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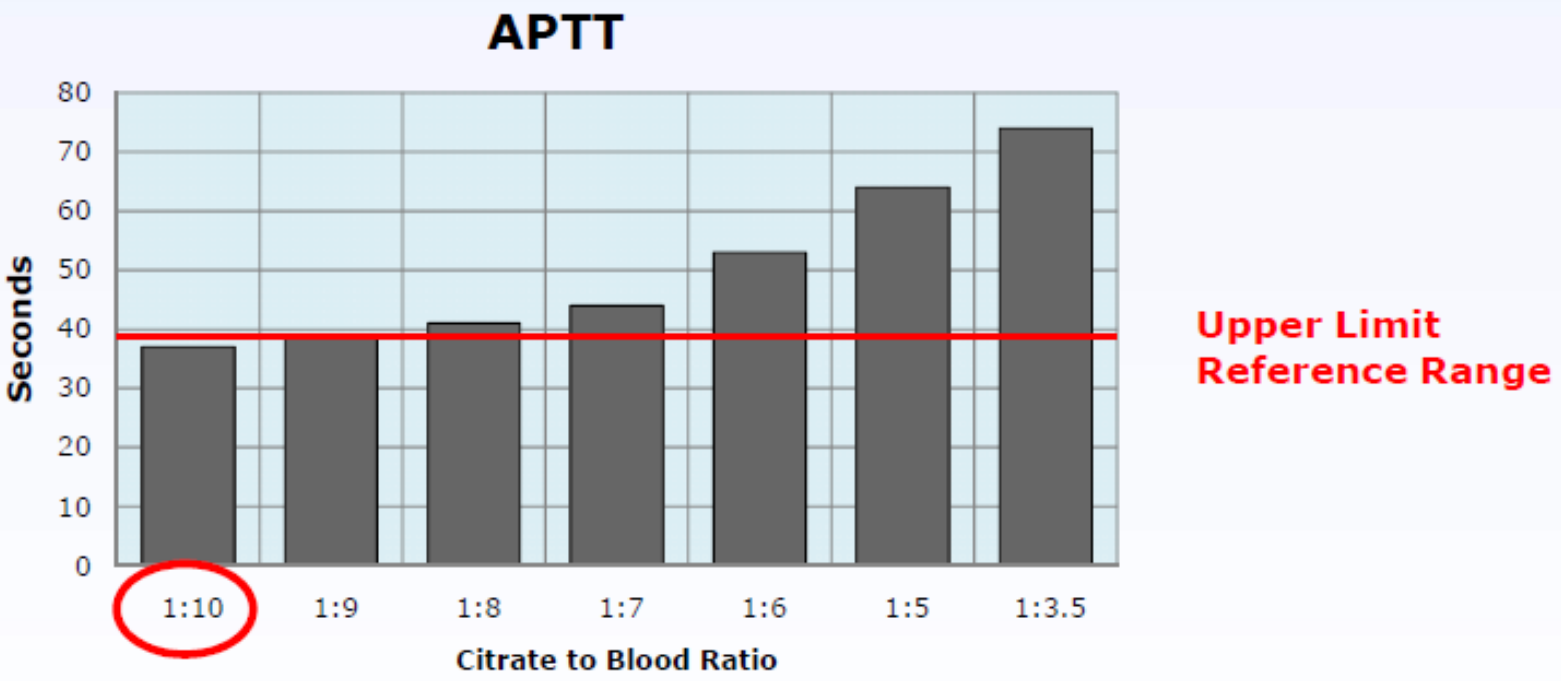
Effect of under filling tube

- High Citrate concentration
- Dilution of clotting factors
- Inadequate recalcification

PROLONGED CLOTTING TIMES!

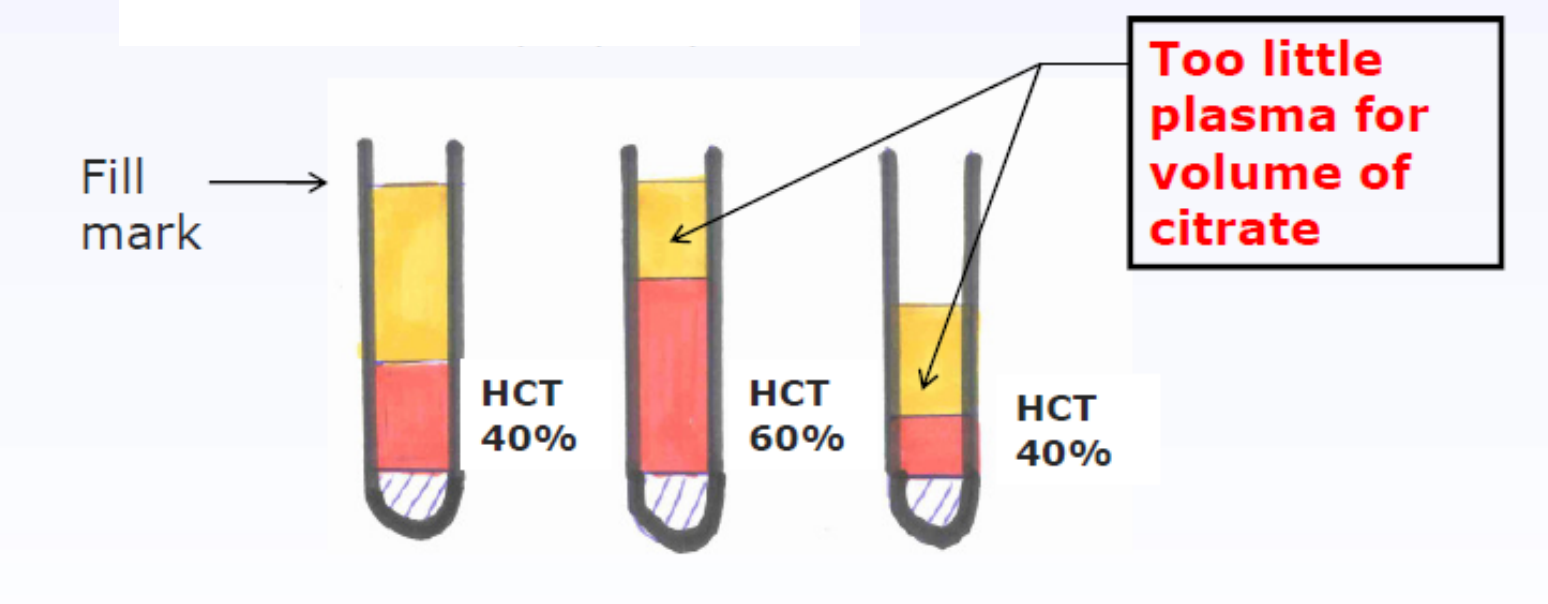


What constitutes underfilling?

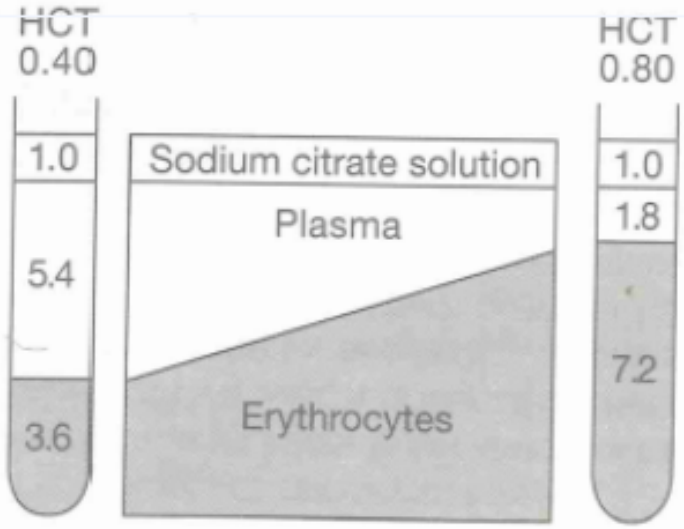
A 4.5ml vacutainer collection tube should contain at least 4ml of blood

Less than that could give falsely prolonged clotting times

ALSO be aware that a high Haematocrit may give false results even if tube is properly filled.



Citrate Ratios



- HCT – 0.25 – 0.55 – clotting tests generally unaffected
- HCT >0.55 false results (prolonged times)
  - Neonates
  - Polycythaemia (cardiac, pulmonary, haematological)
- Correct – as per graph

Haemostatic challenges in Critical Care

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The ICU challenge…..

Maintain or restore haemostatic balance in inherently unstable patients

Disseminated intravascular coagulopathy

Thrombotic microangiopathies

Massive transfusion

Thromboprophylaxis in ICU

Heparin induced thrombocytopenia

The role of the laboratory

DISSEMINATED INTRAVASCULAR COAGULOPATHY

Normal Response to vessel damage

Normal Response to vessel damage:

Release of **Tissue factor** – coagulation cascade – THROMBIN formation – fibrinogen converted to fibrin

VWF mediated platelet adhesion – platelet activation and aggregation

→ processes initiated simultaneously – clot "seals the gap"

→ fibrinolysis activated – clot breakdown – "maintains flow"

Highly regulated process – localisation of clot formation maintained through fine balance of procoagulant and anticoagulant mechanisms.

Disseminated Intravascular Coagulopathy

DIC when:

There is widespread endothelial damage or

Thrombin generation overwhelms inhibitory mechanisms

⟶ **free thrombin becomes systemic**

Definition of DIC :

An acquired clinico-pathologic syndrome caused by unregulated release of thrombin into the general circulation with loss of localisation arising from different causes.

⟶ **widespread endothelial dysfunction**

What are the common causes of DIC?

- Infections
- Trauma
- Obstetric complications
- Malignancy
- Severe allergic/toxic reactions
- Severe immunologic reactions
- Vascular disorders

Pathogenesis of DIC

Widespread generation of fibrin clots throughout microvasculature

⟹ obstruction of vessels → multiple organ dysfunction

(especially kidney, brain, lung, liver, heart)

⟹ Red cell fragmentation - haemolysis

⟹ Consumption of clotting factors, platelets and fibrinogen → bleeding manifestations

Clinical manifestations

Highly variable – depends on underlying cause and rapidity of process

Subclinical laboratory abnormalities

multiorgan failure
metabolic derangement
haemodynamic instability
widespread bleeding
DEATH

Challenge #1
Recognition of DIC!

Does the patient have an underlying disorder associated with DIC?

Be vigilant – can develop at any time

DIC is not a disease

- it is always secondary manifestation of another pathology
- Must take into account clinical and laboratory findings

Be aware of subtle signs of thrombotic process

- Reduced urine output
- Change in alertness/confusion
- Drop in PO_2

By the time bleeding is observed – late stage!

- Oozing at venepuncture sites
- Increased bleeding into surgical drains
- Petechia/bruising

Laboratory manifestations

Drop in platelet count – regular monitoring is essential

- Multiple causes of thrombocytopenia in ICU setting
- Platelet count <100 x 10^9/L

Elevated D-Dimers

- Other causes of ↑ D-Dimers in ICU
- Rising levels are highly significant

Prolonged prothrombin time

- >3 seconds above UL of normal

Diagnostic scoring systems in use – Overt DIC or non-Overt DIC

Other lab findings:

- ↓ Antithrombin/Protein C/FXII
- ↓ multiple clotting factors
- Red cell fragments

Management of DIC

Manage the underlying condition!

Haemodynamic support - maintain good perfusion

If actively bleeding (or at high risk)

- Platelets – maintain ≥ 50 x 10^9/L
- FFP – maintain PT/APTT close to normal range as possible
- Cryoprecipitate – maintain fibrinogen ≥ 1 g/L
- Packed red cells – as required

No real evidence to support widely held belief that blood product support "Fuels the Fire"!

Systemic anticoagulation

- No consensus on this issue – generally reserved for overt thrombosis
- Major vessel thombosis – Rx with full therapeutic dose heparin anticoagulation
- Microvascular occlusion – lower doses of heparin

Management of DIC II

Antifibrinolytic therapy

- Generally contraindicated
- APL – may be considered in exceptional cases (high risk of hyperfibrinolytic intracranial bleeding)

Specific inhibitors of coagulation

- Antithrombin concentrate
  - Randomised control trials – no significant benefit in overall mortality reduction
- Activated protein C concentrate
  - Some benefit shown in severe sepsis
  - Improved survival but increased bleeding
  - Avoid if platelets <30 x 10^9/L

THROMBOTIC MICROANGIOPATHIES

Thrombotic microangiopathies

Group of related disorders characterised by widespread microvascular occlusion by platelet-rich aggregates

Thrombotic thrombocytopenic purpura (TTP)

HELLP syndrome

Haemolytic uraemic syndrome

TTP – clinical features

Classic symptoms:

- Thrombocytopenia
- Microangiopathic haemolytic anaemia
- Fluctuating neurological signs
- Renal impairment
- Fever

Hallmark

- Excessive platelet aggregation because of ultra large VWF multimers
- Deficiency of ADAMTS13

TTP – precipitating factors

Infection

- HIV – CD4 <250 x 10^9/L
- Hepatitis

Pregnancy

Malignancy

Drugs

Autoimmune disease

Post bone marrow transplant

(familial form)

TTP – laboratory findings

- Severe thrombocytopenia
- Red cell fragments – but may only appear after 24-48 hours after clinical presentation
- Coagulation profiles usually normal
- ADAMTS13 levels reduced/absent
  - Not routinely available

Investigations required in suspected TTP

- FBC and peripheral smear review
- Reticulocyte count
- PT, APTT, fibrinogen and D-Dimers
- Urea and electrolytes
- Urinalysis

Immediate treatment of TTP

High index of suspicion

Low platelets, neurological signs and MAHA – treat as TTP

Very high mortality – sudden coronary artery occlusion

Immediate plasma exchange – life saving!!

Commence within <24 hours

Daily single volume exchange

Continue until at least 2 days after complete remission

If plasma exchange not possible – plasma infusions

TTP-Concomitant treatment

- Folate supplementation
- Adjuvant corticosteroid therapy for 3 days can be considered
- Platelet transfusions are contraindicated unless there is life threatening haemorrhage
- Red cell transfusions – according to clinical need
- Upon platelet recovery (>50 x 10^9/L) – low dose aspirin

TTP outcome

- Prior to plasma exchange - mortality rates >90%
- With prompt plasma exchange - ~10-30%
- Reduced level of consciousness at presentation – overall survival ~50%
- Average number of plasma exchange procedures to achieve remission 15.8 (range 3 – 36 in one series)
- Relapses common - urgent self referral is advised if patient develops symptoms suggestive of relapse

MASSIVE TRANSFUSION

Coagulopathies associated with massive transfusion

Definition: replacement of ½ blood volume in 4 hours;
1 blood volume in 24 hour (adult 70ml/kg; child 80ml/kg)
~ adult 4 units/4 hours

- Underlying condition necessitating transfusion must always be considered
- Excessive haemorrhage (trauma, surgical, obstetric, GIT bleeds etc)
- Factors that exacerbate bleeding
  - Hypothermia
  - Metabolic acidosis

Coagulopathy associated with massive transfusion

1. Dilutional
   - Replacement of blood volume with packed red cells
   - Displacement of plasma and platelets
   - There is insufficient evidence that the use of blood product replacement ratios of RBCs to component therapy (FFP, platelets, cryoprecipitate) influences morbidity and mortality
   - Some institutions use ratio RBC:FFP:PLTs ~2:1:1
   - (PLT = adult unit)
2. Transfusion reaction
   - Signs may be subtle – especially in anaesthetised or comatose patients
   - Must be acutely alert and perform regular vital sign observations (BP, T °C, pulse)
   - DIC may develop due to acute haemolysis

Management of massive transfusion

Should have massive transfusion protocol

Vigilant monitoring

Include measurement early on and frequently:

Parameter	Values to Aim for
Temperature	> 35°C
Acid-base status	pH >7.2, base excess <-6, lactate <4mmo/L
Ionised calcium	>1.1mmol/L
Platelets	> 50 x 10^9/L
PT/APTT	<1.5 x normal
Fibrinogen	>1g/L
Hb	In context of haemodynamic status and tissue perfusion

THROMBOPROPHYLAXIS IN ICU

Risk of VTE in ICU

- Patients at substantially increased risk
- Significant contributor to morbidity and mortality
  - Post-mortem reviews of patients dying in ICU
    - Pulmonary embolism attributable as cause of death ~27%
  - 15% of all in-patient deaths - PE
- Most have multiple risk factors (predate ICU admission)
  - Recent surgery
  - Immobilisation
  - Trauma
  - Sepsis
  - Malignancy
  - Increased age
  - Respiratory failure
  - Previous VTE

Risk of VTE in ICU - II

- Initial risk factors confounded by new ones acquired in ICU
  - Immobilisation
  - Pharmacological paralysis
  - Central venous catheterisation
  - Additional surgical procedures
  - Sepsis
  - Vasopressors
  - Haemodialysis
- Clinically undetected DVT may be present on admission to ICU
  - 5 studies using Doppler ultrasound (990 pts 5.5% DVTs on admission, 29% for those with no prior thromboprophylaxis)
  - Most DVTs located in calf veins and asymptomatic – BUT
  - ➢ Cannot predict who will become symptomatic and develop complications
  - ➢ Massive PE frequently occurs without warning – often fatal

Risk of VTE in ICU - III

- Without adequate prophylaxis
  - Major trauma
  - Multisystem failure

    → > 50% risk of DVT

    → PE 3rd commonest cause of death after day 1
- Extensive trials of thromboprophylaxis in medical and surgical patients but very few in critical care
- Risk-benefit ratio may be different

Thromboprophylaxis in ICU

Based on 2 systematic reviews:

- With few exceptions – required for ALL ICU patients
- Decision regarding initiation and method based on balance of bleeding and thrombotic risk i.e. mechanical vs heparin
- Prophylaxis reviewed daily an altered based on clinical status
- Prophylaxis should not be interrupted for procedures unless high risk of bleeding
- Procedures such as insertion or removal of epidural catheters – planned for nadir of anticoagulant effect
- Patients with no/suboptimal prophylaxis – Doppler US screening
- High risk patients - continue until discharge (includes in-patient rehabilitation) and beyond if immobility ongoing

Suggested VTE prophylaxis in critically ill patients

Bleeding Risk	Thrombosis Risk	Prophylaxis
Low	Moderate	Low dose heparin (5000u sc bd) or LMWH at prophylactic dose
Low	High	LMWH at prophylactic dose
High	Moderate*	Stockings ± intermittent pneumatic compression
High	High#	Stockings ± intermittent pneumatic compression and LMWH

* Medical, post general surgery
# Trauma, orthopaedic surgery

HEPARIN INDUCED THROMBOCYTOPENIA

HIT pathogenesis

Definition: transient drug induced autoimmune prothrombotic disorder initiated by heparin

- Heparin exposure can induce formation of pathogenic IgG antibodies → platelet activation via PF4/heparin complex on platelet surface

- Thrombocytopenia and thrombin generation

⟶ Increased risk of venous and arterial thrombosis

Incidence of HIT

- Varies widely based on type of heparin and patient group
- Unfractionated heparin >> LMWH
- Surgical patients >> medical/obstetric patients with equal heparin exposure
- Postoperative orthopaedic patients on UFH highest risk (up to 5%) – require more intense platelet count monitoring
- Pregnant woman on LMWH – very low risk

Overall incidence ~0.2% of patients exposed to heparin

Clinical diagnosis of HIT

- **High index of suspicion**
- Thrombocytopenia or significant drop in platelet count (>50%) with or without any of the following:
- Venous thrombosis
  - Warfarin induced limb necrosis, PE, DVT, cerebral venous thrombosis etc
- Arterial thrombosis
  - Lower limb thrombosis, CVA, myocardial infarction etc
- Skin lesions
  - At heparin injection site, skin necrosis, erythematous plaques
- Acute systemic reaction to heparin (25% of HIT patients)
  - Fever, chills, respiratory distress, hypertension, cardiorespiratory arrest

Clinical diagnosis II

- Isolated HIT – drop in platelets without thrombosis
- Retrospective studies
  - ~25% develop clinically overt thrombosis after stopping heparin, usually after 1 week
  - ~ 50% subclinical thrombosis on Doppler
- Early heparin cessation does not eliminate risk – alternate anticoagulation required
- Thrombocytopenia usually only develops after 5-10 days of Rx
- Median nadir ~55 x 10^9/L
- Bleeding and PLT count <10x 10^9/L – think of alternate cause (e.g. post transfusion purpura)
- Patients who have received heparin in past 100 days – may develop fall in PLT count within 1 day of heparin re-exposure

Laboratory diagnosis of HIT

- Commercially available PF4-dependent antigen immunoassays
  - Assays high sensitivity but poor specificity – not diagnostic if POS
- Functional assays of platelet activation and aggregation
  - Technically demanding and not readily available

⟶ In most settings, diagnosis is based on clinical picture alone

Furthermore:

- Clinically insignificant HIT abs common – patients with heparin exposure 5-100 days earlier
- In the ICU setting, HIT is uncommon (0.3 – 0.5%) whereas thrombocytopenia from other causes is very common (30 – 50%)
- **BUT – must be considered as thrombosis can be fatal**

Treatment of HIT

- Stop heparin immediately and do not reinstate
  - In patients who develop thrombocytopenia (or ↓ 50%)
  - HIT strongly associated with thrombosis (OR 12 – 40)
- Alternate anticoagulant must be commenced
- Alternative anticoagulants approved for Rx of HIT
  - Direct thrombin inhibitors (parenteral)– Argatroban and Bivalirudin
  - Heparanoid – Danaparoid (not in USA)
  - Fondaparinux - in pregnancy if Danaparoid not available
  - Direct oral anticoagulants have not been validated and approved
- Therapeutic doses of anticoagulation recommended even in absence of thrombosis
- Platelets transfusions –contraindicated

Direct Thrombin Inhibitors - Bivalirudin

- Trade name Angiomax
- Synthetic form of hirudin
- Given IV
- Dose adjusted to APTT – 1.5 – 2.5 x Normal
- Measure APTT 4 hours after Rx started or infusion rate altered, and then once daily
- Very short half-life – reversible
- Renal excretion
  - Dose must be reduced by 50 - 80% in mild renal impairment
  - Relatively contraindicated in severe failure

Direct Thrombin Inhibitors - Argatroban

- Alternative for HIT – rarely used
- Increases INR
  - Must consider this if patient is on warfarin co-therapy– may need higher therapeutic target
- Given IV
- APTT target – 1.5 – 3 x normal baseline
- Hepatobiliary excretion
  - Dose must be reduced in liver failure

Heparanoid - Danaparoid Sodium

- Trade name Orgaran
- There must be no evidence of cross-reactivity(?)
- Given IV
- Anti-FXa target range 0.5 – 0.8 anti-Xa u/ml
- Must monitor if renal impairment or >90kg
- 24 hour dose can be divided into 3 bolus doses

Fondaparinux

- Pentasaccharide
- Synthetic heparin derivative
- Does not generate anti-heparin antibodies and has been safely used
- BUT – not licensed for this use.
- Occasionally used off label in pregnancy as does not cross the placenta

General Comments - HIT

- 5-20% frequency of new thrombosis despite treatment of HIT patients with alternate anticoagulant
- ACCP guidelines – patients receiving heparin or did so within previous 2 weeks should be investigated for diagnosis of HIT if
  - PLT count falls >50%
  - And/or thrombotic event occurs

THE ROLE OF THE LABORATORY

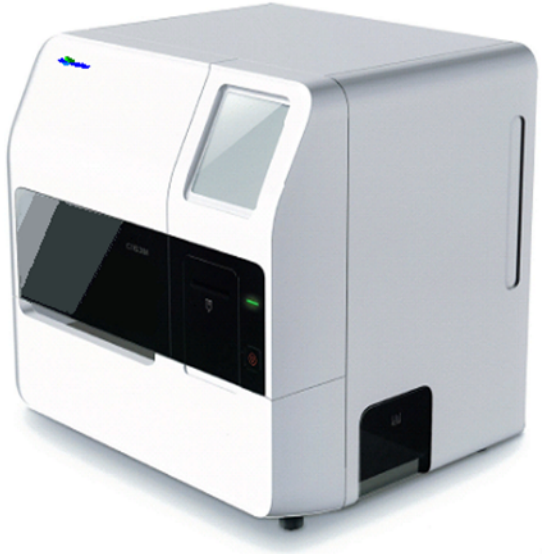
Patient monitoring

- Vigilance - Platelet counts
  - Trend analysis is critical
  - Must provide early alert to clinicians or any drop in PLT count
- Vigilance – RBC fragments
  - Alerts for unsuspected microangiopathies
- Speedy TATS – coagulation testing
  - Suspected DIC
  - Massive transfusion
  - Anticoagulation monitoring

Concluding Comments

- Thrombotic and bleeding problems are common in the ICU setting
- Patients are inherently unstable and can deteriorate rapidly
- High index of clinical suspicion is paramount
- Vigilant laboratory monitoring with proactive communication with clinical team could be life saving.

The CA Series



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Thank you very much for your attention!