Anticoagulant reversal

February 11, 2017 by Josh Farkas

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considerations when approaching anticoagulation reversal

How coagulopathic is the patient?
Critically ill patients often have several coagulopathies (e.g. thrombocytopenia plus supra-therapeutic INR on warfarin). Consider all medications and coagulation labs in order to get a global sense of how coagulopathic the patient is.

For patients with cirrhosis or disseminated intravascular coagulation (DIC), traditional coagulation parameters (e.g. INR) don't necessarily reflect the true coagulation state. In this situation, thromboelastography (TEG) may be more accurate.

**pharmacology specifics**

- Review all medications the patient is taking which may affect coagulation (including over-the-counter aspirin or aspirin-containing products).
- Determine what doses of medication the patient is on, and when is the last time a dose was taken.

**why was the patient initially anti-coagulated?**

- Most patients are anti-coagulated for atrial fibrillation or deep vein thrombosis. Short-term interruption is generally OK.
- Some patients are anti-coagulated for higher-risk conditions (e.g. a mechanical mitral valve, which has a high risk of thrombosis). This may shift the risk/benefit ratio.

**how important is it to reverse the anticoagulation?**

- Life-threatening bleeding requires aggressive normalization of coagulation parameters, but minor bleeding may respond to local measures.
- There is little evidence that moderately elevated INR correlates with post-procedural bleeding after many procedures (e.g. ultrasound-guided central line placement or thoracentesis). Anticoagulation reversal for minor procedures may be unnecessary.

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**warfarin: urgent reversal**

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**assessment & target**

- Assessed by measuring INR.
- Note that pre-procedure INR correlates poorly with bleeding risk. For most procedures (e.g. thoracentesis), an INR <2 is entirely adequate.

**intravenous vitamin K**

- Probably the most important intervention to reverse warfarin is vitamin K.
- 10 mg should be given intravenously, as soon as possible (infused over 30 minutes).
  - FFP or PCC will work only for ~8 hours.
  - Vitamin K will do the job after the FFP/PCC wears off. It takes Vitamin K 6-12 hours to start working, so it must be given up-front, simultaneously with FFP or PCC.
- Intravenous vitamin K may theoretically cause an anaphylactoid response if infused rapidly.
  - This is exceedingly rare (~1/30,000 patients)[22315259](https://www.ncbi.nlm.nih.gov/pubmed/22315259).
  - This is an anaphylactoid reaction (not anaphylactic), so it can be avoided by infusing the vitamin K slowly (e.g. over 30 minutes).
    - (An anaphylactoid reaction is due to a drug's directly stimulating mast cells to release histamine – unlike an anaphylactic reaction, which involves IgE antibodies. Anaphylactoid reactions can present similarly to anaphylactic reactions and may be treated similarly. However, anaphylactoid reactions are generally less severe and can be avoided by infusing a drug slowly.)
  - Fear of this reaction should never be a barrier to giving intravenous vitamin K to patients who need it.
    - If you're absolutely terrified about this reaction, then infuse the vitamin K incredibly slowly (e.g. over an hour). An anaphylactoid reaction is rate-related, so the likelihood of a severe adverse reaction at this slow of a rate is really zero.
- Other routes are inferior for emergent reversal:
  - Subcutaneous administration has erratic absorption.
  - IM administration may cause hematoma formation.
  - PO administration has slower absorption.

**four-factor prothrombin complex concentrates (PCC)**

- Advantages compared to fresh frozen plasma are listed below (the only disadvantage of PCC is the cost).

https://emcrit.org/ibcc/anticoagulant-reversal/
• Lower volume, which reduces risk of volume overload.
• Faster reversal (low volume of PCC allows for complete reversal in <30 minutes).
• More consistent reversal than fresh frozen plasma.
• No need to be thawed and cross-matched prior to administration.
• No risk of transfusion related acute lung injury (TRALI).

• Traditional dosing:
  • INR 2-4: 25 units/kg (max 2500 units)
  • INR 4-6: 35 units/kg (max 3500 units)
  • INR >6: 50 units/kg (max 5000 units)

• Emerging evidence that fixed-dosing is effective and less expensive. The following fixed-dose protocol is based on one by Scott Dietrich at the University of Colorado (https://empharmd.com/2017/10/26/ftfy-prothrombin-complex-concentrate-that-is/).
  • Initial dose:
    • If patient wt >95 kg or INR >7.5, give 2000 units.
    • Otherwise, give 1500 units (may be given immediately, even prior to INR results, in some emergencies).
  • Repeat INR 10-60 minutes after giving prothrombin complex concentrates. If repeat INR is >2, consider an additional 500-1000 units.

**fresh frozen plasma (FFP)**

• Alternative to PCC, which may be used for less acute bleeding.
• Dose depends on INR elevation:
  • A reasonable initial dose may be ~10-15 cc/kg, followed by repeat INR.
  • One unit of FFP is 250 ml, so 10-15 cc/kg equates to roughly 3-4 units of FFP.
• FFP contains clotting factors at their *normal concentration* in the plasma (it doesn’t contain *concentrated* levels of clotting factors). This makes it impossible to achieve an INR below ~1.7. Given the risks of FFP, it’s impossible to achieve an INR below ~1.7. Given the risks of FFP, it’s non-beneficial to give FFP to a patient whose INR is 1.7 or lower (16753596).

**warfarin: non-urgent supratherapeutic INR**

Patients with supratherapeutic INR without bleeding are commonly encountered. Below is a general rubric which may help guide management. However, this isn’t based on strong evidence. Most importantly, management should be individualized based on patient-specific factors (e.g. risk factors for bleeding/clotting etc.).

<table>
<thead>
<tr>
<th>INR management in the absence of bleeding or planned procedure</th>
</tr>
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<tbody>
<tr>
<td><strong>INR</strong></td>
</tr>
<tr>
<td>INR 3-5</td>
</tr>
<tr>
<td>INR 5-7.5</td>
</tr>
<tr>
<td>INR 7.5-10</td>
</tr>
<tr>
<td>INR &gt;10</td>
</tr>
</tbody>
</table>

*IV route may be substituted if patient is NPO. Never give vitamin K intramuscularly or subcutaneously!

**Direct thrombin inhibitor: Dabigatran**

**lab assessment of drug levels**

• **Crude assay = PTT**

https://emcrit.org/ibcc/anticoagulant-reversal/
Anticoagulant reversal - EMCrit Project

- Normal PTT argues against clinically significant dabigatran effect, but doesn't exclude this possibility.
- Better assay = Thrombin Time (TT)
  - Better correlation with dabigatran levels, but may be unmeasurably elevated at therapeutic dabigatran concentrations.
  - Normal thrombin time excludes clinically significant dabigatran effect (31339254).
  - Availability may vary, and often cannot be run STAT.

### Pharmacology

#### Pharmacology of Direct Thrombin Inhibitors & Xa-inhibitors

<table>
<thead>
<tr>
<th>Bivalirudin</th>
<th>Argatroban</th>
<th>dabigatran (Pradaxa®)</th>
<th>Fondaparinux</th>
<th>riveroXaBAN (Xareltro®)</th>
<th>apiXaBAN (Eliquis®)</th>
<th>edoXaBAN (Savaysa®)</th>
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<tr>
<td>Mechanism</td>
<td>Direct thrombin inhibitor</td>
<td>Direct thrombin inhibitor</td>
<td>Direct Thrombin Inhibitor</td>
<td>Xa inhibitor</td>
<td>Xa inhibitor</td>
<td>Xa inhibitor</td>
</tr>
<tr>
<td>Route</td>
<td>IV infusion</td>
<td>IV infusion</td>
<td>oral</td>
<td>subcutaneous</td>
<td>oral</td>
<td>oral</td>
</tr>
<tr>
<td>Half-life</td>
<td>25 minutes</td>
<td>40 minutes</td>
<td>12-17 hours (Doubles if QFR &lt;30 m/min)</td>
<td>17-21 hours</td>
<td>6-9 hours (11-13 in elderly)</td>
<td>9-14 hours</td>
</tr>
<tr>
<td>Renal</td>
<td>20%</td>
<td>20%</td>
<td>80%</td>
<td>80%</td>
<td>66%</td>
<td>25%</td>
</tr>
<tr>
<td>elimination (%)</td>
<td>~25%</td>
<td>~ 20%</td>
<td>~ 65%</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Crude lab</td>
<td>PTT</td>
<td>PTT</td>
<td>PTT</td>
<td>INR</td>
<td>INR</td>
<td>INR</td>
</tr>
<tr>
<td>measurement</td>
<td>PTT</td>
<td>PTT</td>
<td>Thrombin time</td>
<td>Anti-Xa level*</td>
<td>Anti-Xa level*</td>
<td>Anti-Xa level*</td>
</tr>
<tr>
<td>Antidote</td>
<td>PCC can be attempted (but dubious efficacy)</td>
<td>Idarucizumab</td>
<td>Four-factor PCC (possibly Adrenanist Alfa if available for oral agents)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Any anti-Xa level can be used (e.g. those designed to measure the level of unfractionated heparin or low molecular weight heparin). The most readily available assay will often be an anti-Xa level designed to measure unfractionated heparin (which may be available STAT in hospitals using this assay to titrate heparin infusions). *(The Internist Book of Critical Care, by Dhami et al.)*

### tx: idarucizumab (PRAXBIND)

- Monoclonal antibody binds and inactivates dabigatran.
- **Possible indications for reversal** (in addition to the presence of major bleeding or planned procedure)
  - (a) Last dose taken within <12 hours (with normal renal function)
  - (b) Significantly abnormal PTT and/or thrombin time (especially thrombin time >25 seconds)
- **Dose**
  - A total of 5 grams is usually sufficient. This is typically provided as two separate 2.5-mg doses
  - However, for patients with an unusually high level dabigatran (e.g. new-onset renal failure with drug accumulation), there is a possibility that additional doses might be needed.
- **Monitoring**
  - Follow PTT (or thrombin time if available) and clinical signs of bleeding. Risks and benefits of repeat dosing remains unknown.
  - Side-effects may include hypokalemia, delirium, pyrexia, and bankruptcy.
  - Little high-quality evidence is available regarding this drug.

### tx: hemodialysis

- Due to its low percent protein binding, dabigatran can be removed by dialysis (whereas other DOACs cannot be).
- Dialysis may be considered if idarucizumab is unavailable.

#### factor Xa inhibitors (riveroXaBAN, apiXaBAN, edoXaBAN, fondaparinux)

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### lab assessment of drug levels

- **Crude assay = INR**
  - Rough assay
  - Normal INR argues against a significant drug level, but doesn't exclude this entirely (31317796).
- **Better assay = Anti-Factor Xa level**
  - Anti-Xa activity correlates well with drug level, but not necessarily with anticoagulant effect (31339254).

https://emcrit.org/ibcc/anticoagulant-reversal/
Anticoagulant reversal - EMCrit Project

- Normal anti-Xa level excludes the presence of clinically relevant Xa-inhibitors (but not dabigatran). Any anti-Xa assay may be used (e.g. assays designed for use with unfractionated heparin or low molecular-weight heparin) — the key issue is whether there is any detectible anti-Xa activity (https://www.ncbi.nlm.nih.gov/pubmed/30916798).
- Availability and turn-around time may vary, limiting its use in emergency settings.

pharmacology

<table>
<thead>
<tr>
<th>Pharmacology of Direct Thrombin Inhibitors &amp; Xa-Inhibitors</th>
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<td><strong>Pharmacology:</strong></td>
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<td><strong>Crude lab measurement</strong></td>
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<tr>
<td><strong>Preferred lab measurement</strong></td>
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<tr>
<td><strong>Antidote</strong></td>
</tr>
</tbody>
</table>

*Any anti-Xa level can be used (e.g. those designed to measure the level of unfractionated heparin or low molecular-weight heparin). The most readily available assay will often be an anti-Xa level designed to measure unfractionated heparin (which may be available STAT in hospitals using this assay to titrate heparin infusions). The interval of clinical care, by @DanielCMT

**tx: four-factor PCC**

- Overall
  - Generally recommended as mainstay of reversal (with in vitro evidence and some clinical data).
  - Generally works for ~6-8 hours. Depending on the pharmacology of the anti-Xa agent, the DOAC may out-last this, causing rebound bleeding.
  - Contraindicated in patients with a history of heparin-induced thrombocytopenia (contains small amounts of heparin).

- Various dosing schemes
  - (1) Maryland Shock-Trauma algorithm recommends 50 units/kg or max 5,000 units (27894493)
  - (2) Alternative approach is to give 25 units/kg, and then follow clinically and repeat INR. This dose may be repeated if hemostasis is not achieved.
  - (3) Fixed dosing with 2000 units may be used. This strategy has the advantage that it is simple and also has the best evidentiary support (30916798).

- Monitoring
  - Follow INR after giving PCC and then subsequently q6hr. Rebounding INR might be an indication of waning effectiveness of PCC (but this remains unclear).

**tx: Adnexanet Alfa ??**

- Specifically designed as a reversal agent for Xa-inhibitors.
- Clinical data is limited, and this agent is insanely expensive.
- Many hospitals have chosen not to include this agent in their formularies.

**thrombolitics (e.g. tPA)**

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**pharmacology of alteplase**

- Alteplase has a very short half-life, so it is gone from the blood within minutes.
- Even after alteplase has left the bloodstream, levels of many clotting factors (especially fibrinogen) are profoundly reduced. Therefore, the effects of alteplase last much longer than the tPA molecules themselves.

**reversal of tPA?**

https://emcrit.org/ibcc/anticoagulant-reversal/
Initial cocktail:
- 10 units of cryoglobulin
- 2 units of fresh frozen plasma
- Tranexamic acid: 1 gram IV bolus, then 1 gram infused over the next 8 hours
- In dire emergency, also may add 6 units of platelets

Repeat coagulation studies and provide additional products as needed to address deficiencies. It might be reasonable to target a slightly higher fibrinogen level than usual (e.g. fibrinogen > 200 mg/dL).

protamine for reversal of heparin & LMWH

**general approach**

- Protamine may cause anaphylaxis or pulmonary hypertension.
- In *most* cases of bleeding due to a heparin infusion, discontinuing the infusion alone is adequate.
- Protamine may be considered for severe bleeding (e.g. heparin-associated intracranial hemorrhage).

**dose** ([Medscape](http://reference.medscape.com/drug/protamine-343746#01))

- General rules
  - Usually *avoid giving more than 50 mg at once*.
  - Give *slowly* over 15 minutes (rapid administration may cause hypotension, bradycardia, and anaphylactoid reaction).
- Reversal of heparin given via bolus:
  - Heparin given within <30 minutes: 1 mg protamine per 100 units heparin
  - Heparin given 30-60 minutes ago: 0.5-0.75 mg protamine per 100 units heparin
  - Heparin given 60-120 minutes ago: 0.375-0.5 mg protamine per 100 units heparin
  - Heparin given 2-6 hours ago: 0.25-0.375 mg protamine per 100 units heparin
- Reversal of heparin infusion:
  - Determine amount of heparin infused over the last two hours (usually the infusion rate multiplied by two).
  - Give 1 mg protamine per 100 units of heparin which the patient has received over the last two hours.
- Dose required to reverse enoxaparin
  - Enoxaparin within <8 hours: 1 mg protamine per 1 mg enoxaparin. If bleeding continues, may give additional 0.5 mg protamine per mg enoxaparin.
  - Enoxaparin given 8-12 hours previously: 0.5 mg protamine per 1 mg enoxaparin.
  - Enoxaparin given >12 hours previously: Protamine less likely to be beneficial.
- Dose required to reverse dalteparin or tinzaparin
  - Dalteparin or tinzaparin given within <4 hours: 1 mg protamine per 100 units of dalteparin or tinzaparin. May repeat half this dose four hours later.
  - Given 4-8 hours previously: 0.5 mg protamine per 100 units dalteparin or tinzaparin.
- Monitoring
  - Protamine lasts for ~2 hours, so multiple doses may be required (especially for low molecular-weight heparin).
  - Reversal of unfractionated heparin: monitor PTT 10 min after protamine is given, then again in 2-8 hours.
  - Reversal of enoxaparin:
    - Follow Xa level after giving protamine and then q2hr. May consider re-dosing at 0.5 mg protamine per mg enoxaparin if bleeding persists (max 25 mg).
    - Note that protamine will reverse enoxaparin only by ~50%.

anti-platelet agent reversal
**Anticoagulant reversal - EMCrit Project**

**Pharmacology of antiplatelet agents**

<table>
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<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Time to antiplatelet effect</th>
<th>Serum half-life</th>
<th>Irreversible inhibition of platelet?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>COX 1-inhibitor</td>
<td>&lt;60 minutes</td>
<td>0.5-3 hours</td>
<td>Reversible inhibition</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>COX 1-inhibition</td>
<td>Varies with specific agent</td>
<td>Reversible inhibition.</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>P2Y12 inhibitor</td>
<td>&lt;2 hours</td>
<td>6-8 hours</td>
<td>Irreversible inhibition</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>P2Y12 inhibitor</td>
<td>&lt;30 minutes</td>
<td>4-7 hours</td>
<td>Irreversible inhibition</td>
</tr>
<tr>
<td>Ticagrelot</td>
<td>P2Y12 inhibitor</td>
<td>&lt;30 minutes</td>
<td>7-9 hours</td>
<td>Reversible inhibition</td>
</tr>
<tr>
<td>Cangrelot</td>
<td>P2Y12 inhibitor</td>
<td>&lt;5 minutes</td>
<td>3-6 minutes</td>
<td>Reversible inhibition</td>
</tr>
<tr>
<td>Vorapaxar</td>
<td>PAR-1 antagonist</td>
<td>Several days</td>
<td>8 days</td>
<td>Reversible inhibition</td>
</tr>
<tr>
<td>Abciximab</td>
<td>GP IIb/IIIa inhibitor</td>
<td>&lt;10 minutes</td>
<td>10-30 minutes</td>
<td>Irreversible inhibition</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>GP IIb/IIIa inhibitor</td>
<td>&lt;5 minutes</td>
<td>2.5 hours</td>
<td>Reversible inhibition</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>GP IIb/IIIa inhibitor</td>
<td>&lt;5 minutes</td>
<td>2 hours</td>
<td>Reversible inhibition</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>PDE inhibitor</td>
<td>&lt;60 minutes</td>
<td>12 hours</td>
<td>Reversible inhibition</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>PDE inhibitor</td>
<td>&lt;6 hours</td>
<td>12 hours</td>
<td>Reversible inhibition</td>
</tr>
</tbody>
</table>

**Assessment of anti-platelet medication effects**

- This is impossible to do with most assays. Specifically, platelet agents will not affect conventional coagulation tests or standard thromboelastography (TEG).
- Numerous assays exist to evaluate platelet function, but most have poor availability or prolonged turn-around time. The most useful assays for emergent use might be the following:
  - (1) Platelet Functional Assay (PFA) – more widely available, useful to evaluate aspirin effect.
  - (2) Thromboelastography with platelet mapping – may be superior for P2Y12 inhibitors.
- In practice, decisions about reversal agents often need to be made in the absence of any laboratory data regarding platelet function. Thus, the best approach to assessment may be a clinical history of whether the patient is adherent with anti-platelet agents and when the last dose was taken.

**Overview of approaching anti-platelet agents**

- There is no specific "reversal" agent which truly counteracts these medications.
- Medications seem to be the safest, fastest, and most effective strategy:
  - (1) Desmopressin (DDAVP) is arguably the front-line agent to improve platelet function. This is widely recommended in guidelines regarding anti-platelet reversal.
  - (2) Tranexamic acid may improve platelet function as well. Evidence is of fair quality, albeit not robust. However, tranexamic acid is inexpensive, generally safe, and widely available.
- Fibrinogen or cryoprecipitate – Targeting a slightly higher level than usual might be helpful, but evidence on this is scant.
- Platelet transfusion – Although often recommended, evidence doesn't really support this. Given the numerous risks involved, this may be harmful in many situations.

**1) Desmopressin (DDAVP) improves platelet function**

- **General**
  - DDAVP improves platelet function in various ways (perhaps most notably by increasing the release of von Willebrand Factor and factor VIII from endothelium). von Willebrand factor binds the GPIIb-IIIa receptor on platelets, causing platelet aggregation.
  - DDAVP appears to function as a nonspecific booster of platelet function, which may be used in a variety of situations. Traditionally, desmopressin has been used to counteract uremic platelet dysfunction (25933676). Evidence also shows benefit in platelet function among patients on anti-platelet medications, including P2Y12-inhibitors (18068065, 1434725, 8330156).
- **Dose** (Medscape monograph on desmopressin here)
  - 0.3 micrograms/kg IV infused over 20-30 minutes.

https://emcrit.org/ibcc/anticoagulant-reversal/
May be repeated q12hr for up to 6 doses, but complications may increase in likelihood over time (especially hyponatremia). In practice, DDAVP is usually given only as a one-time dose.

**Side effects**

- (1) Blocks renal excretion of free water, which may lead to hyponatremia. This can be avoided by limiting administration of water while giving desmopressin.
- (2) Hypotension does seem to occur – this has been demonstrated in a meta-analysis (27893176 (https://www.ncbi.nlm.nih.gov/pubmed/27893176)). In a critical care setting this is manageable; the main problem may be incorrectly attributing the hypotension to hemorrhage (e.g. using it as a trigger to initiate massive transfusion). Hypotension might be prevented or mitigated by slower administration.
- (3) Thrombosis is a theoretical risk. However, the most recent meta-analysis detected no increase in thrombotic events (27893176 (https://www.ncbi.nlm.nih.gov/pubmed/27893176)).

**(2) tranexamic acid (TXA)**?

- Tranexamic acid inhibits the conversion of plasminogen into plasmin. Tranexamic acid is generally conceptualized as an inhibitor of fibrinolysis, but it’s actually a lot more than that. For example, plasmin is involved in bradykinin generation, so tranexamic acid may have a role in the treatment of bradykinin-mediated angioedema (https://emcrit.org/pulmcrit/bradykinin-spiral/). Plasmin also degrades the glycoprotein Ib receptors on the surface of platelets, impairing their ability to interact with von Willebrand Factor (30474416 (https://www.ncbi.nlm.nih.gov/pubmed/30474416)). By preventing this interaction, tranexamic acid could potentially improve platelet function.
- Several studies suggest that tranexamic acid could improve platelet function, particularly in the context of anti-platelet agents:
  - Two studies involving CABG patients found that tranexamic acid improved in vitro platelet function among patients who had received anti-platelet therapy (20962655 (https://www.ncbi.nlm.nih.gov/pubmed/20962655), 27388281 (https://www.ncbi.nlm.nih.gov/pubmed/27388281)).
- Tranexamic acid isn’t widely recommended to reverse anti-platelet medications. However, it is widely available, relatively inexpensive, safe, and overall has a favorable track record for use in a variety of types of bleeding. The risk/benefit ratio is probably more favorable for tranexamic acid than for platelet transfusion (more discussion on both of these therapies below).

**(3) target a slightly higher fibrinogen level ??**

- Platelets cooperate together with fibrinogen to form a clot. Thus, to a certain extent, increased activity of either platelets or fibrinogen may compensate for a deficiency of the other.
- Evidence regarding the use of fibrinogen to reverse anti-platelet agents is nearly nonexistent. However, one study which investigated this confirmed that increasing the fibrinogen level may increase clot firmness in blood treated with anti-platelet agents, as measured by thromboelastography (28159767 (https://www.ncbi.nlm.nih.gov/pubmed/28159767)).
- The optimal fibrinogen target in a bleeding patient is controversial (different guidelines recommend values ranging between ~150-200 mg/dL). For a patient on anti-platelet agents who is hemorrhaging, it might be sensible to target a *slightly* higher fibrinogen target than usual (if you’re on the fence about whether to give fibrinogen).

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**platelet transfusion & why it’s generally not a wise idea**

**When might we expect exogenous platelets to help reverse anti-platelet agents?**

- From a pharmacological standpoint, platelet transfusion would make the most sense if the following conditions were met:
  - (#1) The anti-platelet drug should cause *permanent* inhibition of platelet function (drugs which do this include aspirin, clopidogrel, and prasugrel).
  - (#2) The anti-platelet drug itself should *already* be cleared from the body (otherwise, residual drug may cause inhibition of the new platelets).
  - (#3) *Immediate* hemostasis is essential (e.g. for an intracranial hemorrhage).
- Based on these principles, we can *theoretically* stratify the predicted effectiveness of platelet transfusion for common anti-platelet agents as follows:
  - #1 = Most effective for aspirin. This drug causes permanent inhibition of platelet function and has a short half-life.
• #2 = Intermediate effect for clopidogrel. This drug causes permanent inhibition of platelet function, but it has a moderate half-life of 6 hours. Thus, if the patient took a dose of clopidogrel within the past 6-12 hours, residual drug could interfere with transfused platelets.

• #3 = Minimal effect for ticagrelor. Ticagrelor is a reversible platelet inhibitor, so platelet inhibition is a reflection of the real-time serum drug levels of ticagrelor. Transfused platelets will be inhibited by ticagrelor along with native platelets – adding little benefit (30395148).

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**clinical evidence: PATCH trial**

- This is a multi-center RCT regarding the use of platelet transfusion in patients with spontaneous intracranial hemorrhage who were taking anti-platelet agents. ~90% of the patients were taking aspirin, with relatively few patients using P2Y12-inhibitors. In short, this is precisely the situation where we would expect platelet transfusion to be beneficial.

- The study found no benefit from platelet transfusion – in fact, patients receiving platelets had worse neurologic outcomes and a trend towards more bleeding.

- This is an enormously important trial, which reminds us that we cannot assume that platelet transfusion will reverse anti-platelet drugs.
  - More platelets doesn’t equate with a better outcome.
  - Patients undergoing neurosurgery were excluded from the trial, so this is one potential limitation.

**understanding the PATCH trial: why doesn’t platelet transfusion improve clinical outcomes in patients prescribed anti-platelet drugs**

- The PATCH trial was a bit surprising, but in retrospect perhaps it shouldn't have been. There are numerous signals in the literature that platelet transfusion isn’t great for reversal of anti-platelet drugs. The following are some reasons that platelet transfusion may fail to work clinically.

- (1) Many patients who are prescribed anti-platelet agents don't experience clinical platelet inhibition:
  - (a) Some patients are non-adherent and simply aren't taking the medications.
  - (b) Some patients may have altered drug metabolism, causing the anti-platelet agent to be ineffective (particularly in the case of clopidogrel).

- (2) Among patients whose platelets are truly inhibited, platelet transfusion often doesn’t cause a substantial improvement in platelet function! This result has been found by several studies (30814031, 27653814, 26553698, 24256671). This might be explained as follows:
  - (a) Especially with newer anti-platelet drugs, longer half-life may lead to the persistence of drug in the body. Residual anti-platelet medication may cause dysfunction of transfused platelets.
  - (b) Transfused platelets may not be as effective as normal platelets, due to changes which occur during storage.
  - (c) It’s conceivable that even if functional platelets are transfused into the patient, the dysfunctional platelets still get in the way and impair coagulation.

- (3) Platelet function is only one of many determinants of clinical outcome. Other factors may be more important (e.g. fibrinogen levels, blood pressure, features of the anatomic lesion which is bleeding).

- (4) Platelet transfusion has several risks (e.g. transfusion reaction, TRALI, cytokine release, infection, suppression of native platelet synthesis). These may serve to counterbalance any potential benefit.

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**possible prerequisites for platelet transfusion**
• The final word remains to be written regarding the use of platelet transfusion to reverse anti-platelet medications. Routine use of platelet transfusion certainly seems misguided. However, there may be situations where platelet transfusion is reasonable (e.g. a surgeon or interventional consultant strongly feels that platelets are needed).
• Four prerequisites are suggested which could define patients who might potentially benefit from a platelet transfusion:
  1. Patient is taking an anti-platelet agent which causes permanent platelet inhibition (e.g., aspirin, clopidogrel, or prasugrel).
  2. The last dose of medication should ideally be >3 half-lives previously. Otherwise, residual drug may inhibit transfused platelets (this is discussed further above).
  3. There is some laboratory evidence that the patient's platelets are inhibited (if platelet function labs are available and time permits this evaluation).
  4. There is significant ongoing hemostatic stress (e.g. active bleeding or planned procedures).

(tranexamic acid)

Emerging evidence suggests that tranexamic acid may be useful for bleeding from a variety of causes (e.g. trauma, post-partum hemorrhage, orthopedic surgery) (28432428). Numerous large RCTs and meta-analyses show it to be safe and potentially beneficial. Below is a general discussion of tranexamic acid, which will not apply perfectly to every application.

**Potential indications for IV tranexamic acid**

- Trauma (CRASH-2)
- Post-partum hemorrhage (WOMAN)
- Perioperative bleeding (especially cardiothoracic and orthopedic surgery)
- Gastrointestinal bleeding (limited evidence; HALT-IT trial ongoing)
- Intracranial hemorrhage (lower incidence of hematoma extension; 30741383, 29778325)
- Laboratory evidence of hyper-fibrinolysis; Bleeding after receiving fibrinolytic therapy (e.g. alteplase)
- Massive transfusion protocol
- Patients on anti-platelet agents (discussed above)

**Pharmacology**

- Excreted unchanged in the urine.
- Half-life of ~3 hours.
- IV tranexamic acid must be infused slowly over 10-20 minutes (to avoid hypotension).

**Cautions & relative contraindications**

- Seizure history (may reduce seizure threshold)
- Disseminated intravascular coagulation
- Patient at high risk of venous thromboembolic disease
- End-stage renal disease

**Dosing**

- Generally:
  1. Loading dose = 1 gram as a slow IV push over 10 minutes
  2. Maintenance dose(s) = 1 gram IV as a gradual infusion over 8 hours. This should be started immediately following the loading dose. This maintenance dose is often repeated three times to create a continuous infusion over 24 hours.
- In renal failure: Increase time interval between dosing (95% excreted in urine).

(pre-procedure coagulation management for common critical care procedures)

(basics)
Most bedside ICU procedures carry a relatively low risk of bleeding and don't require aggressive coagulation reversal (an exception being lumbar puncture). Prophylactic coagulation optimization is generally driven by fear rather than evidence.

- Please note the above discussion about the futility of giving FFP to patients with an INR of 1.7 or lower.
- Thromboelastography has a demonstrated ability to guide hemostatic replacement in the operating room. When in doubt about whether factor replacement is needed, ordering a thromboelastograph may provide a "second opinion."

**central line placement**

- The procedure should be done by an expert operator using ultrasound guidance.
- Do not attempt the procedure if there isn't a favorable ultrasound view (e.g. clear visualization of the vein and separation between vein and artery).
- Coagulation optimization doesn't help reduce risk. The key is avoiding an arterial puncture.

**pleural procedures**

- Available data suggests that thoracentesis is safe unless the platelet count is <20,000 or INR is above 2 (23493971). 
- The key is avoiding laceration of the intercostal artery. This may be achieved by the following:
  - Avoiding thoracentesis near the spine.
  - Staying close to the upper edge of the rib.
  - When possible, ultrasound may be used to visualize the intercostal artery. This allows for pre-procedure identification of aberrant vessels and avoidance of them.
  - As the syringe is advanced, there should be continuous negative suction. If arterial blood appears in the syringe, pull out! Do not advance into the pleura (this may create an arterial-pleural fistula).

**paracentesis**

- The performance of paracentesis on patients with elevated INR and thrombocytopenia is well accepted.
- Avoidance of bleeding should be achieved as follows:
  - Use a very small-bore needle (e.g. 24-gauge lumbar puncture needle, with the stylet removed of course).
  - Before performing the procedure, use ultrasound with doppler to make sure that there are no arteries in the vicinity. The inferior epigastric arteries should ideally be identified and avoided, as any trauma to these arteries may cause massive peritoneal hemorrhage.

**summary**

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Rapid guide to anticoagulant reversal in hemorrhage

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<tr>
<th>Medication</th>
<th>Investigation</th>
<th>Reversal</th>
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<tbody>
<tr>
<td>Warfarin</td>
<td>INR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg IV vitamin K over 30 minutes <em>plus</em> either PCC or fresh frozen plasma</td>
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</tr>
<tr>
<td></td>
<td>INR 2-4: 25 units/kg (max 2500 units)</td>
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<td>INR 4-6: 35 units/kg (max 3500 units)</td>
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<tr>
<td></td>
<td>INR &gt;6: 50 units/kg (max 5000 units)</td>
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<td></td>
<td>Alternative: 5 units fresh frozen plasma</td>
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<td></td>
<td>- if ingested in &lt;2 hours may consider activated charcoal 50g</td>
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<thead>
<tr>
<th>Dabigatran</th>
<th>PTT (ideal = thrombin time)</th>
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<tbody>
<tr>
<td></td>
<td>5 mg</td>
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<thead>
<tr>
<th>Rivaroxaban</th>
<th>INR (ideal = anti-Xa level, using any assay)</th>
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<tbody>
<tr>
<td></td>
<td>Fixed dose of 2000 units often recommended</td>
</tr>
<tr>
<td></td>
<td>50 units/kg (max 5000 units)</td>
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<tr>
<td></td>
<td>If ingested in &lt;2 hours may consider activated charcoal 50g</td>
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<tr>
<td></td>
<td>Consider 10 mg IV vitamin K to exclude vitamin K deficiency (if INR elevated)</td>
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<thead>
<tr>
<th>Edoxaban</th>
<th>INR, PTT, fibrinogen</th>
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<tbody>
<tr>
<td></td>
<td>Fixed dose of 2000 units</td>
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<td></td>
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<td>Consider 10 mg IV vitamin K to exclude vitamin K deficiency (if INR elevated)</td>
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<thead>
<tr>
<th>Thrombolysis (Ipa)</th>
<th>INR, PTT, fibrinogen</th>
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<tbody>
<tr>
<td></td>
<td>Cocktails vary, reasonable starting place might be:</td>
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<tr>
<td></td>
<td>- Aggressive fibrinogen replacement (e.g. 10 U cryoprecipitate)</td>
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<tr>
<td></td>
<td>- 2 Units fresh frozen plasma</td>
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<td></td>
<td>- Tranexamic acid (1 gram bolus, then 1 gram over 8 hr)</td>
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<table>
<thead>
<tr>
<th>Heparin</th>
<th>PTT (ideal = anti-Xa level)</th>
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<tr>
<td></td>
<td>Protamine (complex dosing, see above)</td>
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<tr>
<th>Anti-platelet agents</th>
<th>Platelet function assays (if available)</th>
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<tbody>
<tr>
<td></td>
<td>Desmopressin (DDAVP) 0.3 ug/kg infuse over 20-30 minutes</td>
</tr>
<tr>
<td></td>
<td>May consider addition of tranexamic acid?</td>
</tr>
<tr>
<td></td>
<td>Evidence generally doesn’t support platelet transfusion</td>
</tr>
</tbody>
</table>

- The Internet Book of Critical Care, by @PulmCrit

https://emcrit.org/ibcc/anticoagulant-reversal/
A common error is trying to reverse warfarin with PCC or FFP alone. If either of these is given without simultaneous vitamin K, it will wear off over several hours.

For serious bleeding, vitamin K should be given intravenously (NOT im, sq, or orally).

Vitamin K should never be given subcutaneously (erratic absorption) or intramuscularly (risk of hematoma).

Beware of patients on NOACs who develop renal failure, but keep on taking their NOACs. They may accumulate drug and become severely supratherapeutic, without any screamingly abnormal lab values (unlike, for example, the patient on warfarin with an INR of 9 – who is quite obviously supratherapeutic).

Aggressive reversal of anticoagulation prior to minor procedures (e.g. ultrasound-guided central line placement in a patient with a gigantic, superficial internal jugular vein).

Don't try to correct the pre-procedure INR to <1.7 using FFP – this is impossible and dangerous.

**Going further:**

- Adnexanet Alfa:
  - I have issues with Adnexanet (https://emcrit.org/emcrit/issues-andexanet/) (Kristina Kipp on EMCrit RACC)
  - RebelEM by Salim Rezaie on Annexa 4 (https://rebelem.com/annexa-4-andexanet-alfa-and-factor-xa-inhibitors/)
  - First10EM on Annexa 4 (More Garbage Science in the NEJM) (https://first10em.com/andexanet-alfa/)
  - SGEM on Annexa 4 (http://thesgem.com/2019/04/sgem251-nothing-compares-to-you-because-there-was-no-comparison-group/)
  - EM Lit of Note on Annexa 4 (http://www.emlitofnote.com/?p=4384)
  - St. Emlyn's: JC: Reversal of DOACs with Andexanet Alfa, St Emlyn's (https://www.stemlynsblog.org/jc-reversal-of-noacs-andexanet/)