Poison/Potion/Placebo?
IV Ig & sepsis
Immune to shock?

Nepean WTET summary 18/8/20

Background and Rationale

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated immune response to infection. The syndrome is complex, can be caused by a variety of organisms (e.g. bacteria, fungi) that vary in virulence and endotoxin production and furthermore vary in their immune response (hyperinflammation through to immune paralysis) depending on a number of factors including host
- Anti-inflammatory agents have not been shown to improve outcomes. Intravenous immunoglobulin (IVIg) can potentially modulate both pro and anti-inflammatory processes & neutralise endo/exo-toxins
- IVIg is advocated as a management strategy for toxic shock syndrome (and less so as an adjunct therapy for necrotising fasciitis). Superantigens mediate hypotension and multiorgan failure (MOF) which contributes to the high mortality (up to 80% despite early appropriate antimicrobial therapy). IVIg is thought to neutralise superantigens and facilitate opsonisation of strep/staph
- In gram negative sepsis, endotoxin forms an important part of MOF and thereby could benefit by IVIg by similar mechanisms as staph/strep toxic shock
- IgMA enriched immunoglobulin contain superior antibody (Ab) content against bacterial lipopolysaccharides

Advantages and Disadvantages

- Advantages
    - Overall well tolerated and safe (no viral transmission reported)
- Disadvantages
    - IVIg and IgMA in particular is expensive, limited resource, often not available on site (delay)
    - Skin reactions and anaphylaxis may occur, volume of fluid associated with administration

Key studies

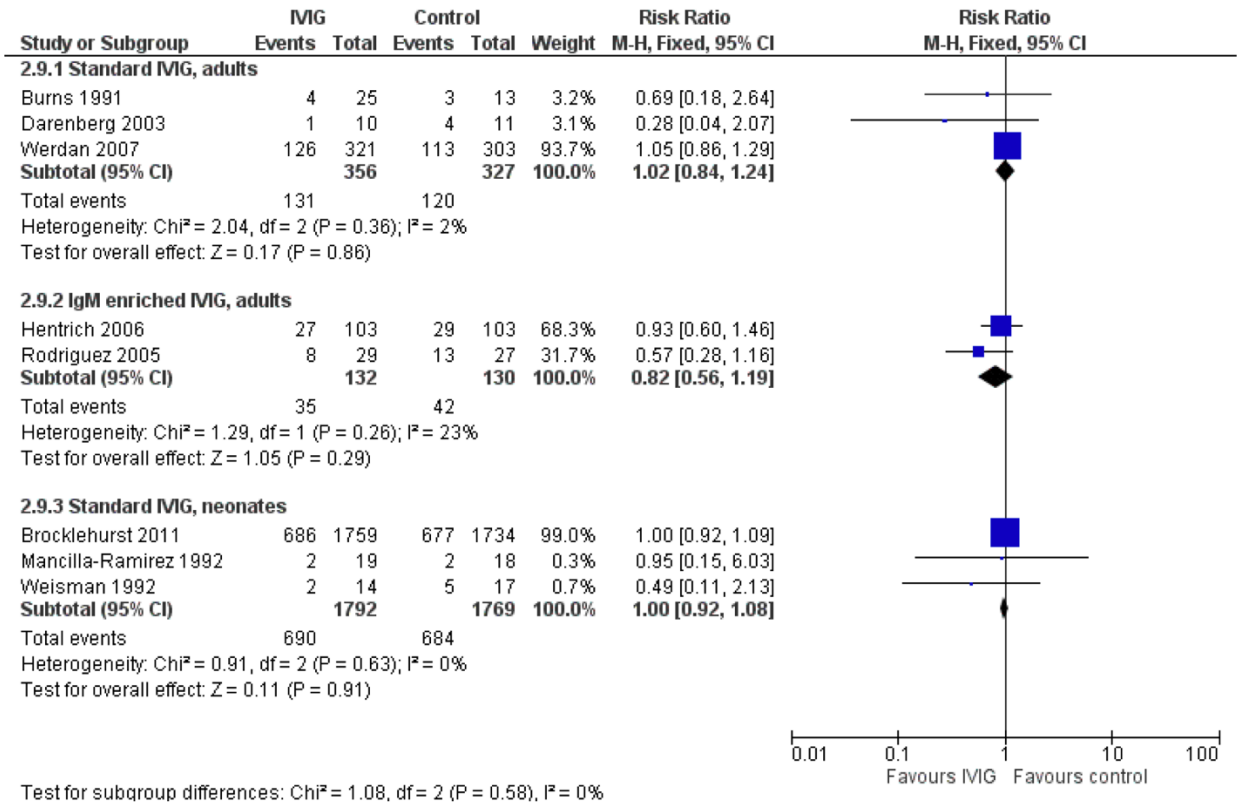
- Septic shock
    - Schedel; 1991 Crit Care Med (gram negative)
        - RCT SS; Septic shock <24h and endotoxaemia (>12.5pg/ml, no +ve culture needed) randomised to standard care +/- IVIg (16x IgA, 4x IgG and IgM activity against core polysaccharide endotoxin, lipid A) given 600mls day 1, then 300mls day 2 & 3. N=55
        - Groups comparative APACHE2; but significantly fewer deaths by 6 weeks in IVIg group (1/27 dead vs 9/28 dead, P<0.01). Mostly pseudomonas & e-coli
    - Hentrich; 2006 Crit Care Med (neutropenic; IgM/A enriched)
        - MC RCT; Neutropenic patients (post chemo) with haematological malignancies and sepsis syndrome or septic shock. Standard care with either Iv IGMA 1300ml over 72h (200ml initially followed by 11x 100ml every 6h) vs 1300ml 5% albumin. N=211
        - Primary end point; all-cause d28 mortality no difference 26.2% vs 28.2% (P=0.93)
        - Similarly no difference in 60d mortality, or benefit in those with septic shock
    - SBITS (Werdan); 2007 Crit Care Med (severe sepsis)

        - MC RCT DB; High sepsis score (12-27) and APACHE2 score (20-35) randomised to IVIg (day 0; 0.6g/kg & day 1 0.3g/kg = total 0.9g/kg) vs placebo (0.1% albumin). N=624
        - Primary outcome; 28d mortality no different (39.3% vs 37.3%, P=0.6695)
        - 90.5% mechanically ventilated; no improvement in A/a. No difference in gram -ve vs +ve infections. Reduction in scoring systems with IVIg. Published >10y later (1995)
    - Cochrane Review; 2018
        - Monoclonal and polyclonal IVIg studied, adults and neonates. Total of 43 RCTs
        - 10 polyclonal (n=1430; RR 0.81, 95% CI 0.70-0.93) and 7 IgM enriched (n=528; 0.66, 95% CI 0.51-0.85) RCTs showed significant reductions in mortality in adults with sepsis compared to placebo/no intervention. However, looking at trials with low risk of bias there was no benefit with polyclonal IVIg seen; as for IgM enriched IVIg trials with low risk of bias they were small and insufficient to support a robust conclusion
- Toxic Shock Syndrome (TSS)
    - Darenberg; 2003 Clin Infect Dis
        - MC RCT DB; Patients with streptococcal TSS (+/- necrotising fasciitis) including hypotension and MOF, could be enrolled before micro if strep suspected (soft tissue involvement with local pain, tonsillitis/pharyngitis); IVIg (1g/kg day 1 then 0.5g/kg day 2&3) vs equal volume of 0.1% albumin. N=21
        - Primary outcome; 28d mortality 10% vs 36% (all-comers) and 12.5% vs 30% (proven GAS) – not statistically significant (P=0.3, despite difference) as underpowered…
        - Stopped early due to slow recruitment. Significant reduction in SOFA score

Summary (my practice)

- I do not use polyclonal IVIg in sepsis or septic shock. I do routinely use it in TSS however and occasionally as an adjunct in necrotising fasciitis. It can be difficult however to differentiate TSS from septic shock where strep/staph most likely organisms clinically
- I await further (higher quality) studies looking at IgM enriched IVIg and its role in septic shock

Figure 4. Polyclonal IVIG versus placebo or no intervention, outcome: all-cause mortality by type of polyclonal IVIG, sensitivity analysis, low risk of bias trials.



Taken from Cochrane review 2018