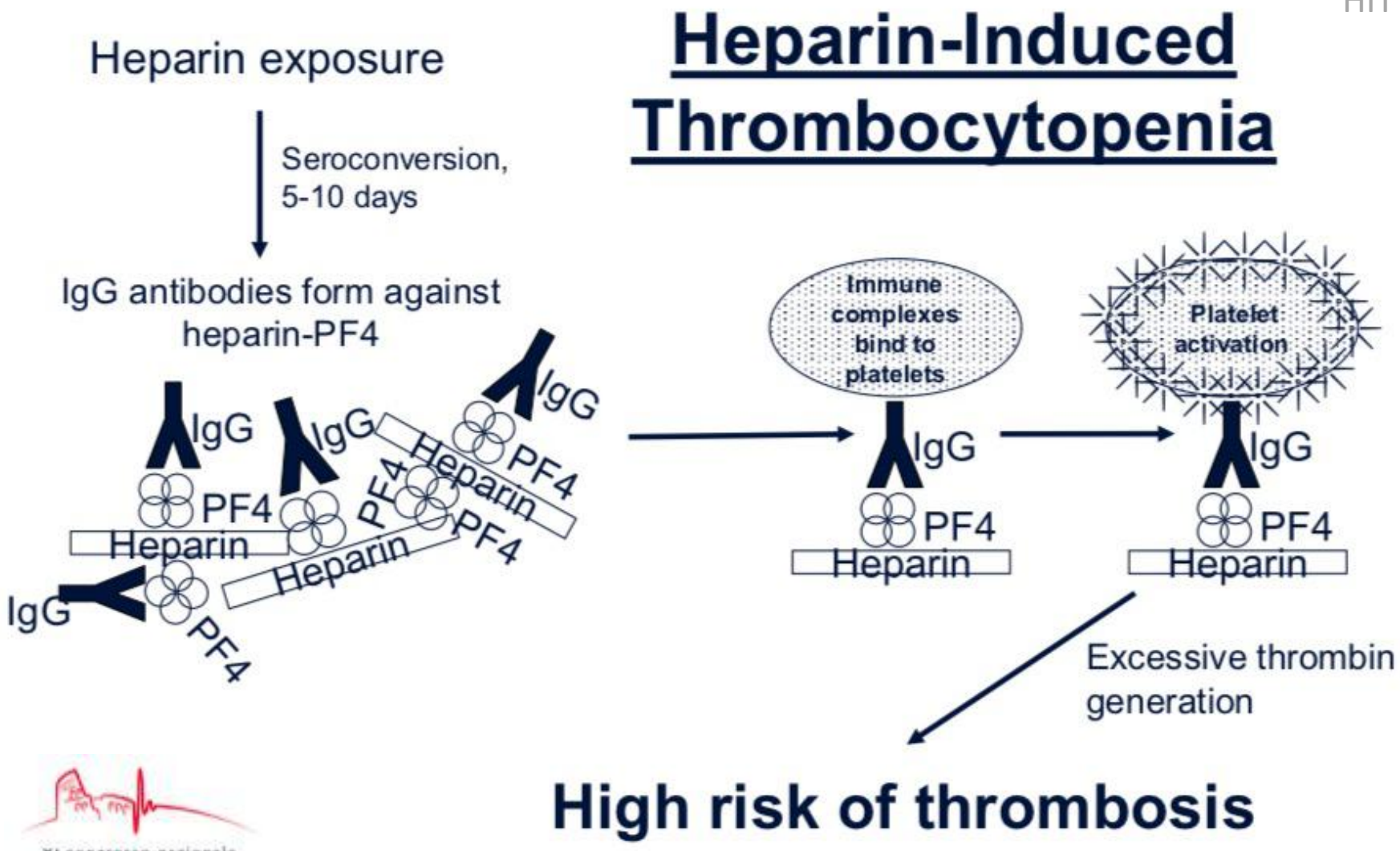


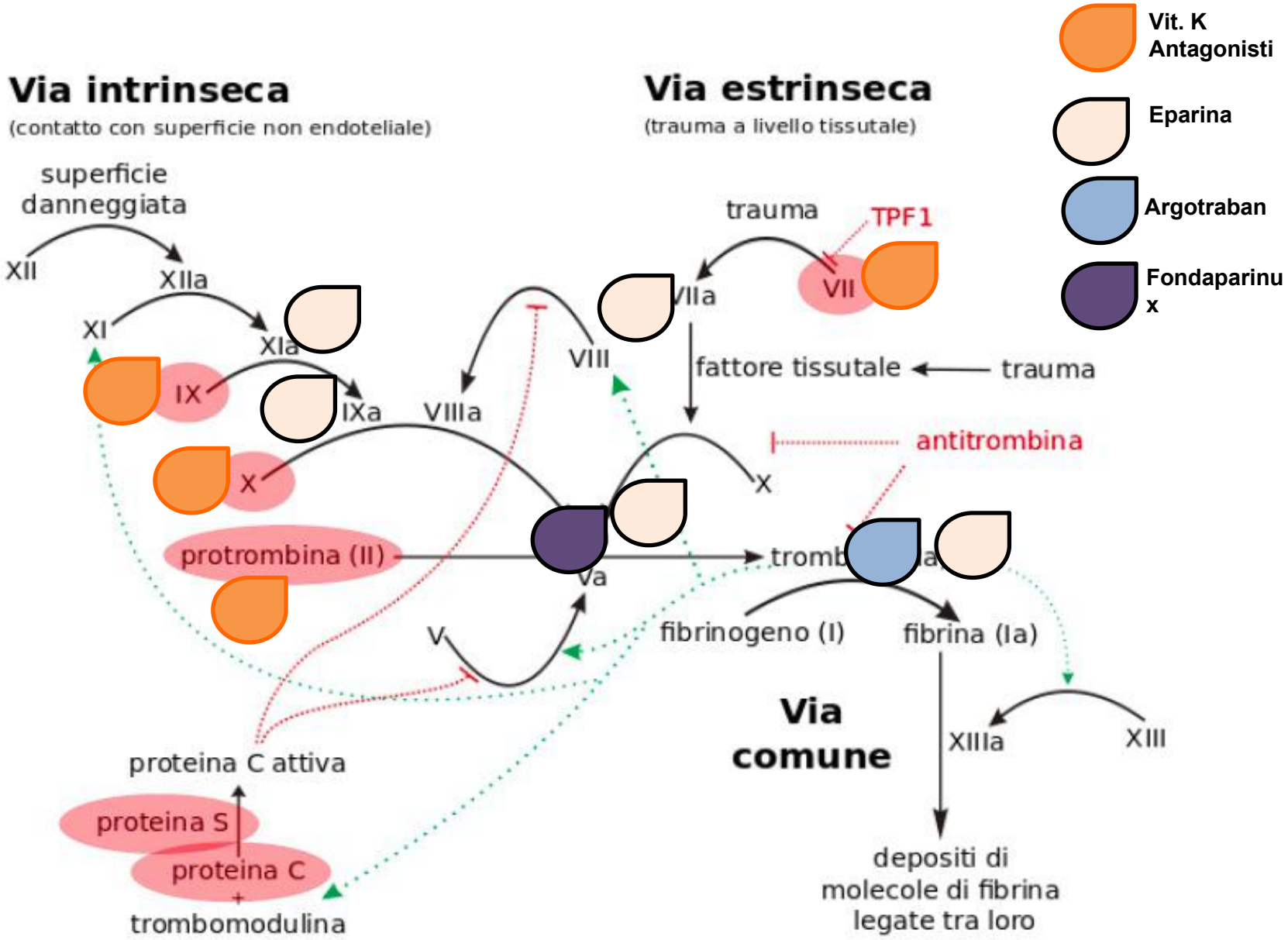
Platelet activation: release of PF4 and microparticles. Administered heparin interacts with PF4 to form PF4-heparin complexes. Immunoglobulin G (IgG) antibodies react with the PF4-heparin complexes to form immune complexes (PF4-heparin-IgG). These immune complexes bind to Fc receptors on circulating platelets. Binding of immune complexes to platelet Fc receptors results in platelet activation and further release of PF4. Activated platelets trigger a number of events. These form additional targets for antibody binding and **promote thrombin generation as a result of immune activation.**

Platelet activation of the coagulation pathways, plus tissue factor expression on activated endothelial cells and monocytes lead to enhanced thrombin generation.

Patogenesi

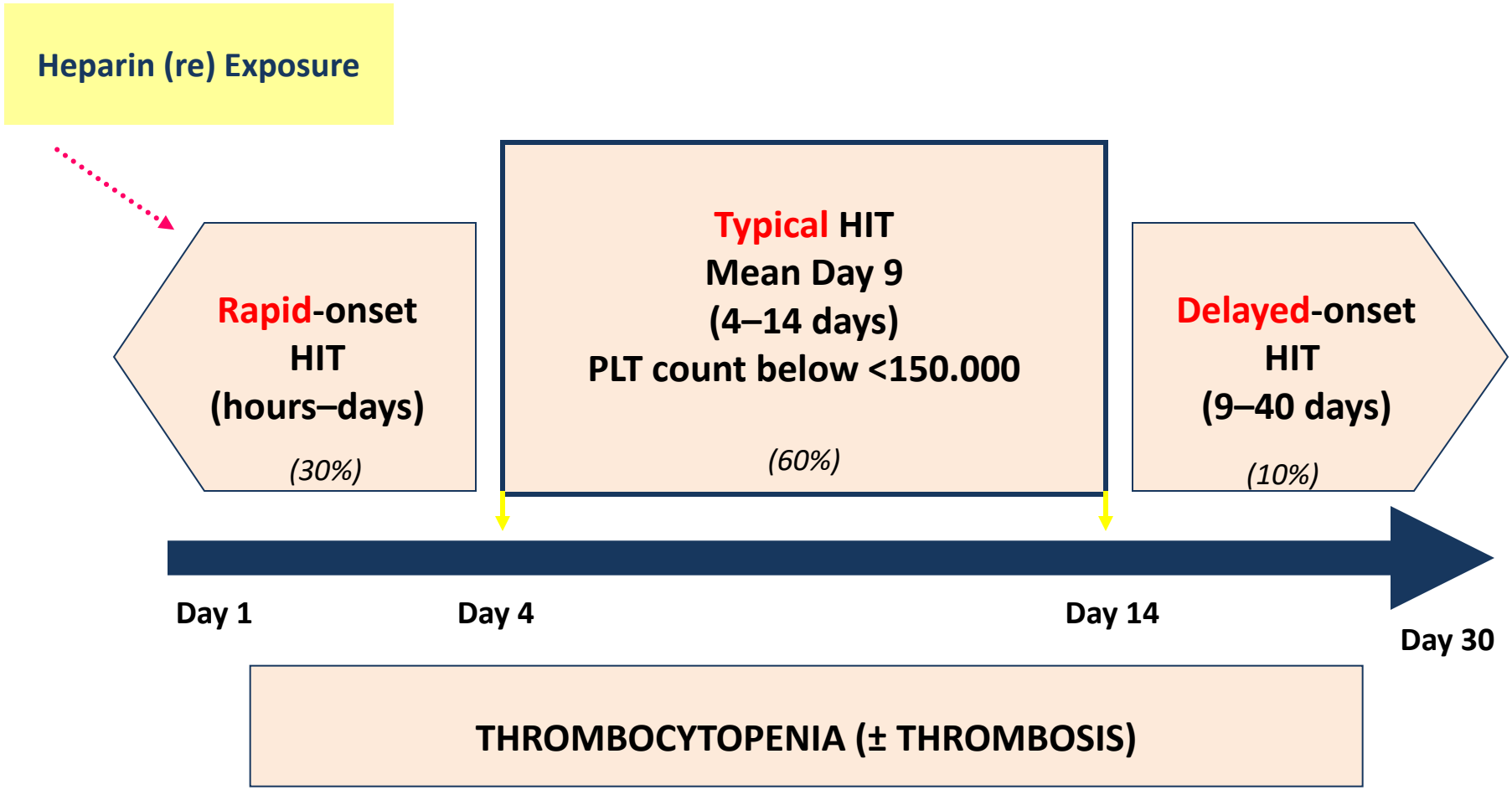
HIT




Via intrinseca
(contatto con superficie non endoteliale)
superficie danneggiata
XII
XIIa
XI
XIa
IX
IXa
VIIIa
X
protrombina (II)
V
Va
proteina C attiva
proteina S
proteina C
trombomodulina
Via estrinseca
(trauma a livello tissutale)
trauma
TPF1
VII
VIIa
VIII
fattore tissutale
trauma
antitrombina
X
fibrinogeno (I)
fibrina (Ia)
Via comune
XIIIa
XIII
depositi di molecole di fibrina legate tra loro
Vit. K Antagonisti
Eparina
Argotraban
Fondaparinux

Presentazione clinica

HIT Temporal Variants



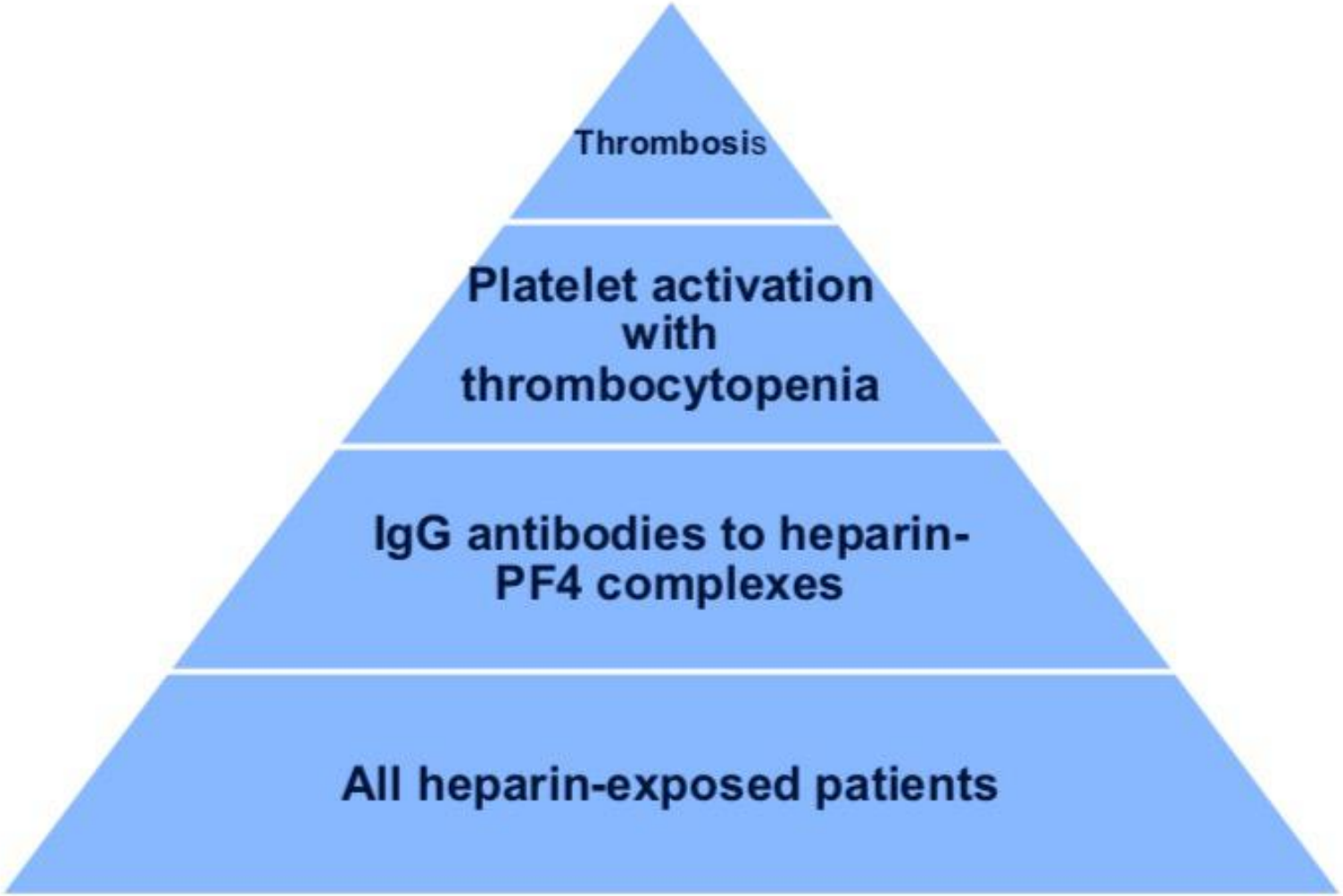
Il paradosso della HIT

- Eparina, l'anticoagulante più potente del ventesimo secolo, che ha salvato milioni di vite, produce anche il disordine più estremo, legato all'ipercoagulabilità, e costa migliaia di vite o amputazioni/anno

- HIT, una reazione immunitaria a un anticoagulante che riduce la conta piastrinica, raramente causa sanguinamento, mentre più frequentemente provoca trombosi

- I professionisti dovrebbero conoscere questa entità, spesso catastrofica, a volte prevenibile, curabile, iatrogena e una fonte di importanti contenziosi, ma in generale le riviste scientifiche prestano poco attenzione ed è incredibile la mancanza di conoscenza spesso, di questa patologia

HIT

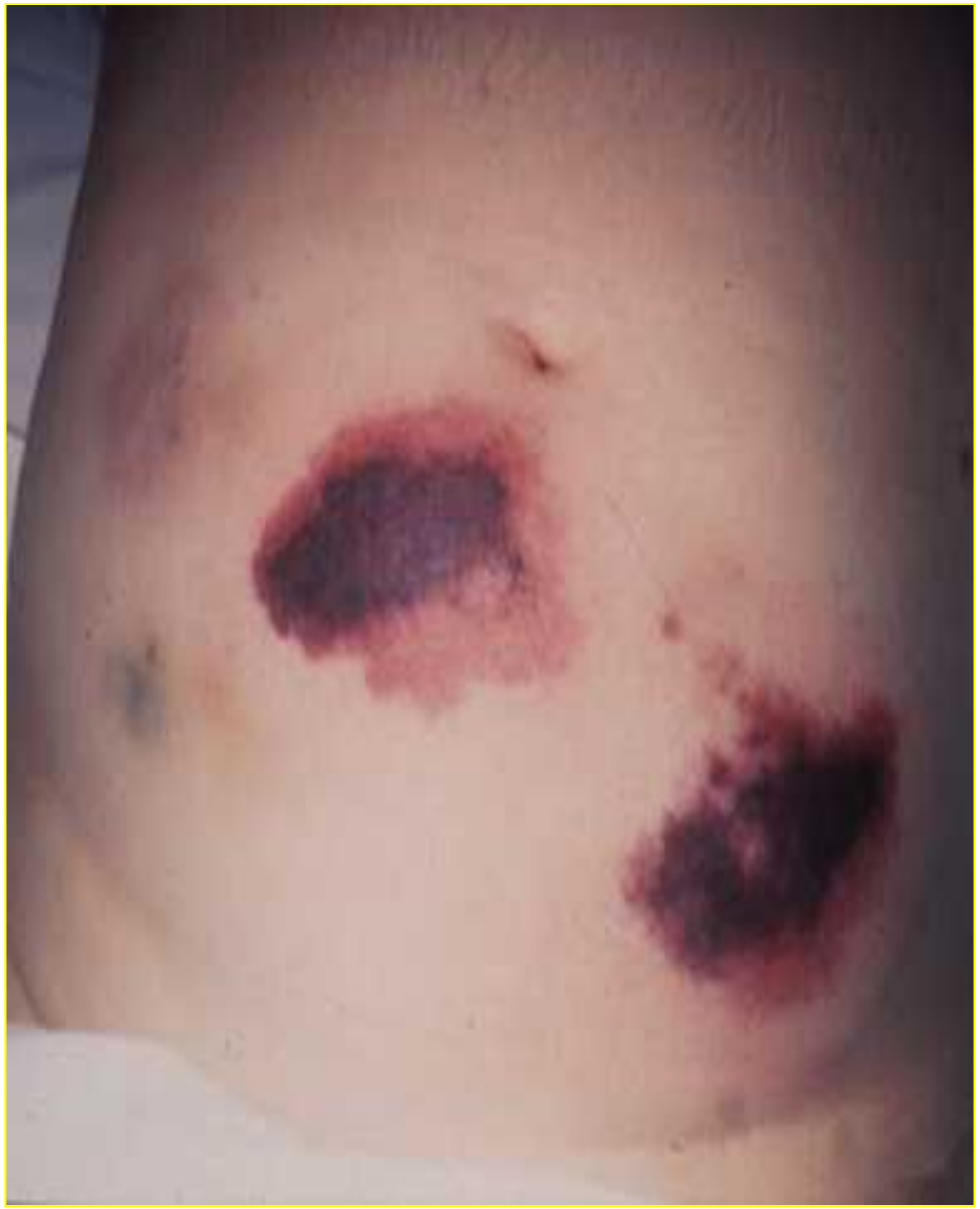

Thrombosis
Platelet activation with thrombocytopenia
IgG antibodies to heparin-PF4 complexes
All heparin-exposed patients

Heparin-Induced Thrombocytopenia (HIT): Clinical Consequences if Untreated

Sequelae	Incidence
New thromboses (arterial or venous)	~50%
Amputation	~21%
Death	~30%

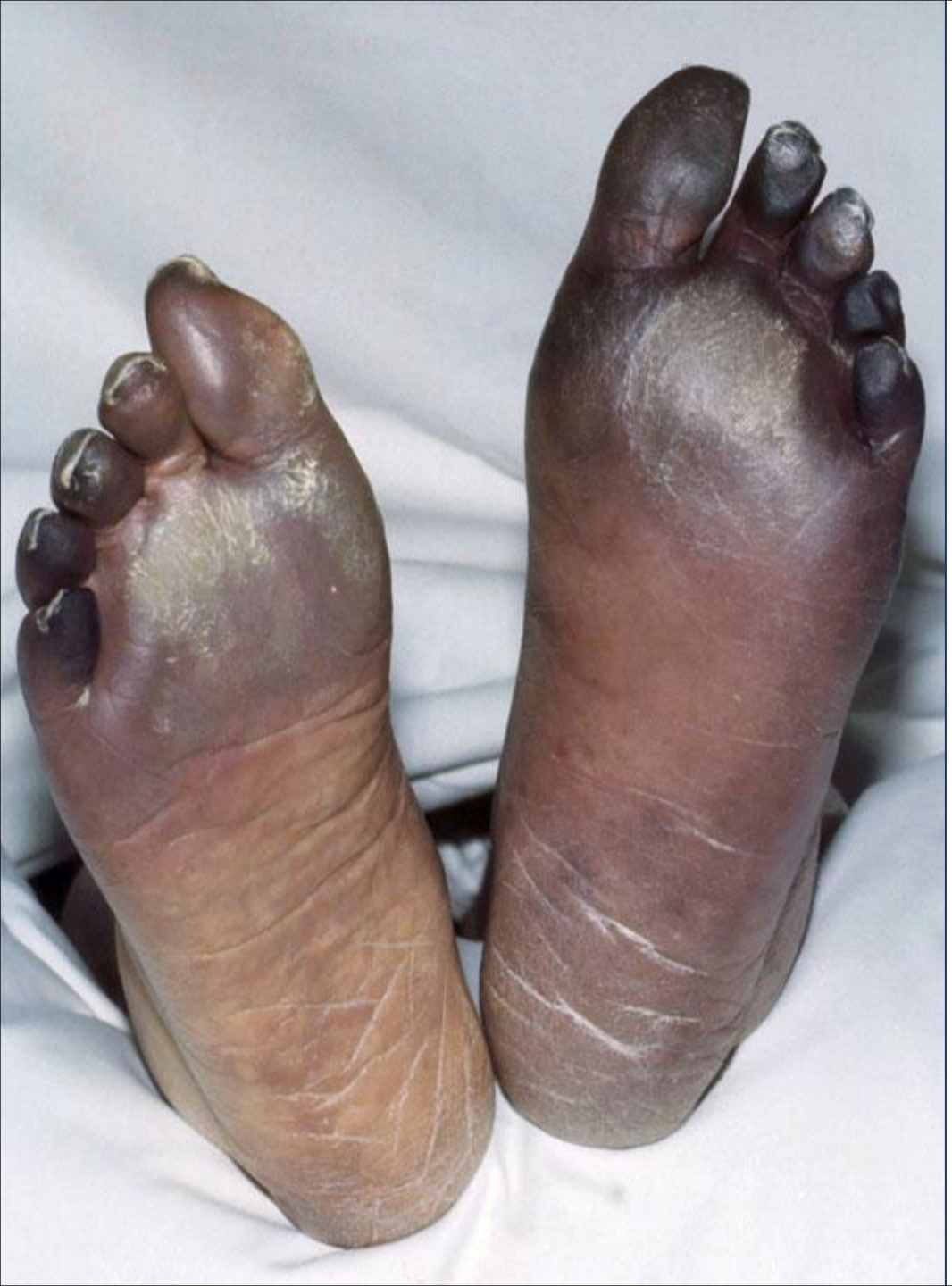
HIT:
Clinical Events if Untreated

- **Venous thrombosis (30-70%) :** DVT/PE, cerebral sinus thrombosis, adrenal necrosis, venous limb gangrene
- **Arterial thrombosis (15-30%) :** Stroke, MI, arterial ischemia
- **Skin lesion at heparin site (10%)**
- **Acute reaction (10%)**
- **CID (10%)**

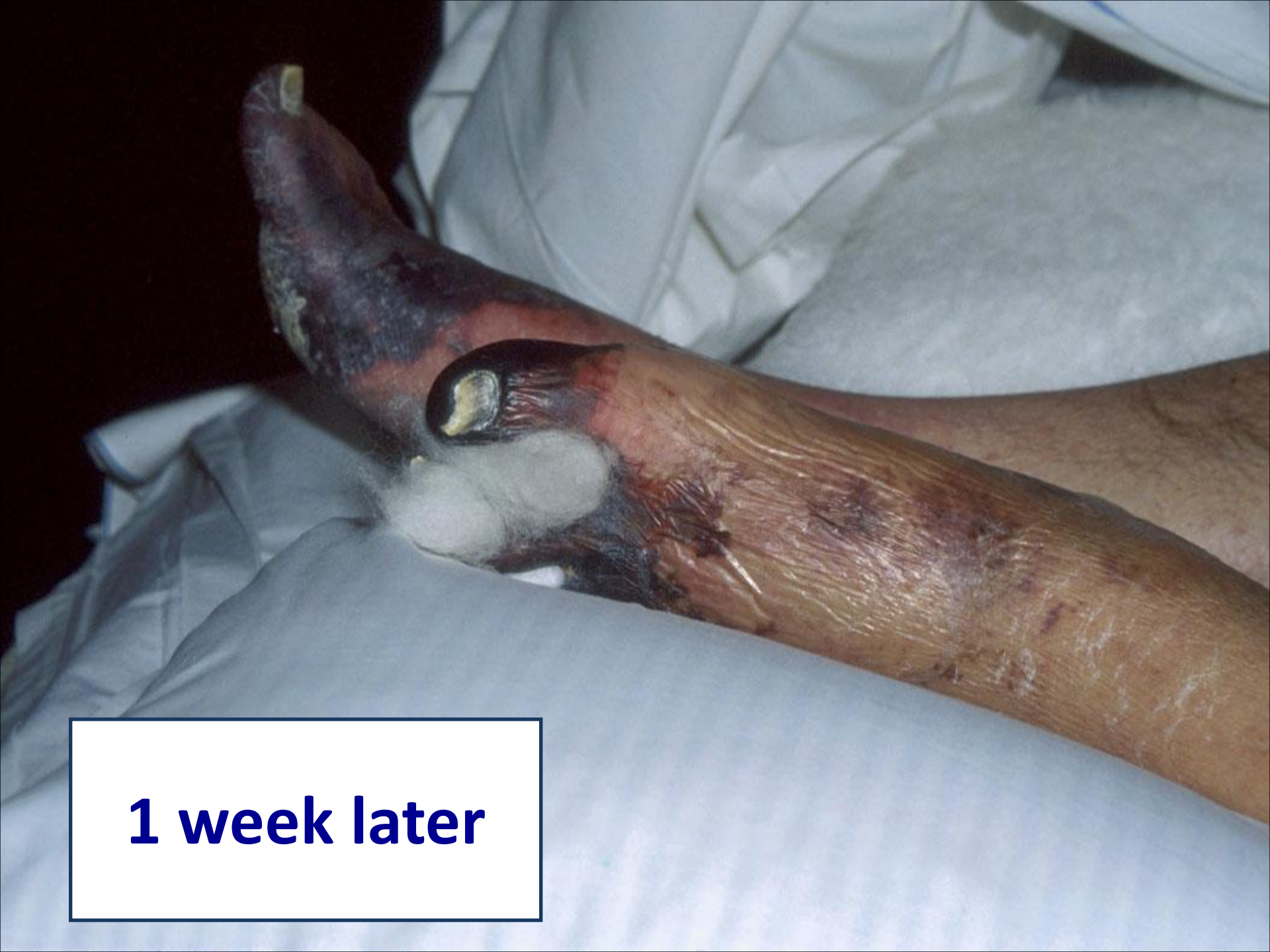


Warkentin TE. *Br J Haematol*. 1996;92:494–497.

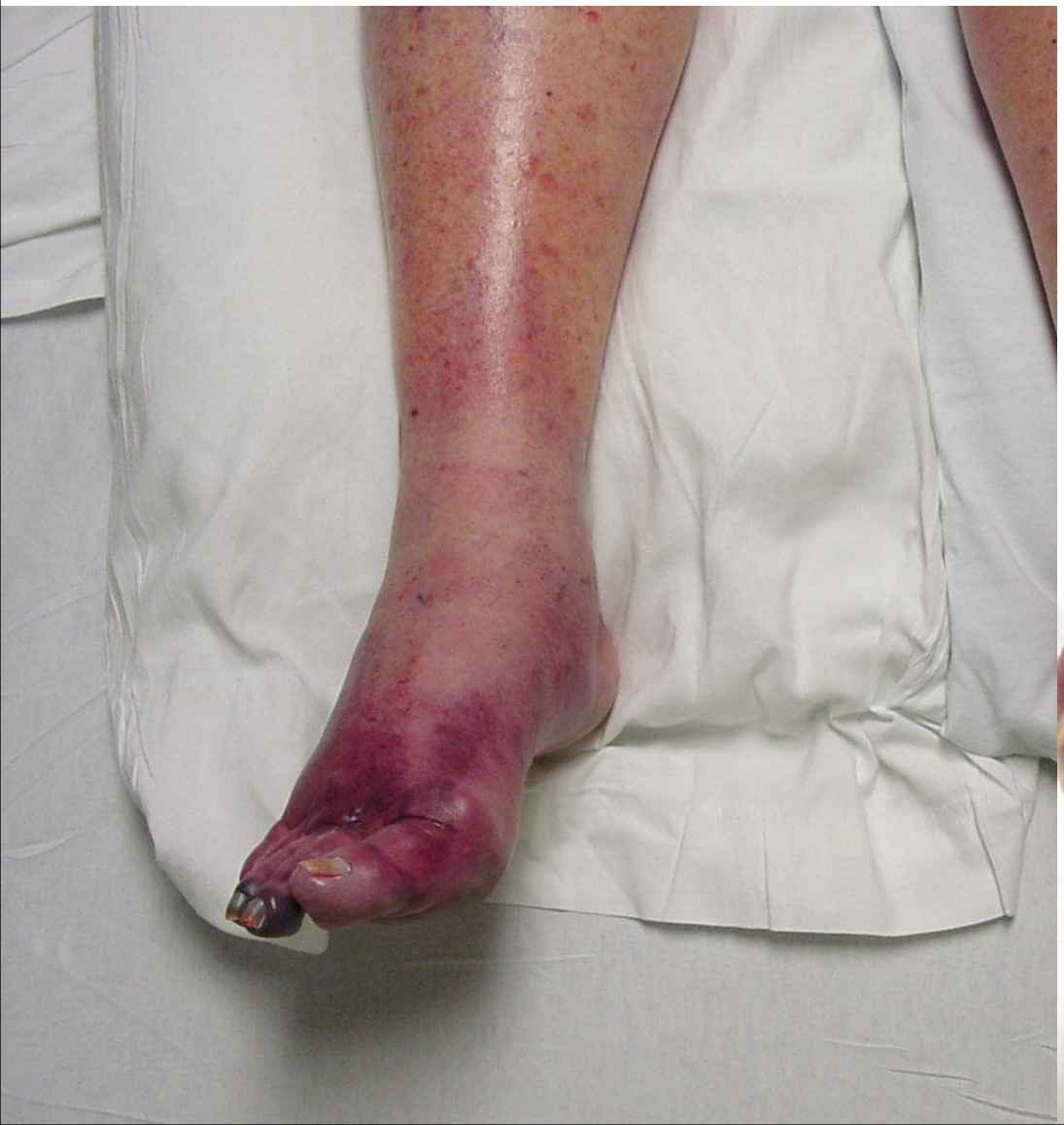
Skin Necrosis at LMWH injection Sites (Prophylactic dose)

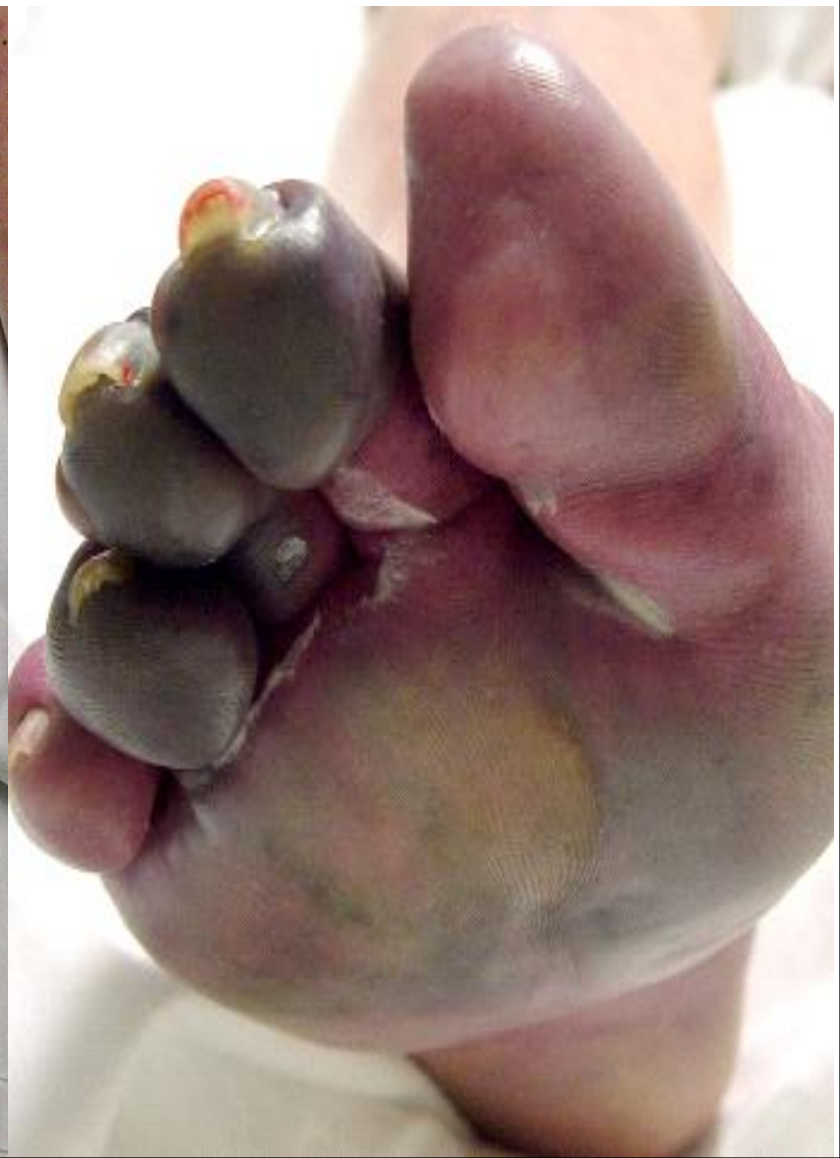


Paziente con controindicazioni a DTI per bleeding gastrointestinale ricorrente


1 week later

HIT With Cancer





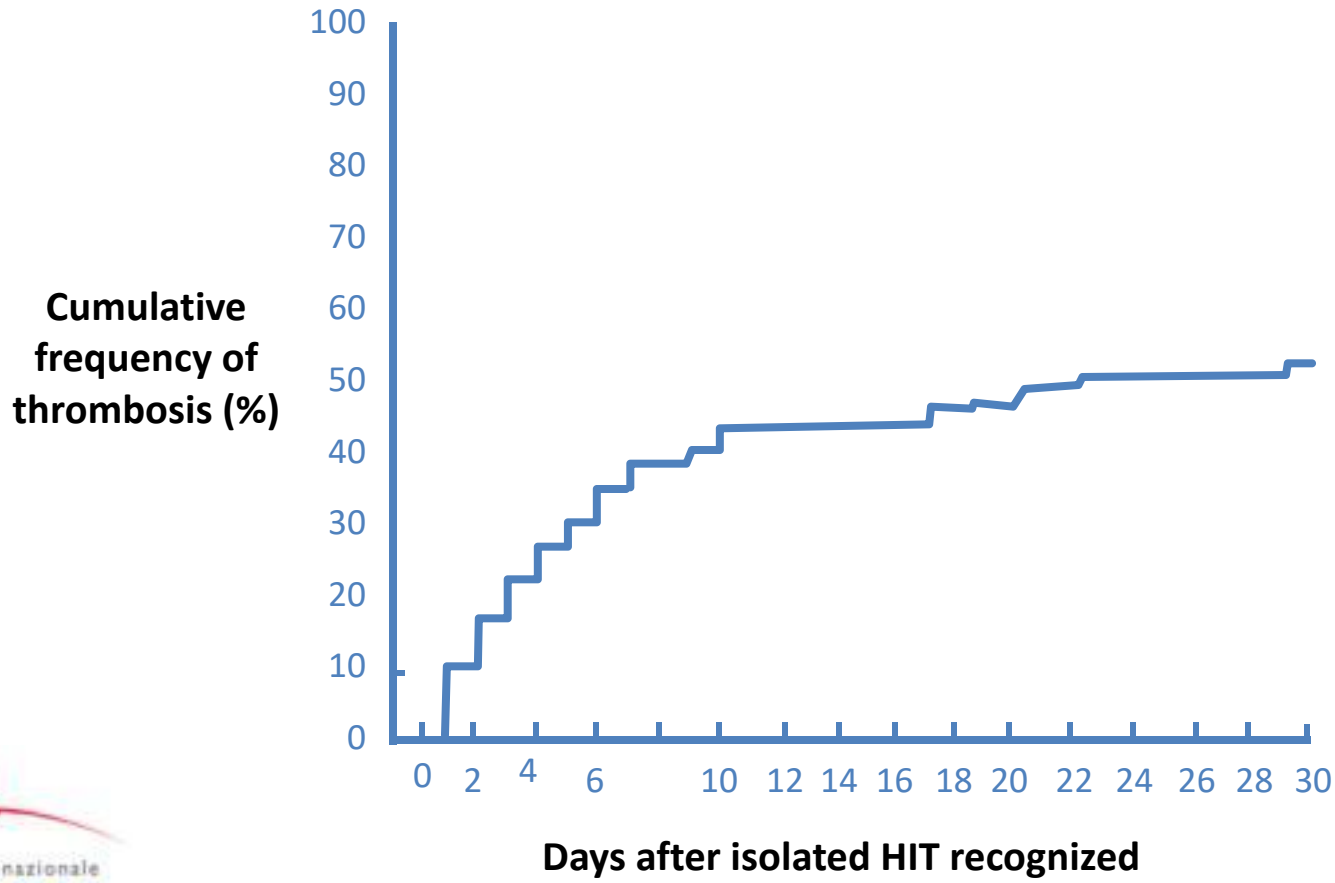
Just hold Heparin and It will Go Away!

How can we justify anticoagulating thrombocytopenic patients with medications that do not have antidotes?

- A transient increase in risks of new thrombosis is observed once heparin is stopped w/o an alternative AC ***(Greinacher Blood 2000)***
- Patients with the lowest platelet counts are most likely to experience devastating thrombosis and are in greatest need of alternative anticoagulation ***(Rice, Arch Intern Med 2004)***
- 10 of HIT pts have platelets 10,000-20,000. Bleeding is rare even when fully anticoagulated. ***(Rice, Arch Intern Med 2004)***

- 6% per day incidence of new thrombosis while awaiting serologic confirmation w/o DTI Rx. This was decreased to 1.3% per day after Refludan Rx ***(Greinacher et al Blood 2000)***
- Therapeutic dose Argatroban lowered new thrombosis from 23% to 6-8% ($P < 0.001$) and lowered the frequency of composite end point of new thrombosis, all cause mortality, and limb amputation from 39% to 26-28% ($P = 0.04$) ***(Lewis BE. Circulation 2001 and Arch Intern Med 2003)***

Risk of Thrombosis with HIT After Heparin is Stopped (if an effective alternative is not begun)



Qualche calcolo...

12 million patients exposed annually	X	Up to 5% incidence of HIT	=	**Up to 600,000 cases every year**

How many cases are recognized and treated properly?

18,000 !!!

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Diagnosi nel setting dell'urgenza

Definizione

CAPITOLO 1

[Contemporary Reviews in Critical Care Medicine]

CHEST

Heparin-Induced Thrombocytopenia in the Critically Ill Patient

James M. East, MD; Christine M. Cserti-Gazdewich, MD; and John T. Granton, MD

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HIT is a Clinicopathologic Syndrome!

(Clinical)

- Appropriate time after heparin initiation (5-12 days)
- Extreme risk for venous or arterial thromboembolic complications

(Pathological)

Fall in platelet counts (generally >50%)

Eventually:

- Serologic confirmation of platelet-activating heparin-PF4 antibodies

Score

HIT

La diagnosi include parametri clinici e test di laboratorio

- HIT Expert Probability Score di Cuker et al.
- Post-CPB (Post CardioPulmonary Bypass) scoring system di Lillo-Le Louët et al.
- Il più usato 4T test di Warkentin et al

Post-CPB scoring system

(Lillo-Le Louët)

TABLE 1 Post-CPB Scoring System

Variable	Clinical Scenario	Points
Platelet count	Pattern A (platelet count begins to recover after CPB but then begins to fall again >4 days after CPB)	2
	Pattern B (thrombocytopenia occurs immediately after CPB and persists for >4 days without recovery)	1
Time from CPB to index date	≥5 days	2
	<5 days	0
CPB duration	≤118 min	1
	>118 min	0

Total score: ≥2 points = high probability of HIT, <2 points = low probability of HIT. Reprinted with permission from Lillo-Le Louët et al. (39).

CPB = cardiopulmonary bypass; HIT = heparin-induced thrombocytopenia.

Clinical Suspicion for HIT

The 4 T (Warkentin, 2003)

- **T**hrombocytopenia
- **T**iming
- **T**hrombosis
- o**T**her causes for low platelets

award 0–2 points for how typical for HIT
high prob 6–8 pts; intermed 4-5; low 0-3

The 5th T: The Test

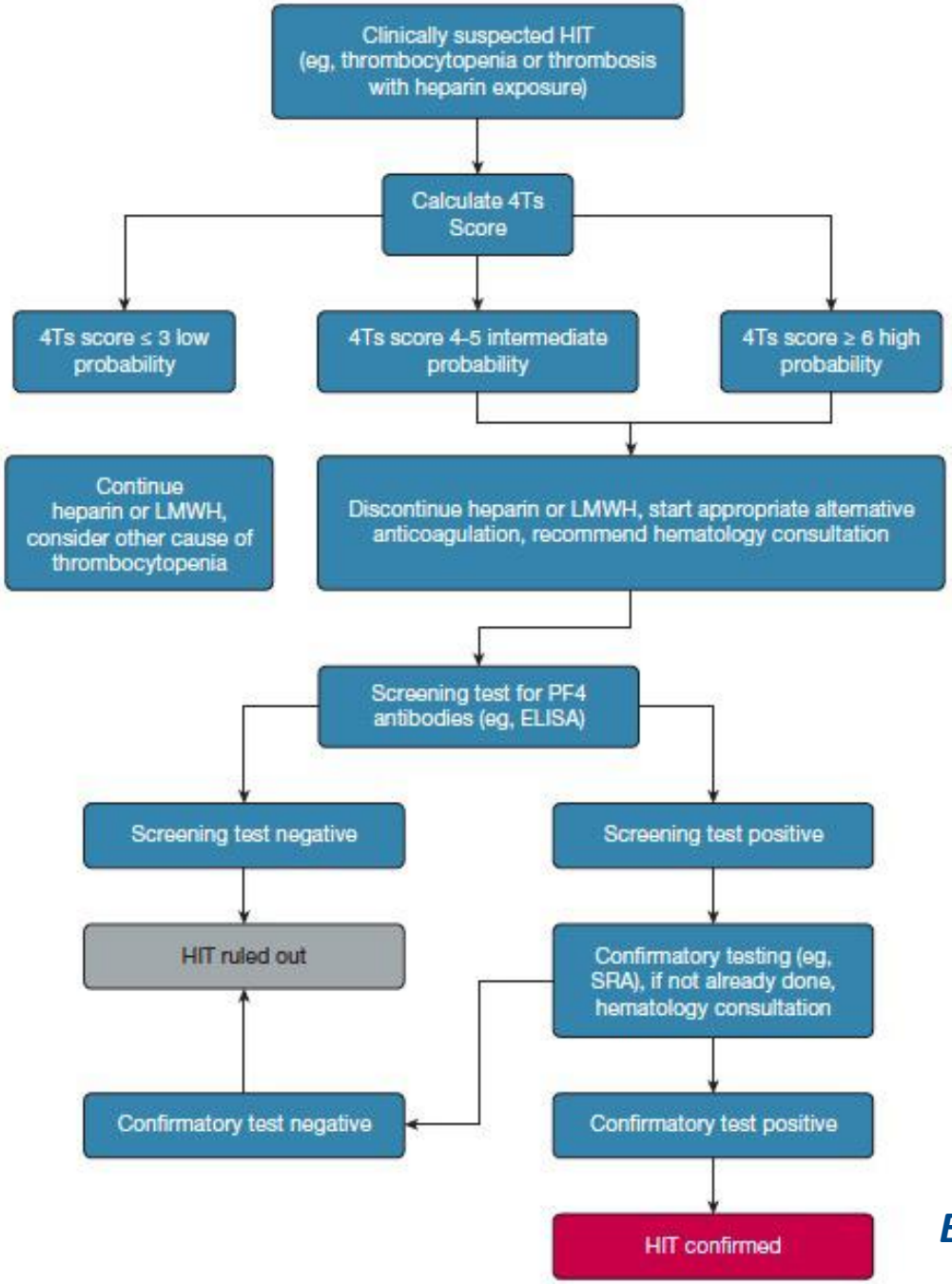

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Figure 1 – *Algorithm for the diagnosis and treatment of heparin-induced thrombocytopenia (HIT). ELISA = enzyme-linked immunosorbent assay; LMWH = low-molecular-weight heparin; PF4 = platelet factor 4; SRA = serotonin-release assay.*

4Ts e Modified 4Ts score

Diagnosi

TABLE 2] 4Ts and Modified 4Ts Score

Variable	Score		
	2	1	0
Thrombocytopenia	> 50% platelet count decrease to nadir ≥ 20	30%-50% platelet count decrease; or nadir 10-19	< 30% platelet count decrease; or nadir < 10
Timing of platelet count decrease	Decrease in days 5-10 or decrease ≤ 1 d (with heparin exposure in past 30 d)	Consistent with days 5-10 decrease but not clear; decrease ≤ 1 d (heparin exposure within past 31-100 d)	Decrease ≤ 4 d (with no recent exposure to heparin)
Thrombosis or other sequelae	Proven new thrombosis or skin necrosis or anaphylactoid reaction after heparin bolus	Progressive or recurrent thrombosis, erythematous skin lesions, suspected thrombosis or hemofilter thrombosis	None
Other causes of thrombocytopenia[a]	No explanation for platelet count decrease	Possible other cause is evident	Definite other cause is present

See Table 1 legend for expansion of abbreviation. (Adapted with permission from Lo et al.[42])
[a]Excluded from the modified 4Ts score.

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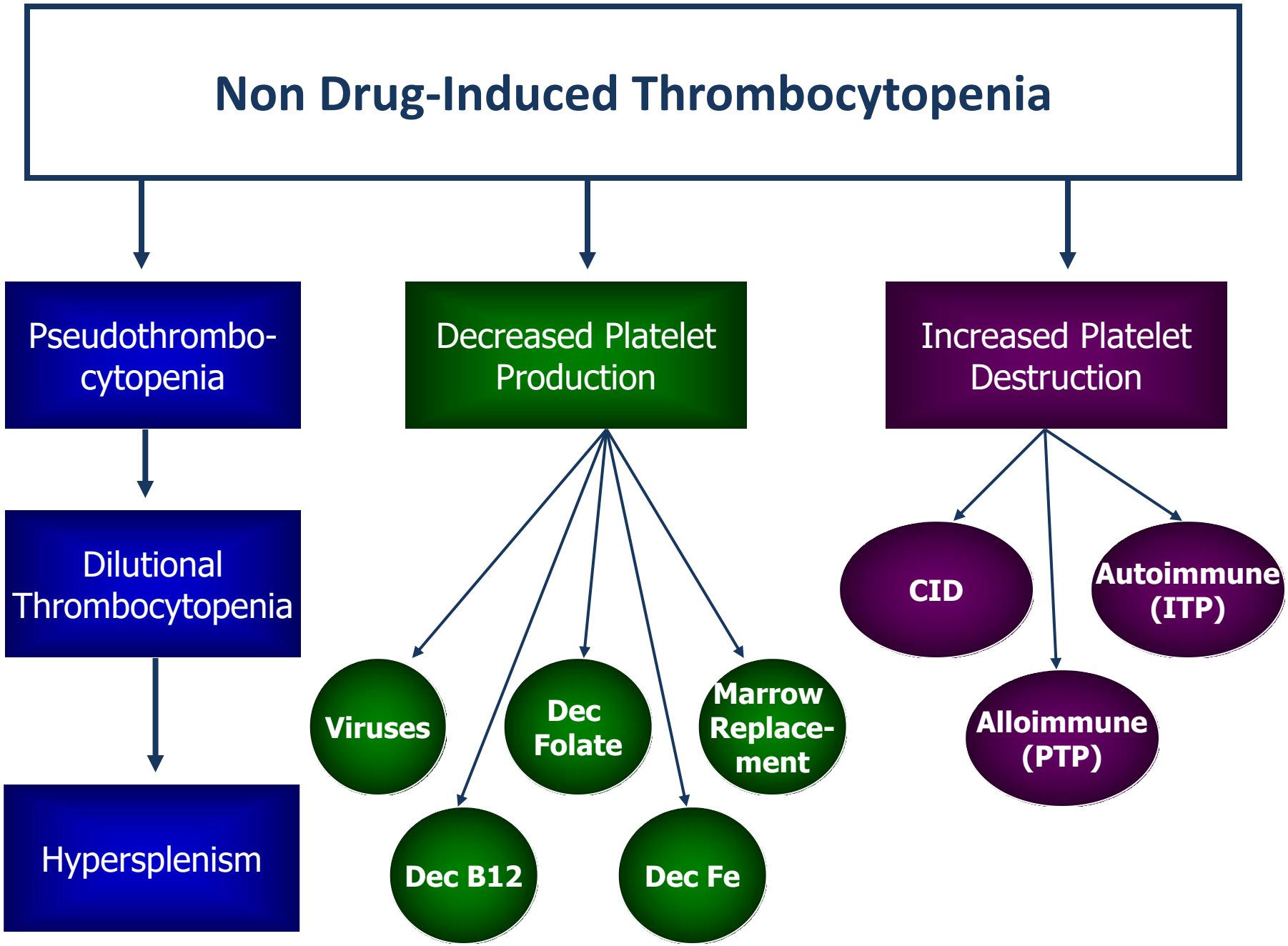
Diagnosi differenziale

HIT

TABLE 3] Differential Diagnoses of HIT and Their Potential Distinguishing Clinical Features

Condition	Diagnostic Clues
Sepsis	SIRS criteria, positive blood cultures
DIC	Increased PT and APTT, decreased fibrinogen
Massive blood loss	Source of bleeding, large-volume transfusions, increased PT and APTT, hypocalcemia, hypothermia
Thrombotic microangiopathy	Schistocytes on blood film, acute kidney injury, stroke or neurologic deficits, hemolysis
Immune thrombocytopenia	Diagnosis of exclusion, no universally accepted antibody test
Drug-induced thrombocytopenia	Decreased megakaryocytes in bone marrow, rebound of platelets after discontinuation of drug
Cardiopulmonary bypass and extracorporeal membrane oxygenation	...
Intraaortic balloon pump	...

APTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; PT = prothrombin time; SIRS = systemic inflammatory response syndrome. See Table 1 legend for expansion of other abbreviation.


Non Drug-Induced Thrombocytopenia
Pseudothrombo-cytopenia
Dilutional Thrombocytopenia
Hypersplenism
Decreased Platelet Production
Viruses
Dec Folate
Marrow Replace-ment
Dec B12
Dec Fe
Increased Platelet Destruction
CID
Autoimmune (ITP)
Alloimmune (PTP)

Diagnosi

HIT

Due test diagnostici:

immunodosaggio (antigenico) e funzionale (platelet activation assay - attivazione delle PLT).

Ognuno di questi test definisce uno step nella patogenesi:

Immunodosaggio: rileva la risposta immunologica iniziale mentre il secondo test l'attivazione delle piastrine che porta alla trombosi.

Immunodosaggio (ELISA) alto grado di sensibilità (99%) e quindi un valore predittivo negativo molto alto: se negativo, rule out.

Take Home Message

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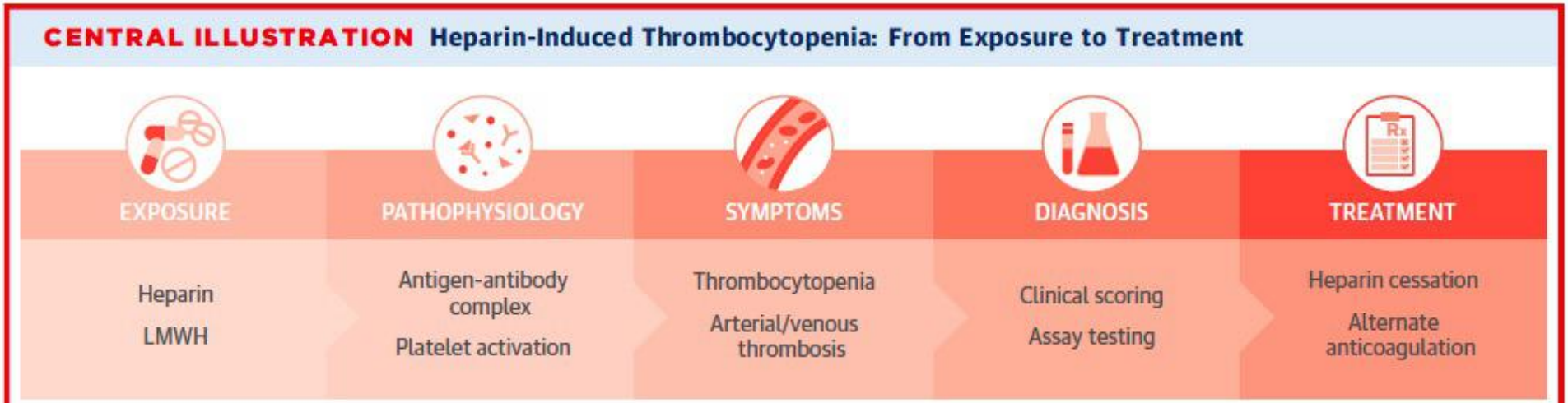
Take home message

HIT: dall'esposizione al trattamento

CENTRAL ILLUSTRATION **Heparin-Induced Thrombocytopenia: From Exposure to Treatment**



Salter, B.S. et al. J Am Coll Cardiol. 2016;67(21):2519-32.

LMWH = low-molecular weight heparin.

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Take home message

HIT

- HIT: effetto avverso da farmaco, più frequentemente legato all'uso di UFH che non LMWH
- E' una diagnosi clinico-patologica!
- Ha un elevato rischio di trombosi
- I pazienti ad alto rischio richiedono il monitoraggio continuo delle PLT

Take home message

HIT

- **Da fare:**
  1. sospendere le eparine
  2. utilizzare anticoagulanti specifici per questa patologia

- **Da NON fare:**
  1. Trafusioni di PLT routinariamente
  2. evitare il warfarin

- **Da fare:**
  Test per il riscontro degli anticorpi responsabili della HIT
  ECD degli arti

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GRAZIE PER L'ATTENZIONE!