Case 2

Intravenous Immunoglobulins for Staphylococcal sepsis

Clinical Problem & Domain

This expanded case summary has been chosen to explore the rationale and evidence behind the administration of intravenous immunoglobulins (IVIG) for Staphylococcal sepsis. It falls into domain 4.

A 43 year old man presented to the intensive care unit (ICU) post operatively after drainage of an ilio-psoas abscess, washout of the hip joint and Girdlestone procedure. His initial admission to hospital had been approximately 3 months previously with discitis. Staphylococcus aureus had been identified on several sets of blood cultures. Long term flucloxacillin was ongoing.

He had a past medical history of alcoholic liver disease (ALD), but was otherwise well prior to his admission to hospital. His liver disease had decompensated whilst an inpatient. He was admitted to ICU from theatre having decompensated haemodynamically. He was profoundly septic and had suffered significant bleeding intra-operatively.

Management

On arrival on ICU he was requiring noradrenaline (0.3microg/kg/min) to maintain a mean arterial pressure (MAP) of 70mmHg. His lactate was elevated at 12 mmol/l. His antibiotic regime had been altered to flucloxacillin, clindamycin and gentamicin. He had ongoing bleeding from the surgical site.

He was initially treated with further fluids, packed red cells and escalating inotrope doses. His fluid balance was optimized based on clinical parameters including stroke volume variability. Vasopressin was added to the noradrenaline at a rate of 1.6 units/hr. He was also treated with hydrocortisone (50mg QDS) for the inotrope unresponsive septic shock. Blood tests demonstrated hepatic and renal impairment with low haemoglobin and platelet counts and elevated prothrombin and activated partial thromboplastin times. Fresh frozen plasma, cryoprecipitate and platelets were administered with the aim of normalising his abnormal clotting. The surgical team were made aware of the ongoing bleeding and blood requirements, a plan was made to return to theatre if the bleeding continued with a normalised coagulation profile.

The possibility of toxic shock syndrome was considered. He did not at the time meet the diagnostic criteria for toxic shock (figure 1) but it was felt that given the identified microorganism IVIG may be appropriate if he failed to improve.
He deteriorated despite this treatment, inotropic requirements escalated further (noradrenaline 1.0 microg/kg/min) and his metabolic acidosis and lactate levels worsened despite the initiation of renal replacement therapy and bicarbonate. He was taken back to theatre for further washout and packing. On his return he deteriorated further with his blood pressure dropping as low as a MAP of 25 for several hours. The decision to administer IVIG (2g/kg) was made. Prior to administration his MAP improved to 60mmHg. IVIG was initiated at around midnight.

On review the following morning his acidosis and lactate had failed to improve and his blood pressure dropped further despite ongoing fluid and inotropic support. He suffered with recurrent episodes of pulsed ventricular tachycardia. Support was withdrawn on the grounds of futility and he died shortly after.

**Discussion**

IVIG’s postulated role in sepsis is to inactivate toxins and stimulate leucocytes. It has also been suggested that they may attenuate the complement cascade and thus reduce the systemic inflammatory response syndrome (SIRS).²

A recently updated Cochrane review of the use of IVIG in sepsis found no high quality evidence of a reduction in mortality³. The majority of the studies included in this review were intensive care based. Meta-analysis of four adult trials showed a reduction in all cause mortality (RR 0.45; 95% CI 0.29 to 0.63, 11.5% mortality versus 26%) but the trials were small and contained a variety

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**Figure 1 – Diagnostic criteria for toxic shock syndrome¹**

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<td>1. Body temperature &gt; 38.9 °C</td>
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<td>2. Systolic blood pressure &lt; 90 mmHg</td>
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<td>3. Diffuse rash, intense erythoderma, blanching with subsequent desquamation, especially of the palms and soles</td>
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<td>4. Involvement of three or more organ systems:</td>
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<td>- Gastrointestinal (vomiting, diarrhoea)</td>
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<td>- Mucous membrane hyperaemia (vaginal, oral, conjunctival)</td>
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<tr>
<td>- Renal failure (serum creatinine &gt; 2 times normal)</td>
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<tr>
<td>- Hepatic inflammation (AST, ALT &gt; 2 times normal)</td>
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<tr>
<td>- Thrombocytopenia (platelet count &lt; 100,000 / mm³)</td>
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<td>- CNS involvement (confusion without any focal neurological findings)</td>
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<td>5. Negative blood, throat, or cerebrospinal fluid cultures (blood culture may be positive for Staphylococcus aureus)</td>
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<td>6. No rise in titre to Rocky Mountain spotted fever, leptospirosis, or measles</td>
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A probable case demonstrates five of the six clinical findings described above. A confirmed case shows all six of the clinical findings.
of methodological flaws, the largest trial included showed no mortality benefit. No evidence of reduced length of stay was shown during meta-analysis of the included trials, this was the only other widely used outcome measure. The heterogeneity of the trials and groups makes definitive conclusions difficult. Inclusion criteria, dose, duration and timing all varied.

The subgroup of patients who develop toxic shock syndrome (TSS) may have a greater benefit from IVIG. TSS is rare, the incidence is reported to be approximately 2 in 100,000, although lack of recognition and therefore under-reporting is possible. Mortality is variably reported, one epidemiological study estimated overall mortality to be 2-4%, several randomised controlled trials (RCT’s) have shown higher rates. In TSS the presence of exotoxins are a predominant part of the pathophysiology and IVIG may aid in neutralization.

The patient we treated did not have a rash and did not meet criteria for definite TSS, it is possible he died before a rash or desquamation could occur.

There is some human clinical evidence for the effectiveness of IVIG in Streptococcal TSS. A case series, cohort study and RCT all showed some potential mortality benefit. The RCT was unfortunately terminated early due to difficulty with recruitment, it failed to reach statistical significance with 1 death in treatment group (n10) versus 4 in the placebo group (n11). The treatment group did show a statistically significant decrease in Sequential Organ Failure Assessment (SOFA) score on day 2 and day 3.

Evidence in Staphylococcal TSS is weaker still. It is based upon lab studies and anecdotal reports of effectiveness. There is in vitro evidence that higher doses of IVIG may be required in Staphylococcal illness when compared to Streptococcal, higher concentrations of IVIG being required to inhibit cytokine production in Staphylococcal infection laboratory models. Furthermore, if a benefit for this therapy exists then trial findings may be clouded by variations in effectiveness of different preparations of IVIG. There is in vitro evidence of variable potency, potentially due to differing exposure to the relevant microorganisms between populations that the IVIG is donated from.

If treatment with IVIG is instigated it is not clear what the most appropriate dose is, nor choice of timing or duration. It has been suggested that use early in the disease process may be preferable. It would appear that beneficial effects can be seen in 24 hours or less.

Adverse reactions have been reported and include allergic phenomena, nausea, breathlessness and shock. Incidence of such reactions is difficult to calculate given the small size of most trials and the difficulty of ascertaining a causal relationship.

Cost is also a consideration. Prices in 2007 were approximately £30-35/g. In an era of increasing healthcare rationing a cost-benefit analysis has to be
made. Given the absence of evidence of clinical effectiveness this has not been formally undertaken in the setting described.

**Lessons learnt**

Clear and decisive evidence in Intensive Care Medicine is very difficult to obtain. As such we often use therapies that have a limited evidence base. The evidence to support IVIG in sepsis is poor. In the case described there was no clear evidence of TSS, although it was possible. When a patient is dying despite maximal conventional therapy an argument can be made for “trying everything”.

It would appear that there is still equipoise for this treatment and indication. An RCT with clear and focused inclusion criteria, i.e. only including TSS patients treated within 24 hours of diagnosis, would be of benefit. Perhaps, a high and low dose regime compared to placebo should also be considered. The relative rarity of the condition makes this difficult however.

Having reviewed the evidence I would in future consider the use of IVIG where TSS was likely. It is unlikely, but possible, that the patient in our case had TSS. The use of IVIG for the more generalised indication of sepsis is not supported by the current evidence.
References