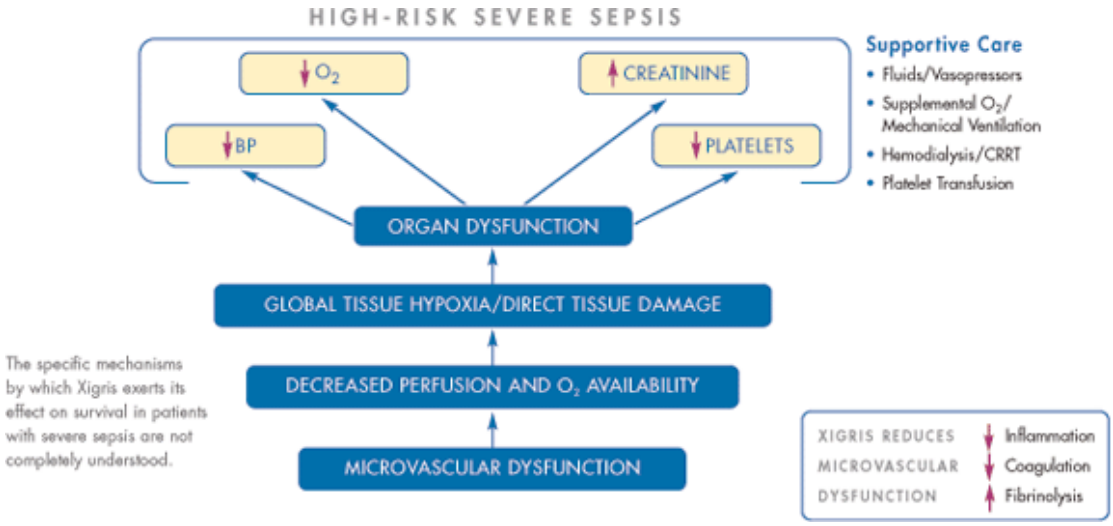
XIGRIS

Drug Action:

Xigris reduces microvascular dysfunction by reducing inflammation and coagulation and increasing fibrinolysis. Activated protein C – an endogenous protein, promotes fibrinolysis and inhibits thrombosis and inflammation. During sepsis inflammatory and procoagulant host responses are stimulated- inflammatory cytokines- TNF and interleukins activate coagulation and inhibit fibrinolysis whilst thrombin stimulates may pathways. Thrombin coupled with thrombomodulin converts protein c to activated protein C: during sepsis thrombomodulin is down regulated by inflammatory cytokines- Reduced levels of protein C are found in majority of patients with sepsis and are associated with an increased risk of death.
Activated protein C inactivates factors Va and VIIa, limiting thrombin production, inhibits production of TNF-alpha, IL-1 and IL-6- limiting monocyte and neutrophil binding to endothelial cells.



PROWESS STUDY: July 1998- 1690 patients randomised double blind, placebo controlled, multi-centre trial. Ref: Efficacy and safety of Recombinant Human Activated Protein C for severe sepsis- The New England Journal of Medicine Vol 344: 699- 709.
Endpoints: at 28 days-death, adverse events- vital signs, lab variables, cultures, antibodies to activated protein C.

29% relative reduction in risk of deaths in the high risk (APACHE II > 25) patients p= 0.0002).
Survival rate 69% for Xigris as opposed to 56% for standard therapy- sustained at 2.5 years.

Initial baseline bloods showed decreased level of protein C in 87.6% patients (1379/1574 tested) D dimer and Il-6 elevated at beginning in 99.7% and 98.5%.
D-dimer and IL-6 levels were lower post treatment in the treated group.
Occurrence of serious bleeding event was 3.5% with Xigris as opposed to 2.0% in placebo group (p= 0.06).
Trial was stopped at second interim.

Dosage: 24 micrograms/ kg/ hr for 96 hours.