SEPSIS AND ACTIVATED PROTEIN C

HOW DOES IT WORK?

- Anti-coagulant: Inactivates factors Va and VIIIa, thus blocking thrombin generation.
- Anti-inflammatory: Indirectly decreased levels of thrombin decreases neutrophil recruitment and mast cell degranulation. Directly (in vitro), inhibits neutrophil activation, cytokine production and E-selectin-mediated adhesion of cells to vascular endothelium.
- Pro-fibrinolysis: Inhibits PAI-1 thus promoting fibrinolysis.

WHO SHOULD GET IT?

- Bernard et al. reported in NEJM (3/2002) the results of a large, multi-center, DBRCT of 1690 patients randomized to receive drotrecogin alfa (APC) infusion vs. placebo for 96 hours.
  - Inclusion criteria: sepsis due to known or suspected infection +
    ¾ SIRS criteria T>38 or <36, HR>90, RR>20 or PaCO2 <32,
    WBC>12,000 or < 4,000 or >10% bands +
    1/5 end organ dysfunction SBP <90 or MAP <70 for one hour despite adequate fluid resuscitation, UOP< 0.5 ml/kg for 1 hour, PaO2/FIO2 < 200, platelets < 80,000, metabolic acidosis pH< 7.30.
  - Exclusion criteria: age < 18 or weight >135 kg, pregnancy
  - Platelets < 30,000
  - Conditions with increased risk of bleeding (recent/impending surgery within 12 hours, recent head trauma/stoke/surgery within 3 months, any hx of CNS mass/lesion/aneurysm, recent GI bleed within 6 weeks, congenital bleeding diathesis).
  - Known hypercoaguable states, acute pancreatitis
  - Comorbid medical conditions (cirrhosis with portal hypertension, HIV with CD4 < 50, s/p transplant, ESRD on HD/PD,
  - Recent medication use of the following: heparin < 8 hours, warfarin < 7 days, thrombolytics < 3 days, G2B3a antagonist < 7 days.
• SFGH Policy
  • Inclusion criteria: as above
  • Revised exclusion criteria: APACHE II score < 25, INR > 3.0, active bleeding from
    any site, epidural catheter or spinal puncture within 12 hours; NOT NECESSARILY
    ESRD, AIDS, s/p Tx.
  • Approval by critical care attending and fellow

WHY DO IT?
  • There is a clear mortality benefits in-patients with severe sepsis which when untreated carries a
    50% mortality. RRR 19%, ARR 6%, NNT 14.

WHY NOT?
  • Increased serious bleeding complications in APC group defined as any intracranial hemorrhage,
    any life threatening bleed or any bleed that required 3 or more PRBC transfusion on 2
    consecutive days.
    • 30 vs. 17 (3.5% vs. 2.0)