Dear Sir,

We are writing to request that Polyvalent Human Immunoglobulin should be reinstated to the WHO Model List of Essential Medicines (Section 19.2). We are surprised that this was removed from the List last year, and support the application of the Plasma Protein Therapeutics Association on this matter.

Immunoglobulin was previously used to provide preventive immunisation against infections such as Hepatitis A for which specific vaccinations were not then available, and we agree that this use now seems less important. However, the List does not mention the fact that immunoglobulin is being increasingly used worldwide as immunotherapy to treat immunodeficiency, haematological and neurological disease. It appears that the decision to remove immunoglobulin from the List last year was largely due to this not being recognised.

We are British neurologists and shall restrict our comments to neurological diseases. Controlled clinical trials have shown that immunoglobulin is effective as first-line therapy in patients with Guillain-Barré Syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and multifocal motor neuropathy (MMN), and as second-line therapy in multiple sclerosis, myasthenia gravis, dermatomyositis, Lambert-Eaton myasthenic syndrome and stiff-person syndrome (Dalakas 2004). Vaccinations have no role in the prevention of these diseases. We act as medical advisers to the GBS Support Group, which exists to help patients with GBS.

The paragraph numbers below refer to the headings in the application form. To be brief, we have answered only the most important points.

6. Public health relevance. GBS affects people in all countries and of any age. It causes severe paralysis of the whole body, with loss of sensation and sometimes inability to breathe. It is usually an acute monophasic illness followed by incomplete recovery. Although it is uncommon (the incidence is approximately 20 per million per year), it has serious consequences, in that different studies have shown 2-18% of patients die, and another 7-10% are left with permanent physical disability such that they cannot walk unaided one year later. CIDP and MMN are chronic relapsing forms of GBS, which can also cause severe disability. The prevalence of CIDP is 2 – 8 per million.
7. *Treatment details.* For GBS, CIDP, MMN and most of the neurological indications, the standard dose of immunoglobulin is 2 g/kg, given as an intravenous infusion over usually 2-5 days, and requiring frequent nursing observations. In GBS only one treatment course is needed, but in CIDP and MMN this may need to be repeated at intervals of months or years. It would be more appropriate for immunoglobulin to be on the Complementary List than the Core List, as GBS may require specialist medical care (intensive care in 20% of patients), and CIDP and MMN require specialist diagnostic facilities (neurophysiology).

8. *Comparative effectiveness.* The evidence for the efficacy of immunoglobulin in GBS includes six randomised controlled trials and a Cochrane systematic review, showing that IVIg was equally efficacious to plasma exchange (Hughes et al., 2004). Plasma exchange had previously been shown to be efficacious in improving recovery at four weeks and residual disability at one year, compared with supportive treatment only (Raphael et al, 2001). Both treatments are recommended by the American Academy of Neurology (Hughes 2003). Immunoglobulin is generally preferred to plasma exchange in clinical practice in most countries, because it is more convenient (plasma exchange requires specialist equipment and highly trained staff) and of similar cost. In developing countries, it is likely that plasma exchange would be far less readily available than immunoglobulin.

In CIDP, a Cochrane systematic review of another six randomised controlled trials showed that IVIg was significantly more efficacious than placebo, but equally efficacious to plasma exchange and prednisolone (Van Schaik 2002). Prednisolone is cheaper than immunoglobulin, but has significant long term adverse effects and is not always efficacious. In MMN and the pure motor variant of CIDP, prednisolone is not efficacious so immunoglobulin is the preferred first-line treatment.

9. *Safety.* Immunoglobulin is generally considered fairly safe, but may cause the following adverse effects: mild common reactions such as headaches, myalgia, or fever, which disappear at lower infusion rates; moderate but inconsequential events, such as aseptic meningitis and skin rash; and rare severe complications, such as thromboembolism and renal tubular necrosis. Since the mid 1990s all licensed products are considered safe from viral infection, though a very small theoretical risk remains (Eibl 2003). We are not aware of significant quality control problems.

10. *Cost.* Although immunoglobulin is expensive, we believe it is cost-effective, because it shortens the length of time that patients require mechanical ventilation and stay in hospital, and reduces the chance of long-term disability and inability to work.

11. Immunoglobulins are listed in the British National Formulary, section 14.5: Human Normal Immunoglobulin for intravenous use

In summary, we consider that immunoglobulin is an essential medicine because it is the preferred first-line treatment for several disabling neurological diseases. We hope that you will include Polyvalent Human Immunoglobulin in future editions of the WHO Model List of Essential Medicines.

Yours faithfully,

RAC Hughes
Professor of Neurology
on behalf of
The Medical Advisory Board of the Guillain-Barré Syndrome Support Group of the United Kingdom
References


