Multiple Sclerosis Vaccines

Vacunas de la esclerosis múltiple.

Profile

Vaccines based on T cells have been investigated for the management of multiple sclerosis.

The use of vaccine-derived polyclonal antibodies from the serum of goats is also under investigation.

◊ References.

1. Hellings N, *et al.* T-cell vaccination in multiple sclerosis: update on clinical application and mode of action. *Autoimmun Rev* 2004; **3:** 267–75.
2. Sospedra M, Martin R. Antigen-specific therapies in multiple sclerosis. *Int Rev Immunol* 2005; **24:** 393–413.
3. Fontoura P, *et al.* Antigen-specific therapies in multiple sclerosis: going beyond proteins and peptides. *Int Rev Immunol* 2005; **24:** 415–46.
4. Correale J, *et al.* Vaccines for multiple sclerosis: progress to date. *CNS Drugs* 2008; **22:** 175–98.

Mumps Immunoglobulins

Inmunoglobulinas contra la parotiditis.

ATC — J06BB15.

Profile

Preparations containing antibodies against mumps virus have been used in some countries for passive immunisation against mumps.

Mumps Vaccines

Vacunas de la parotiditis.

ATC — J07BE01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Mumps Vaccine (Live); Vaccinum Parotitidis Vivum). A freeze-dried preparation containing a suitable live attenuated strain of mumps virus (*Paramyxovirus parotitidis*) grown in cultures of human diploid cells or chick-embryo cells or the amniotic cavity of chick embryos. It is prepared immediately before use by reconstitution from the dried vaccine. The cell-culture medium may contain the lowest effective concentration of a suitable antibacterial. The virus concentration is not less than 3.7 log $CCID_{50}$ per dose. The dried vaccine should be stored at 2° to 8° and be protected from light.

The BP 2008 states that Mumps may be used on the label.

USP 31 (Mumps Virus Vaccine Live). A bacterially sterile preparation of a suitable strain of mumps virus grown in cultures of chick-embryo cells. It contains not less than the equivalent of 5×10^3 $TCID_{50}$ in each immunising dose. It may contain suitable antimicrobial agents. It should be stored at 2° to 8° and be protected from light.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Parotid swelling may occur. Unilateral nerve deafness, aseptic meningitis, and encephalitis have occurred rarely (see below for further discussion).

Mumps vaccines are not generally recommended for children below the age of 1 year in whom maternal antibodies might prevent a response.

Effects on hearing. For a report of sensorineural hearing loss following measles, mumps, and rubella vaccination, see p.2223.

Effects on the nervous system. There have been a few reports of neurological reactions including meningitis and encephalitis after vaccination with measles, mumps, and rubella vaccines. These reactions have been attributed to the mumps component. However, it has not been possible to isolate the virus from the CSF in every case and identify it as either the vaccine strain or a wild-type strain. Meningitis develops up to 35 days after immunisation, is mild, and sequelae are rare.[1,2] One study[3] found the incidence of virus-positive post-immunisation meningitis from the Urabe strain of mumps vaccine to be about 1 in 11 000 immunised children, with the incidence following Jeryl Lynn mumps vaccine being much lower. This result was supported by the incidence of about 1 in 4000 in another study,[4] making it less likely that this was a chance result, and much higher than the estimates of up to 1 in 1 million reported previously.[5] Subsequent research[6] identified the Urabe vaccine strain in CSF samples from all of 20 children with post-vaccination meningitis in the UK, and no isolates of the Jeryl Lynn strain in patients with meningitis among 80 samples tested. Thus, vaccines containing the Urabe strain, including combined measles, mumps, and rubella vaccines are no longer used in the UK and some other countries.[7] A relatively high incidence of meningitis of about 1 in 1000 has also occurred after use of a measles and mumps vaccine prepared from the Leningrad-3 strain of mumps virus.[8,9]

Encephalitis has been associated with mumps vaccination less frequently than meningitis, but may be more serious.[1] The Advisory Committee on Immunization Practices in the USA has reported that the incidence of encephalitis within 30 days of receiving a mumps-containing vaccine is 0.4 per one million doses.[10] This is no higher than the observed background incidence for CNS dysfunction in the general population.

In considering the above data it should be remembered that mumps is the most common cause of meningoencephalitis in children under 15 years of age in the UK and an important cause of permanent sensorineural deafness in childhood.[1] Meningitis after natural mumps infection is estimated to occur in 1 in 400 cases, an incidence that is very considerably above any reported with vaccination.

1. Anonymous. Mumps meningitis and MMR vaccination. *Lancet* 1989; **ii:** 1015–16.
2. Maguire HC, *et al.* Meningoencephalitis associated with MMR vaccine. *Commun Dis Rep* 1991; **1** (review 6): R60–R61.
3. Miller E, *et al.* Risk of aseptic meningitis after measles, mumps, and rubella vaccine in UK children. *Lancet* 1993; **341:** 979–82.
4. Colville A, Pugh S. Mumps meningitis and measles, mumps, and rubella vaccine. *Lancet* 1992; **340:** 786. Correction. *ibid.*: 986.
5. McDonald JC, *et al.* Clinical and epidemiologic features of mumps meningoencephalitis and possible vaccine-related disease. *Pediatr Infect Dis J* 1989; **8:** 751–5.
6. Forsey T, *et al.* Mumps vaccine and meningitis. *Lancet* 1992; **340:** 980.
7. Anonymous. Two MMR vaccines withdrawn. *Lancet* 1992; **340:** 722.
8. Čižman M, *et al.* Aseptic meningitis after vaccination against measles and mumps. *Pediatr Infect Dis J* 1989; **8:** 302–8.
9. Tešović G, *et al.* Aseptic meningitis after measles, mumps, and rubella vaccine. *Lancet* 1993; **341:** 1541.
10. Immunization Practices Advisory Committee. Mumps prevention. *MMWR* 1989; **38:** 388–400.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Mumps vaccines are used for active immunisation against mumps.

For primary immunisation a combined measles, mumps, and rubella vaccine (p.2223) is usually used. For discussion of immunisation schedules, see under Vaccines, p.2202.

Many different attenuated strains of mumps virus have been used in vaccines and those commonly used have included Jeryl Lynn, Urabe, Leningrad-3 (and adapted L-Zagreb), and Rubini strains. Efficacy seems to be broadly similar for these strains with the exception of Rubini which is reported to be less effective than Jeryl Lynn or Urabe.

A vaccine prepared from the Jeryl Lynn (B level) strain of mumps virus is available in the USA, and may be given in a dose of 0.5 mL by subcutaneous injection although combined vaccines are usually preferred.

Preparations

Ph. Eur.: Mumps Vaccine (Live);
USP 31: Mumps Virus Vaccine Live.

Proprietary Preparations (details are given in Part 3)
Arg.: Imovax Parotiditis†; ***Braz.:*** Imovax Mumps†; ***Canad.:*** Mumpsvax†; ***Cz.:*** Pavivac; ***Denm.:*** Mumpsvax†; ***Ger.:*** Mumpsvax†; ***Gr.:*** Mumpsvax†; ***Ital.:*** Vaxipar†; ***Spain:*** Vac Antiparotiditis†; ***Switz.:*** Mumpsvax; ***USA:*** Mumpsvax; ***Venez.:*** Imovax Parotiditis†.

Mycobacterium Vaccae Vaccines

SRL-172; Vacunas de Mycobacterium vaccae.

Profile

Vaccines containing *Mycobacterium vaccae* are under investigation for the prevention and immunotherapy of tuberculosis and other mycobacterial infections. They are also being studied for therapeutic use in asthma, eczema, psoriasis, and some malignant neoplasms.

Asthma. Heat-killed *Mycobacterium vaccae* is a potent down-regulator of T-helper 2 cytokines which play a central role in asthma. In a double-blind, randomised, placebo-controlled study[1] in 24 asthmatic men, a bronchial allergen challenge was given 2 weeks before and 3 weeks after a single intradermal injection of *Mycobacterium vaccae* vaccine. The maximum fall in FEV, during the allergic response to the latter challenge was reduced by a mean of 34%, but this was not statistically significant compared with placebo.

1. Camporota L, *et al.* The effects of Mycobacterium vaccae on allergen-induced airway responses in atopic asthma. *Eur Respir J* 2003; **21:** 287–93.

Eczema. In a double-blind, randomised, placebo-controlled study[1] in 41 children aged 5 to 18 years with moderate to severe atopic dermatitis, an intradermal injection of *Mycobacterium vaccae* vaccine resulted in a 48% reduction in the surface area of the skin affected after 3 months compared with 4% in those given placebo. In a later study[2] in 56 children aged 2 to 6 years, these results could not be replicated because the reduction in affected area was not found to be significantly different from placebo.

1. Arkwright PD, David TJ. Intradermal administration of a killed Mycobacterium vaccae suspension (SRL 172) is associated with improvement in atopic dermatitis in children with moderate-to-severe disease. *J Allergy Clin Immunol* 2001; **107:** 531–4.
2. Arkwright PD, David TJ. Effect of Mycobacterium vaccae on atopic dermatitis in children of different ages. *Br J Dermatol* 2003; **149:** 1029–34.

Malignant neoplasms. *Mycobacterium vaccae* vaccines have been used with limited success as adjunctive therapy in the management of a variety of cancers, notably prostate cancer, malignant melanoma, and non-small-cell lung cancer. In a preliminary study[1] 28 patients with inoperable non-small-cell lung cancer and mesothelioma were randomised to receive chemotherapy either with or without adjunctive intradermal injection of a heat-killed *Mycobacterium vaccae* vaccine (SRL-172). A trend towards improved response rate was found in those patients receiving combined therapy, together with improved median survival and 1-year survival rates; some patients given combined therapy were subsequently able to receive curative surgery or radical radiotherapy. A similar subsequent phase III study[2] in 419 patients found a significant improvement in patient quality of life after combined therapy, but the improvements in survival-time could not be replicated. Secondary analyses of these results[3] suggested an improvement in survival time for patients with adenocarcinoma, but not for those with squamous cell carcinoma. There is also some evidence of beneficial effect in patients with metastatic renal cell carcinoma.[4]

1. O'Brien ME, *et al.* A randomized phase II study of SRL172 (Mycobacterium vaccae) combined with chemotherapy in patients with advanced inoperable non-small-cell lung cancer and mesothelioma. *Br J Cancer* 2000; **83:** 853–7.
2. O'Brien ME, *et al.* SRL172 (killed Mycobacterium vaccae) in addition to standard chemotherapy improves quality of life without affecting survival, in patients with advanced non-small-cell lung cancer: phase III results. *Ann Oncol* 2004; **15:** 906–14.
3. Stanford JL, *et al.* Successful immunotherapy with Mycobacterium vaccae in the treatment of adenocarcinoma of the lung. *Eur J Cancer* 2008; **44:** 224–7.
4. Patel PM, *et al.* An evaluation of a preparation of Mycobacterium vaccae (SRL172) as an immunotherapeutic agent in renal cancer. *Eur J Cancer* 2008; **44:** 216–23.

Psoriasis. Preliminary studies have shown that heat-killed *Mycobacterium vaccae* vaccines may induce periods of remission when given intradermally. An open-label study[1] in 24 patients given 2 intradermal injections into lesion-free deltoid skin at a 3-week interval found, 12 weeks after starting treatment: marked improvement (14 patients), moderate improvement (2), no change (6), and worsening of symptoms (2). By 24 weeks, 11 of 22 patients continued to show a greater than 50% improvement and of these 5 had complete clearance of skin lesions lasting for 6 months or more. In another study,[2] a more potent heat-killed, delipidated, deglycolipidated vaccine was given similarly to 20 patients with moderate to severe psoriasis; after 12 weeks, 13 of the 20 patients showed a marked improvement, 3 were unchanged, 3 had worsened, and 1 withdrawn due to an exfoliative flare. At 24 weeks, 13 of 19 patients continued to show a greater than 50% improvement, and in some this lasted for 6 months or more. A double-blind, randomised, placebo-controlled study[3] with the latter vaccine in 36 patients with psoriatic arthritis found no improvement in psoriatic lesions compared with placebo, although there did appear to be some improvement in pain experienced.

1. Balagon MV, *et al.* Improvement in psoriasis after intradermal administration of heat-killed Mycobacterium vaccae. *Int J Dermatol* 2000; **39:** 51–8.
2. Balagon MV, *et al.* Improvement in psoriasis after intradermal administration of delipidated, deglycolipidated Mycobacterium vaccae (PVAC): results of an open-label trial. *Clin Exp Dermatol* 2001; **26:** 233–41.
3. Dalbeth N, *et al.* A randomised placebo controlled trial of delipidated, deglycolipidated Mycobacterium vaccae as immunotherapy for psoriatic arthritis. *Ann Rheum Dis* 2004; **63:** 718–22.

Tuberculosis. ***IMMUNISATION.*** References.

1. von Reyn CF, *et al.* Cellular immune responses to mycobacteria in healthy and human immunodeficiency virus-positive subjects in the United States after a five-dose schedule of Mycobacterium vaccae vaccine. *Clin Infect Dis* 1998; **27:** 1517–20.
2. Waddell RD, *et al.* Safety and immunogenicity of a five-dose series of inactivated Mycobacterium vaccae vaccination for the prevention of HIV-associated tuberculosis. *Clin Infect Dis* 2000; **30** (suppl 3): S309–S315.
3. Vuola JM, *et al.* Immunogenicity of an inactivated mycobacterial vaccine for the prevention of HIV-associated tuberculosis: a randomized, controlled trial. *AIDS* 2003; **17:** 2351–5.

IMMUNOTHERAPY. A systematic review[1] found that immunotherapy with *Mycobacterium vaccae* produced no beneficial effects in patients with tuberculosis.

1. de Bruyn G, Garner P. Mycobacterium vaccae immunotherapy for treating tuberculosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/12/04).

Normal Immunoglobulins

Inmunoglobulinas inespecíficas.

ATC — J06BA01; J06BA02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Human Normal Immunoglobulin; Immunoglobulinum Humanum Normale). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG) antibodies, of normal subjects. Other proteins may be present; it contains not less than 10% and not more than 18% of total protein. It is intended for intramuscular or subcutaneous injection. It is obtained from the pooled plasma collected from at least 1000 donors who must be healthy, must not have been treated with substances of human pituitary origin, and as far as can be ascertained be free from detectable agents of infection transmissible by transfusion of blood or blood components. No antibacterial is

added to the plasma used. It is prepared as a stabilised solution and passed through a bacteria-retentive filter. Multidose, but not single dose, preparations contain an antimicrobial preservative. The pH of a solution in sodium chloride 0.9% containing 1% of protein is 5.0 to 7.2. The liquid preparation should be stored, protected from light, in a sealed, colourless, glass container. The freeze-dried preparation should be stored, protected from light, in an airtight, colourless, glass container.

Ph. Eur. 6.2 (Human Normal Immunoglobulin for Intravenous Administration; Immunoglobulinum Humanum Normale ad Usum Intravenosum). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG); other proteins may be present and the total protein content is not less than 3%. It contains IgG antibodies of normal subjects; the standard does not apply to products intentionally prepared to contain fragments or chemically modified IgG. It is prepared as a stabilised solution and passed through a bacteria-retentive filter. It does not contain an antimicrobial preservative. The pH of a solution in sodium chloride 0.9% containing 1% of protein is 4.0 to 7.4. Storage requirements are similar to those for Human Normal Immunoglobulin, except that the freeze-dried preparation is stored in an airtight container at a temperature not exceeding 25°.

USP 31 (Immune Globulin). A sterile solution of globulins that contains many antibodies normally present in human adult blood. It is prepared from pooled material (approximately equal quantities of blood, plasma, serum, or placentas) from not fewer than 1000 donors. It contains 15 to 18% of protein, of which not less than 90% is gamma globulin. It is intended for intramuscular injection. It contains glycine as a stabiliser, and a suitable preservative. It contains antibodies against diphtheria, measles, and poliomyelitis. It should be stored at 2° to 8°.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201. Intravenous immunoglobulin preparations should be used with caution in patients with renal impairment. Immunoglobulin products containing sucrose may be associated with an increased risk of inducing acute renal failure (see Effects on the Kidneys, below).

Antibody titres for some common pathogens can vary widely not only between products from different manufacturers, but also from lot to lot. Formulations of intravenous immunoglobulins should therefore not be regarded as equivalent.

◊ Reviews.

1. Nydegger UE, Sturzenegger M. Adverse effects of intravenous immunoglobulin therapy. *Drug Safety* 1999; **21:** 171–85.
2. Wittstock M, *et al.* Therapy with intravenous immunoglobulins: complications and side-effects. *Eur Neurol* 2003; **50:** 172–5.
3. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfus Med Rev* 2003; **17:** 241–51.
4. Ameratunga R, *et al.* Increased risk of adverse events when changing intravenous immunoglobulin preparations. *Clin Exp Immunol* 2004; **136:** 111–13.
5. Singh-Grewal D, *et al.* A prospective study of the immediate and delayed adverse events following intravenous immunoglobulin infusions. *Arch Dis Child* 2006; **91:** 651–4.

Effects on the blood. Adverse effects on the blood have occasionally been reported after intravenous use of normal immunoglobulin to increase the platelet count in patients with idiopathic thrombocytopenic purpura and in the management of other auto-immune diseases. Reduced platelet adhesiveness with multiple subcutaneous haematomas occurred in one patient.[1] Thrombotic events have occurred after intravenous use,[2-4] particularly in elderly subjects (sometimes fatal) suggesting that a rising platelet count during normal immunoglobulin treatment may represent a risk in patients with severe atherosclerotic disease.[2] However, a review of 34 patients over 60 years of age treated with normal immunoglobulin could not confirm the association.[5]

Haemolytic reactions, including a case of haemolytic disease of the newborn, have sometimes been noted[6,7] and passive transfer of anti-A, anti-B, or anti-D antibodies or active immunisation by blood group substances from normal immunoglobulin preparations has been implicated. It has been suggested[7] that blood phenotyping be carried out before treatment with normal immunoglobulin is started.

Transient neutropenia has occurred after use of normal immunoglobulin in patients with thrombocytopenic purpura, but the clinical significance of this effect has been disputed.[8-10]

1. Ljung R, Nilsson IM. High-dose intravenous gammaglobulin: a cautionary note. *Lancet* 1985; **i:** 467.
2. Woodruff RK, *et al.* Fatal thrombotic events during treatment of autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients. *Lancet* 1986; **ii:** 217–18.
3. Go RS, Call TG. Deep venous thrombosis of the arm after intravenous immunoglobulin infusion: case report and literature review of intravenous immunoglobulin-related thrombotic complications. *Mayo Clin Proc* 2000; **75:** 83–5.
4. Marie I, *et al.* Intravenous immunoglobulin-associated arterial and venous thrombosis; report of a series and review of the literature. *Br J Dermatol* 2006; **155:** 714–21.
5. Frame WD, Crawford RJ. Thrombotic events after intravenous immunoglobulin. *Lancet* 1986; **ii:** 468.
6. Potter M, *et al.* ABO alloimmunisation after intravenous immunoglobulin infusion. *Lancet* 1988; **i:** 932–3.
7. Nicholls MD, *et al.* Haemolysis induced by intravenously-administered immunoglobulin. *Med J Aust* 1989; **150:** 404–6.
8. Majer RV, Green PJ. Neutropenia caused by intravenous immunoglobulin. *BMJ* 1988; **296:** 1262.
9. Veys PA, *et al.* Neutropenia following intravenous immunoglobulin. *BMJ* 1988; **296:** 1800.
10. Ben-Chetrit E, Putterman C. Transient neutropenia induced by intravenous immune globulin. *N Engl J Med* 1992; **326:** 270–1.

Effects on the kidneys. There have been occasional case reports of renal failure or impairment associated with the use of intravenous normal immunoglobulin.[1,2] The incidence of renal failure appears to be greatest with immunoglobulin products containing sucrose.[1,3] The FDA in the USA had issued a warning alerting physicians to the potential risks of acute renal failure associated with intravenous use of normal immunoglobulin products, particularly those containing sucrose.[4]

1. Orbach H *et al.* Intravenous immunoglobulin and the kidney—a two-edged sword. *Semin Arthritis Rheum* 2004; **34:** 593–601.
2. Itkin YM, Trujillo TC. Intravenous immunoglobulin-associated acute renal failure: case series and literature review. *Pharmacotherapy* 2005; **25:** 886–92.
3. Zhang R, Szerlip HM. Reemergence of sucrose nephropathy: acute renal failure caused by high-dose intravenous immune globulin therapy. *South Med J* 2000; **93:** 901–4.
4. Food and Drug Administration. Important drug warning (issued 24 September 1999). Available at: http://www.fda.gov/Cber/ltr/igivrenal.pdf (accessed 31/05/06)

Effects on the nervous system. Aseptic meningitis has been reported after intravenous use of normal immunoglobulin.[1-5]

Migraine, associated with intravenous immunoglobulin therapy in a patient on 2 occasions, did not recur after prophylaxis with propranolol was started.[6]

Hemiplegia has been reported in a 4-year-old child given intravenous immunoglobulin for immune thrombocytopenic purpura.[7]

1. Kato E, *et al.* Administration of immune globulin associated with aseptic meningitis. *JAMA* 1988; **259:** 3269–71.
2. Casteels-Van Daele M, *et al.* Intravenous immune globulin and acute aseptic meningitis. *N Engl J Med* 1990; **323:** 614–15.
3. Sekul EA, *et al.* Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. *Ann Intern Med* 1994; **121:** 259–62.
4. Picton P, Chisholm M. Aseptic meningitis associated with high dose immunoglobulin: case report. *BMJ* 1997; **315:** 1203–4.
5. Boyce TG, Spearman P. Acute aseptic meningitis secondary to intravenous immunoglobulin in a patient with Kawasaki syndrome. *Pediatr Infect Dis J* 1998; **17:** 1054–6.
6. Constantinescu CS, *et al.* Recurrent migraine and intravenous immune globulin therapy. *N Engl J Med* 1993; **329:** 583–4.
7. Tsiouris J, Tsiouris N. Hemiplegia as a complication of treatment of childhood immune thrombocytopenic purpura with intravenously administered immunoglobulin. *J Pediatr* 1998; **133:** 717.

Effects on the skin. Diffuse alopecia has been reported[1] in 3 women within 1 to 4 weeks of treatment with intravenous normal immunoglobulin. There have been reports[2,3] of severe and extensive eczema in elderly patients up to 3 weeks after receiving normal immunoglobulin intravenously. There has also been a report of cutaneous vasculitic rash on the face of a woman receiving intravenous normal immunoglobulin.[4] Severe cutaneous vasculitis has been reported in a patient who received intravenous normal immunoglobulin for type II mixed cryoglobulinaemia.[5] An erythematous eruption occurred on the hands and feet of a patient 3 days after completing a 5-day treatment course of normal immunoglobulin for chronic inflammatory demyelinating polyneuropathy;[6] the lesions resolved 2 to 3 weeks after completion of therapy. A similar eruption had occurred following normal immunoglobulin therapy in 5 previous occasions.

For mention of a patient with AIDS who developed erythema characteristic of fifth disease following intravenous normal immunoglobulin, see Infection, below.

1. Chan-Lam D, *et al.* Alopecia after immunoglobulin infusion. *Lancet* 1987; **i:** 1436.
2. Barucha C, McMillan JC. Eczema after intravenous infusion of immunoglobulin. *BMJ* 1987; **295:** 1141.
3. Whittam LR, *et al.* Eczematous reactions to human immune globulin. *Br J Dermatol* 1997; **137:** 481–2.
4. Howse M, *et al.* Facial vasculitic rash associated with intravenous immunoglobulin. *BMJ* 1998; **317:** 1291.
5. Yebra M, *et al.* Severe cutaneous vasculitis following intravenous infusion of gammaglobulin in a patient with type II mixed cryoglobulinemia. *Clin Exp Rheumatol* 2002; **20:** 225–7.
6. Mutasim DF, Sheth PB. An eruption secondary to intravenous immunoglobulin therapy. *Cutis* 2002 **69:** 35–6, 38.

Hypersensitivity. Hypersensitivity reactions may occasionally occur after intramuscular or intravenous use of normal immunoglobulins particularly in hypogammaglobulinaemic or agammaglobulinaemic patients. Both immediate and late[1] reactions have occurred.

The IgA content of normal immunoglobulins can result in the development of IgE and IgG anti-IgA antibodies in immunodeficient patients with IgA deficiency. It has been suggested by some[2] that the IgE anti-IgA antibodies are responsible for anaphylaxis although others have disagreed.[3] Two patients who had reactions to conventional normal immunoglobulin preparations tolerated preparations with a low content of IgA.[2] Some manufacturers of normal immunoglobulin preparations recommend that they should not be used in patients with selective IgA deficiencies who have known antibody against IgA.

The IgE content of some preparations has also been suggested as a cause of hypersensitivity reactions[4] although this has been disputed.[5] Complement-activating IgG aggregates may also be involved although the anticomplementary activity of the products does not appear to be related to the incidence of adverse effects.[5]

1. Hachimi-Idrissi S, *et al.* Type III allergic reaction after infusion of immunoglobulins. *Lancet* 1990; **336:** 55.
2. Burks AW, *et al.* Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. *N Engl J Med* 1986; **314:** 560–4.
3. Hammarström L, Smith CIE. Anaphylaxis after administration of gamma globulin for hypogammaglobulinemia. *N Engl J Med* 1986; **315:** 519.
4. Tovo P-A, *et al.* IgE content of commercial intravenous IgG preparations. *Lancet* 1984; **i:** 458.
5. Newland AC, *et al.* IgE in intravenous IgG. *Lancet* 1984; **i:** 1406–7.

Infection. An association between use of certain intravenous immunoglobulin preparations and hepatitis C infections led to changes in manufacturing procedures and withdrawal of the affected products from the market.[1-3]

In addition, there has been a report[4] of a patient with AIDS who developed fifth disease (erythema infectiosum) after intravenous normal immunoglobulin treatment for infection with parvovirus. Paradoxically, there has also been a report[5] of life-threatening parvovirus B19 infection, resulting in pure red-cell aplasia and aggravation of hepatitis and fulminant disease, from the use of normal immunoglobulin to treat a patient with existing hepatic dysfunction caused by coxsackie B4 virus infection.

1. Quinti I, *et al.* Intravenous gammaglobulin may still infect patients. *BMJ* 1994; **308:** 856.
2. Bader J-M. HCV and Gammagard in France. *Lancet* 1994; **343:** 1628. Corrections. *ibid.*; **344:** 201 and 206.
3. Anonymous. Outbreak of hepatitis C associated with intravenous immunoglobulin administration—United States, October 1993–June 1994. *JAMA* 1994; **272:** 424–5.
4. French AL, *et al.* Fifth disease after immunoglobulin administration in an AIDS patient with parvovirus-induced red cell aplasia. *Am J Med* 1996; **101:** 108–9.
5. Hayakawa F, *et al.* Life-threatening human parvovirus B19 infection transmitted by intravenous immune globulin. *Br J Haematol* 2002; **118:** 1187–9.

Interactions

Normal immunoglobulin may interfere with the immune response to live viral vaccines. Such vaccines should therefore be given at least 3 weeks before, or 3 months after, normal immunoglobulin. This does not apply to yellow fever vaccine for immunoglobulins prepared in the UK, nor for booster doses of oral poliomyelitis vaccines. Where such an interval is impractical for immunisation preceding foreign travel it may have to be ignored.

Poliomyelitis vaccine. For a study indicating that normal immunoglobulin has no effect on the antibody response to oral poliomyelitis vaccine, see p.2233.

Uses and Administration

Normal immunoglobulin is available as two distinct preparations and formulations. One type of injection (Human Normal Immunoglobulin (Ph. Eur. 6.2) and Immune Globulin (USP 31)) generally containing 16% of protein is used for passive immunisation, and sometimes also for primary antibody deficiencies, and should only be given intramuscularly. The second type of preparation is formulated for intravenous use (Human Normal Immunoglobulin for Intravenous Administration (Ph. Eur. 6.2)) and is used in disorders such as primary antibody deficiencies and idiopathic thrombocytopenic purpura; solutions generally contain about 3 to 6% of protein, although some may contain up to 12%.

Doses of normal immunoglobulin often appear confusing, being expressed variously in terms of weight (protein or immunoglobulin G content) or in terms of volume to be given, and the two do not always appear to correspond. It should be remembered that there may be differences between intravenous preparations of normal immunoglobulin including differing IgA content and IgG subclass distribution.

Normal immunoglobulin, being derived from the pooled plasma of blood donors, contains antibodies to bacteria and viruses currently prevalent in the general population; in the UK, and also in some other countries, typical antibodies present include those against hepatitis A, measles, mumps, rubella, and varicella. Normal immunoglobulin therefore may be used to provide passive immunisation against such diseases.

Normal immunoglobulin may be used to control outbreaks of **hepatitis A**, the recommended intramuscular dose for close contacts being 250 mg in those under 10 years of age and 500 mg in older children and adults. It may also be used for prophylaxis against hepatitis A in immunocompromised patients if their response to hepatitis A vaccine is unlikely to be adequate.

Normal immunoglobulin may be used to prevent or possibly modify an attack of **measles** in children and adults at special risk (such as those who are immunocompromised) but should be given as soon as possible after contact with measles. In the UK recommended doses, given intramuscularly, for the prevention of an attack are 250 mg for those under 1 year of age,

500 mg for those aged 1 to 2 years, and 750 mg for those aged 3 years and over; to modify an attack, recommended doses are 100 mg for those under 1 year of age and 250 mg for older children.

Normal immunoglobulin does not prevent **rubella** infection and is not recommended for the protection of pregnant women exposed to rubella; it should only be considered where termination of pregnancy is unacceptable. The dose is 750 mg by intramuscular injection.

Normal immunoglobulin may be used in the management of patients with **primary antibody deficiencies** such as congenital agammaglobulinaemia, hypogammaglobulinaemia, or **immunocompromised patients** including those with immunodeficiency syndromes; the immunoglobulin is given to provide protection against infectious diseases that such patients may suffer. The intramuscular preparation has been used but the intravenous route is usually preferred as it is less painful for the doses required. Alternatively, the subcutaneous route may be used. For intravenous infusion the dose, expressed in terms of weight (protein or immunoglobulin G content), is usually 400 to 800 mg/kg initially, then 200 mg/kg every 3 weeks adjusted as necessary according to trough-immunoglobulin concentrations; the maintenance dose is usually 200 to 800 mg/kg per month. In patients with secondary immunodeficiency syndromes, doses of 200 to 400 mg/kg every 3 to 4 weeks have been recommended. Other dosage regimens have been used. Subcutaneous doses are 200 to 500 mg/kg as an initial loading dose (divided over several days), followed by maintenance doses at repeated intervals to achieve a cumulative monthly dose of 400 to 800 mg/kg. When infused intravenously, normal immunoglobulin should always be given very carefully and slowly with gradual increases in the rate of infusion.

For prophylaxis of infection after **bone marrow transplantation**, normal immunoglobulin is given intravenously in a dose of 500 mg/kg weekly, adjusted according to response.

Intravenous infusion of normal immunoglobulin is also used to raise the platelet count in patients with **idiopathic thrombocytopenic purpura**. Doses of 400 mg/kg are given daily for 2 to 5 consecutive days. Alternatively, a dose of 800 to 1000 mg/kg may be given on day 1 and repeated on day 3 if necessary. Further doses may be given as necessary.

For **Kawasaki disease**, normal immunoglobulin (used with aspirin) is given intravenously in a dose of 1.6 to 2 g/kg in divided doses over 2 to 5 days, or 2 g/kg given as a single dose. Similar doses of intravenous normal immunoglobulin have been tried in a range of disorders believed to have an auto-immune origin. The precise mode of action of normal immunoglobulin in such disorders is unknown.

For the treatment of **Guillain-Barré syndrome**, normal immunoglobulin is given intravenously in a dose of 400 mg/kg for 5 consecutive days, repeated every 4 weeks if required.

Administration. Oral dosage with normal immunoglobulins has been proposed to reduce the incidence and severity of gastrointestinal infections, particularly in patients with defective immune systems including neonates. Although the main immunoglobulin secreted into the gastrointestinal tract in subjects with a normal immune system is IgA, which is not present in large quantities in commercial normal immunoglobulins, beneficial responses, especially in viral infections, have been reported after oral use. Systematic reviews have not, however, supported routine use of oral immunoglobulin for the prevention or treatment of gastrointestinal infections.[1-3] Preparations of immunoglobulin A are available in some countries and have been tried, mainly in bacterial gastrointestinal infections.[4,5]

1. Mohan P, Haque K. Oral immunoglobulin for the prevention of rotavirus infection in low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 22/03/05).
2. Mohan P, Haque K. Oral immunoglobulin for the treatment of rotavirus diarrhoea in low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 22/03/05).
3. Foster J, Cole M. Oral immunoglobulin for preventing necrotizing enterocolitis in preterm and low birth-weight neonates. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 22/03/05).
4. Tjellström B, *et al.* Oral immunoglobulin A supplement in treatment of Clostridium difficile enteritis. *Lancet* 1993; **341:** 701–2.
5. Hammarström V, *et al.* Oral immunoglobulin treatment in Campylobacter jejuni enteritis. *Lancet* 1993; **341:** 1036.

Blood disorders. Intravenous normal immunoglobulins are used in the treatment of symptomatic severe acute and chronic idiopathic thrombocytopenic purpura (p.1505). Other blood disorders in which normal immunoglobulins have been tried include agranulocytosis[1] and haemolytic disease of the newborn (p.2204), haemolytic anaemias (p.1043), red cell aplasia caused by parvovirus B19 infections (see under Passive Immunisation, below), thrombotic thrombocytopenic purpura and haemolytic-uraemic syndrome (see Thrombotic Microangiopathies p.1076), and thrombocytopenia with a variety of causes.[2-10]

1. Fasth A. Immunoglobulin for neonatal agranulocytosis. *Arch Dis Child* 1986; **61:** 86–7.
2. Hoffman DM, *et al.* Human immunodeficiency virus-associated thrombocytopenia. *DICP Ann Pharmacother* 1989; **23:** 157–160.
3. Frame JN, *et al.* Correction of severe heparin-associated thrombocytopenia with intravenous immunoglobulin. *Ann Intern Med* 1989; **111:** 946–7.
4. Howrie DL, *et al.* Use of iv immune globulin for treatment of phenytoin-induced thrombocytopenia. *Clin Pharm* 1989; **8:** 734–7.
5. Landonio G, *et al.* HIV-related severe thrombocytopenia in intravenous drug users: prevalence, response to therapy in a medium-term follow-up, and pathogenic evaluation. *AIDS* 1990; **4:** 29–34.
6. Goulder P, *et al.* Intravenous immunoglobulin in virus associated haemophagocytic syndrome. *Arch Dis Child* 1990; **65:** 1275–7.
7. Larner AJ, *et al.* Life threatening thrombocytopenia in sarcoidosis: response to vincristine, human immunoglobulin, and corticosteroids. *BMJ* 1990; **300:** 317–19.
8. Ray JB, *et al.* Intravenous immune globulin for the treatment of presumed quinidine-induced thrombocytopenia. *DICP Ann Pharmacother* 1990; **24:** 693–5.
9. Salzman MB, Smith EM. Phenytoin-induced thrombocytopenia treated with intravenous immune globulin. *J Pediatr Hematol Oncol* 1998; **20:** 152–3.
10. Majluf-Cruz A, *et al.* Usefulness of a low-dose intravenous immunoglobulin regimen for the treatment of thrombocytopenia associated with AIDS. *Am J Hematol* 1998; **59:** 127–32.

Bowel disorders. Intravenous normal immunoglobulin may be beneficial[1-3] in inducing remission of Crohn's disease and ulcerative colitis and in antibiotic-associated or pseudomembranous colitis associated with *Clostridium difficile* infection.[4,5]

1. Rohr G, *et al.* Treatment of Crohn's disease and ulcerative colitis with 7S-immunoglobulin. *Lancet* 1987; **i:** 170.
2. Knoflach P, *et al.* Crohn disease and intravenous immunoglobulin G. *Ann Intern Med* 1990; **112:** 385–6.
3. Körber J, *et al.* A case of Crohn's disease with increased CD8 T-cell activation and remission during therapy with intravenous immunoglobulins. *Scand J Gastroenterol* 1998; **33:** 1113–17.
4. Leung DYM, *et al.* Treatment with intravenously administered gamma globulin of chronic relapsing colitis induced by Clostridium difficile toxin. *J Pediatr* 1991; **118:** 633–7.
5. Wilcox MH. Descriptive study of intravenous immunoglobulin for the treatment of recurrent Clostridium difficile diarrhoea. *J Antimicrob Chemother* 2004; **53:** 882–4.

Epilepsy. Normal immunoglobulins have sometimes been of benefit[1-3] in the treatment of children with intractable epilepsy, including Lennox-Gastaut syndrome or West's syndrome, but a review of the literature found that few well controlled studies had been conducted,[4] and a Canadian evidence-based guideline recommended against its use.[5] Although a positive trend in favour of intravenous immunoglobulin therapy for refractory epilepsy was noted in one double-blind controlled study[6] involving 61 patients, the results were not considered to be statistically significant.

1. Ariizumi M, *et al.* High dose gammaglobulin for intractable childhood epilepsy. *Lancet* 1983; **ii:** 162–3.
2. Sandstedt P, *et al.* Intravenous gammaglobulin for post-encephalitic epilepsy. *Lancet* 1984; **ii:** 1154–5.
3. van Engelen BGH, *et al.* High-dose intravenous immunoglobulin treatment in cryptogenic West and Lennox-Gastaut syndrome: an add-on study. *Eur J Pediatr* 1994; **153:** 762–9.
4. Duse M, *et al.* Intravenous immune globulin in the treatment of intractable childhood epilepsy. *Clin Exp Immunol* 1996; **104** (suppl 1): 71–6.
5. Feasby T, *et al.* Guidelines on the use of intravenous immune globulin for neurologic conditions. *Transfus Med Rev* 2007; **21** (suppl 1): S57–S107.
6. van Rijckevorsel-Harmant K, *et al.* Treatment of refractory epilepsy with intravenous immunoglobulins: results of the first double-blind/dose finding clinical study. *Int J Clin Lab Res* 1994; **24:** 162–6.

Hypogammaglobulinaemia. See under Primary Antibody Deficiency, below.

Immunocompromised patients. Immunodeficiency states may arise from primary disorders of the immune system, or, more commonly, they are secondary to immunosuppressive therapy, HIV infection, or haematological malignancies. Premature neonates may have deficits in their immune systems due to their immaturity; placental transfer of maternal antibodies usually occurs after about 32 weeks of gestation. Such patients and neonates may be deficient in gammaglobulins and they could potentially benefit from the use of normal immunoglobulins to address their increased susceptibility to infection. For information on the use of immunoglobulins in specific conditions, see the following sections and under Neonatal Infection, below.

Bone marrow transplantation. Normal immunoglobulin is used in patients undergoing allogeneic bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p.1811) with the aim of decreasing the incidence of bacterial and of symptomatic CMV infection, and that of graft-versus-host disease. Prophylaxis and treatment of CMV infection and prophylaxis of graft-versus-host disease are the indications with most clinical support, although there have been few prospective, randomised, controlled studies and these have had small or heterogeneous populations and varying endpoints.[1] Overall survival[2] or overall incidence of CMV infection[2,3] has not decreased. A combination of normal immunoglobulin and ganciclovir appears to improve the outcome of CMV pneumonia subsequent to bone marrow transplantation.[4] However, no patients treated with normal immunoglobulin alone survived and ganciclovir monotherapy may be equally effective, thus casting some doubt on the effectiveness of normal immunoglobulin.[1] Cytomegalovirus immunoglobulins (p.2208) may be more appropriate for the specific prophylaxis and treatment of CMV infections.

Intravenous immunoglobulin therapy has been found to be ineffective in preventing infections in patients receiving autologous bone marrow transplants[5] and may have contributed to an increased incidence of fatal hepatic veno-occlusive disease.

Normal immunoglobulin has been associated with a reduced frequency of acute graft-versus-host disease,[2] possibly as a result of a direct immunomodulatory effect, but this has only been found in one study, and there are no studies showing efficacy of normal immunoglobulin in chronic graft-versus-host disease.[1] Furthermore, there is some suggestion that extended use of normal immunoglobulin for graft-versus-host disease prevention may impair recovery of humoral immunity.[1] Overall, the role of normal immunoglobulin for graft-versus-host disease has yet to be clearly defined.

1. Sokos DR, *et al.* Intravenous immunoglobulin: appropriate indications and uses in hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2002; **8:** 117–30.
2. Sullivan KM, *et al.* Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. *N Engl J Med* 1990; **323:** 705–12.
3. Winston DJ, *et al.* Intravenous immune globulin for prevention of cytomegalovirus infection and interstitial pneumonia after bone marrow transplantation. *Ann Intern Med* 1987; **106:** 12–18.
4. Emanuel D, *et al.* Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of ganciclovir and high-dose intravenous immune globulin. *Ann Intern Med* 1988; **109:** 777–82.
5. Wolff SN, *et al.* High-dose weekly intravenous immunoglobulin to prevent infections in patients undergoing autologous bone marrow transplantation or severe myelosuppressive therapy: a study of the American Bone Marrow Transplant Group. *Ann Intern Med* 1993; **118:** 937–42.

Malignancies. Hypogammaglobulinaemia and the effects of treatment may increase the susceptibility to infection of patients with *chronic lymphocytic leukaemia*.[1] In a study[2] of 81 patients with chronic lymphocytic leukaemia considered to be at an increased risk of infection, intravenous normal immunoglobulin 400 mg/kg given every 3 weeks for one year reduced the incidence of bacterial infection compared with saline placebo. The incidence of viral and fungal infections was not affected. A study in 34 patients[3] suggested that a dose of normal immunoglobulin 250 mg/kg per month was adequate for routine prophylaxis in most patients. Beneficial effects on infection rates have been reported in patients with *multiple myeloma* receiving normal immunoglobulins.[4]

1. Wierda WG. Immunologic monitoring in chronic lymphocytic leukaemia. *Curr Oncol Rep* 2003; **5:** 419–25.
2. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia: a randomized, controlled clinical trial. *N Engl J Med* 1988; **319:** 902–7.
3. Chapel H, *et al.* Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. *Br J Haematol* 1994; **88:** 209–12.
4. Chapel HM, *et al.* Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. *Lancet* 1994; **343:** 1059–63.

Primary antibody deficiency. There are 3 major forms of primary antibody deficiency: X-linked agammaglobulinaemia (XLA, Bruton's agammaglobulinaemia), common variable immunodeficiency (CVID) which includes IgG subclass and specific antibody deficiencies, and selective IgA deficiency. The disease is characterised by a wide range of infective complications as well as auto-immune disorders. Management is by replacement therapy with normal immunoglobulin accompanied by appropriate antimicrobial therapy for breakthrough infections.[1-4] Immunisation against infection is of no value and is contra-indicated for live viral vaccines.

Normal immunoglobulin was traditionally given by the intramuscular route. However, the maximum dose that could be reasonably given by this route was 25 mg/kg weekly, and it was therefore only satisfactory for patients with mild disease.[5] The introduction of intravenous preparations of normal immunoglobulin allowed high doses to be used in those with severe disease. This route should therefore be used for all patients with XLA and for patients with CVID who have more than mild disease.[1] The use of intravenous normal immunoglobulin in IgG subclass deficiency, with or without IgA deficiency, or in specific antibody deficiency is successful, though less well established. The dose and frequency of administration of intravenous normal immunoglobulin is variable and should be adjusted to prevent breakthrough infection. Most patients require 200 to 600 mg/kg every 2 or 3 weeks to maintain optimum protection.[5] In one study,[6] doses of between 260 and 1120 mg/kg every 3 weeks were necessary to maintain residual serum IgG concentrations above 500 mg/dL. These doses were found to be effective in reducing the incidence of severe acute bacterial infections and pulmonary insufficiency in children with XLA. Surgical procedures should be covered with additional normal immunoglobulin and appropriate prophylactic antibacterials. Home treatment with intravenous normal immunoglobulin has been used successfully in sev-

eral countries in both adults and children.[5,7-10] Adverse reactions have been few and generally mild.[5,8,9] They are most likely to occur during the first infusion and during intercurrent illness, and may be precipitated by a high infusion rate.[10] Long-term treatment of children with antibody deficiencies with intravenous normal immunoglobulin has been shown to lead to normal growth and similar rates of infection to those found in non-immunodeficient children.[11]

Immunoglobulin replacement can alternatively be given by subcutaneous infusion as an alternative to intravenous therapy.[2,4,12,13] The intraventricular route has been of benefit in some patients with echovirus encephalitis.[5,14]

1. Carrock Sewell WA, *et al.* Therapeutic strategies in common variable immunodeficiency. *Drugs* 2003; **63:** 1359–71.
2. Schwartz SA. Intravenous immunoglobulin treatment of immunodeficiency disorders. *Pediatr Clin North Am* 2000; **47:** 1355–69.
3. Empson M, *et al.* The assessment and management of primary antibody deficiency. *N Z Med J* 2004; **117:** U914.
4. Durandy A, *et al.* Immunoglobulin replacement therapy in primary antibody deficiency diseases—maximizing success. *Int Arch Allergy Immunol* 2005; **136:** 217–29.
5. Spickett GP, *et al.* Primary antibody deficiency in adults. *Lancet* 1991; **337:** 281–4.
6. Quartier P, *et al.* Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. *J Pediatr* 1999; **134:** 589–96.
7. Ochs HD, *et al.* Intravenous immunoglobulin home treatment for patients with primary immunodeficiency diseases. *Lancet* 1986; **i:** 610–11.
8. Ryan A, *et al.* Home intravenous immunoglobulin therapy for patients with primary hypogammaglobulinaemia. *Lancet* 1988; **ii:** 793.
9. Kobayashi RH, *et al.* Home self-administration of intravenous immunoglobulin therapy in children. *Pediatrics* 1990; **85:** 705–9.
10. Chapel HM. Consensus on diagnosis and management of primary antibody deficiencies. *BMJ* 1994; **308:** 581–5.
11. Skull S, Kemp A. Treatment of hypogammaglobulinaemia with intravenous immunoglobulin, 1973-93. *Arch Dis Child* 1996; **74:** 527–30.
12. Gardulf A. Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route. *BioDrugs* 2007; **21:** 105–16.
13. Helbert M, Farragher A. Subcutaneous immunoglobulin for patients with antibody deficiency. *Br J Hosp Med* 2007; **68:** 206–10.
14. Erlendsson K, *et al.* Successful reversal of echovirus encephalitis in x-linked hypogammaglobulinemia by intraventricular administration of immunoglobulin. *N Engl J Med* 1985; **312:** 351–30.

Kawasaki disease. Kawasaki disease, also known as mucocutaneous lymph node syndrome of childhood, occurs mainly in children under 5 years of age. It is epidemic and endemic worldwide but is a particular problem in Japan. Kawasaki disease presents with high fever which persists for at least 5 days and may be followed by bilateral conjunctivitis, changes in the oropharyngeal mucosa, signs of vasculitis in the extremities, rash, and cervical lymphadenopathy. The major complications of Kawasaki disease are cardiac effects including coronary artery aneurysm, aortic or mitral incompetence, myocarditis, and pericarditis with effusion. The cause of the disease is unknown, although an infective aetiology has been suggested. Early diagnosis, expert cardiac assessment, and immediate treatment are essential for improved outcome.

Treatment aims to reduce inflammation, particularly in the coronary arterial wall and myocardium, and therefore prevent the development of cardiac complications. Long-term antiplatelet treatment is given as necessary to prevent coronary thrombosis.

Initial treatment is with aspirin and normal immunoglobulin.[1,2] Despite the anti-inflammatory and antiplatelet properties of aspirin it does not appear to lower the incidence of coronary abnormalities in Kawasaki disease when used alone; however, high-dose aspirin and normal immunoglobulin appear to possess an additive anti-inflammatory effect when used together and a decreased incidence of coronary-artery abnormalities has been found after such a combination as compared with aspirin alone. Treatment should begin if possible within 10, and preferably within 7, days of the onset of illness. Treatment before day 5 appears to offer no advantage in preventing cardiac sequelae than treating from days 5 to 7, but it may be associated with an increased need for re-treatment with normal immunoglobulin. Treatment should be given to children presenting after the tenth day of illness if they have either persistent unexplained fever or aneurysms with ongoing systemic inflammation.[2]

Normal immunoglobulin has been given by intravenous infusion in divided doses over 2 to 5 days, but high-dose administration as a single dose is now recommended; a meta-analysis[3] and a systematic review[4] have concluded that single-dose therapy is associated with a lower incidence of coronary abnormalities after 30 days than multiple-dose treatment. The optimum dosage and duration of treatment with aspirin is not yet established, but the usual practice is to use an anti-inflammatory regimen until the fever has settled and then to convert to an antithrombotic regimen. A few patients fail to respond to treatment with aspirin and normal immunoglobulin. A small study[5] suggested that re-treatment with normal immunoglobulin may be considered for those with persistent or recurring fever.

The use of corticosteroids remains controversial.[1] They have been given in some centres[6] but since the introduction of immunoglobulin therapy they have not been routinely used as there is a risk that they may exacerbate coronary artery aneurysms. Nevertheless, their use has received renewed attention; randomised studies comparing the adjunctive use of corticosteroids with standard therapy alone have suggested they may be of benefit.[7,8]

Alternative suggested drugs for patients refractory to normal immunoglobulin include ulinastatin,[9] which has been used for adjunctive therapy in Japan, but its effectiveness remains currently unproven. Abciximab has been used to treat patients with large coronary aneurysms; in one study,[10] patients given abciximab in addition to standard therapy showed a greater regression in aneurysm diameter. Other treatments under investigation include infliximab[11] in patients unresponsive to initial normal immunoglobulin and the use of cyclophosphamide with corticosteroids in particularly refractory cases.[2]

Long-term management. Aspirin should be continued for 6 to 8 weeks after the onset of illness and then stopped if there are no coronary abnormalities.[1,2] Some practitioners use aspirin and dipyridamole as antithrombotic therapy although it is not known whether this provides benefit over aspirin alone. Dipyridamole may be used as an alternative antithrombotic agent for patients who cannot tolerate aspirin. Aspirin is usually continued for at least one year if coronary abnormalities are present and should be continued indefinitely if coronary aneurysms persist. Anticoagulation with warfarin or heparin in addition to aspirin may be necessary in some patients such as those with giant or multiple aneurysms.

1. Burns JC, Glodé MP. Kawasaki syndrome. *Lancet* 2004; **364:** 533–44.
2. Newburger JW, *et al.* Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics* 2004; **114:** 1708–33. Correction. *ibid.* 2005; **115:** 1118. Also available at: http://pediatrics.aappublications.org/cgi/reprint/114/6/1708.pdf (accessed 25/05/06) Also published in *Circulation* 2004; **110:** 2747–71. Also available at: http://circ.ahajournals.org/cgi/reprint/110/17/2747.pdf (accessed 12/04/07)
3. Durongpisitkul K, *et al.* The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. *Pediatrics* 1995; **96:** 1057–61.
4. Oates-Whitehead RM, *et al.* Intravenous immunoglobulin for the treatment of Kawasaki disease in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 24/03/05).
5. Sundel RP, *et al.* Gamma globulin re-treatment in Kawasaki disease. *J Pediatr* 1993; **123:** 657–9.
6. Shinohara M, *et al.* Corticosteroids in the treatment of the acute phase of Kawasaki disease. *J Pediatr* 1999; **135:** 465–9.
7. Sundel RP, *et al.* Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial. *J Pediatr* 2003; **142:** 611–16.
8. Okada Y, *et al.* Effect of corticosteroids in addition to intravenous gamma globulin therapy on serum cytokine levels in the acute phase of Kawasaki disease in children. *J Pediatr* 2003; **143:** 363–7.
9. Zaitsu M, *et al.* Ulinastatin, an elastase inhibitor, inhibits the increased mRNA expression of prostaglandin H2 synthase-type 2 in Kawasaki disease. *J Infect Dis* 2000; **181:** 1101–9.
10. Williams RV, *et al.* Does abciximab enhance regression of coronary aneurysms resulting from Kawasaki disease? Abstract: *Pediatrics* 2002; **109:** 132. Full version: http://pediatrics.aappublications.org/cgi/content/full/109/1/e4 (accessed 24/03/05)
11. Burns JC, *et al.* Infliximab treatment for refractory Kawasaki syndrome. *J Pediatr* 2005; **146:** 662–7.

Kidney disorders. Treatment with normal immunoglobulin has been of benefit in some patients with haemolytic-uraemic syndrome and in those with lupus nephritis (see under Musculoskeletal and Nerve Disorders, below). For mention of the use of normal immunoglobulin in IgA nephropathy, see Glomerular Kidney Disease, p.1504.

Musculoskeletal and nerve disorders. High-dose intravenous normal immunoglobulin has been tried with some benefit in various disorders of the nerves, muscles, joints, and connective tissues which may have an auto-immune basis.[1] These include multiple sclerosis,[2-4] chronic inflammatory demyelinating polyneuropathy,[5,6] polymyositis and dermatomyositis,[7-12] myasthenia gravis,[13-17] stiff-man syndrome,[18-22] chronic systemic juvenile arthritis,[23-25] SLE[26] including lupus nephritis,[27] Guillain-Barré syndrome (see below), and motor neurone disease (see also below). Guidelines issued by an expert committee in Canada[28] included recommendations on the use and dose of normal immunoglobulin for acute disseminated encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, dermatomyositis and polymyositis, Guillain-Barré syndrome, Lambert-Eaton myasthenic syndrome and myasthenia gravis, multifocal motor neuropathy, multiple sclerosis, opsoclonus-myoclonus, neuropsychiatric disorders associated with streptococcal infections in children, short-term management of Rasmussen's encephalitis, and stiff man syndrome.

1. Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. *JAMA* 2004; **291:** 2367–75.
2. Fazekas F, *et al.* Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis. *Lancet* 1997; **349:** 589–93.
3. Hommes OR, *et al.* Intravenous immunoglobulin in secondary progressive multiple sclerosis: randomised placebo-controlled trial. *Lancet* 2004; **364:** 1149–56.
4. Achiron A, *et al.* Intravenous immunoglobulin treatment following the first demyelinating event suggestive of multiple sclerosis: a randomized, double-blind, placebo-controlled trial. *Arch Neurol* 2004; **61:** 1515–20.
5. Dalakas MC. Mechanisms of action of IVIg and therapeutic considerations in the treatment of acute and chronic demyelinating neuropathies. *Neurology* 2002; **59** (suppl 6): S13–S21.
6. Brannagan TH. Intravenous gammaglobulin (IVIg) for treatment of CIDP and related immune-mediated neuropathies. *Neurology* 2002; **59** (suppl 6): S33–S40.
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8. Lang BA, *et al.* Treatment of dermatomyositis with intravenous gammaglobulin. *Am J Med* 1991; **91:** 169–72.
9. Dalakas MC, *et al.* A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 1993; **329:** 1993–2000.
10. Brownell AKW. Intravenous immune globulin for dermatomyositis. *N Engl J Med* 1994; **330:** 1392.
11. Collet E, *et al.* Juvenile dermatomyositis: treatment with intravenous gammaglobulin. *Br J Dermatol* 1994; **130:** 231–4.
12. Cherin P, *et al.* Results and long-term followup of intravenous immunoglobulin infusions in chronic, refractory polymyositis: an open study with thirty-five adult patients. *Arthritis Rheum* 2002; **46:** 467–74.
13. Bassan H, *et al.* High-dose intravenous immunoglobulin in transient neonatal myasthenia gravis. *Pediatr Neurol* 1998; **18:** 181–3.
14. Jongen JLM, *et al.* High-dose intravenous immunoglobulin therapy for myasthenia gravis. *J Neurol* 1998; **245:** 26–31.
15. Howard JF. Intravenous immunoglobulin for the treatment of acquired myasthenia gravis. *Neurology* 1998; **51** (suppl 5): S30–S36.
16. Selcen D, *et al.* High-dose intravenous immunoglobulin therapy in juvenile myasthenia gravis. *Pediatr Neurol* 2000; **22:** 40–3.
17. Zinman L, *et al.* IV immunoglobulin in patients with myasthenia gravis: a randomized controlled trial. *Neurology* 2007; **68:** 837–41.
18. Karlson EW, *et al.* Treatment of stiff-man syndrome with intravenous immune globulin. *Arthritis Rheum* 1994; **37:** 915–18.
19. Amato AA, *et al.* Treatment of stiff-man syndrome with intravenous immunoglobulin. *Neurology* 1994; **44:** 1652–4.
20. Barker RA, Marsden CD. Successful treatment of stiff man syndrome with intravenous immunoglobulin. *J Neurol Neurosurg Psychiatry* 1997; **62:** 426–7.
21. Khanlou H, Eiger G. Long-term remission of refractory stiff-man syndrome after treatment with intravenous immunoglobulin. *Mayo Clin Proc* 1999; **74:** 1231–2.
22. Dalakas MC, *et al.* High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med* 2001; **345:** 1870–6.
23. Groothoff JW, van Leeuwen EF. High dose intravenous gammaglobulin in chronic systemic juvenile arthritis. *BMJ* 1988; **296:** 1362–3.
24. Giannini EH, *et al.* Intravenous immunoglobulin in the treatment of polyarticular juvenile rheumatoid arthritis: a phase I/II study. *J Rheumatol* 1996; **23:** 919–24.
25. Uziel Y, *et al.* Intravenous immunoglobulin therapy in systemic onset juvenile rheumatoid arthritis: a followup study. *J Rheumatol* 1996; **23:** 910–18.
26. Francioni C, *et al.* Long term IV Ig treatment in systemic lupus erythematosus. *Clin Exp Rheumatol* 1994; **12:** 163–8.
27. Lin C-Y, *et al.* Improvement of histological and immunological change in steroid and immunosuppressive drug-resistant lupus nephritis by high-dose intravenous gamma globulin. *Nephron* 1989; **53:** 303–10.
28. Feasby T, *et al.* Guidelines on the use of intravenous immune globulin for neurologic conditions. *Transfus Med Rev* 2007; **21** (suppl 1): S57–S107.

GUILLAIN-BARRÉ SYNDROME. Guillain-Barré syndrome[1] (acute idiopathic inflammatory polyneuropathy; acute idiopathic demyelinating neuropathy; acute infectious polyneuropathy) may follow an infection or, more rarely, immunisation, but very often no predisposing factor can be identified. An association with infection with *Campylobacter jejuni* has been suggested,[2] but the syndrome is also commonly associated with infection with CMV, Epstein-Barr virus, and *Mycoplasma pneumoniae*.[1] Reversible demyelination results in pain and progressive flaccid paralysis. An auto-immune aetiology seems likely. Severely affected patients require cardiovascular monitoring and respiratory support if respiratory muscles are affected or autonomic instability is present. Corticosteroids have been given but are generally considered to be of little value[3] (see Polyneuropathies, p.1511). Plasma exchange (see p.1076) is effective if given early,[4] but is not universally available and is not suitable for all patients. A systematic review[5] has concluded that use of normal immunoglobulins is at least as effective as plasma exchange, but that there is no advantage from combining the two forms of treatment. Deterioration has also been noted in some patients after immunoglobulin therapy,[6,7] although one study[8] found that the incidence of relapse was greater after plasma exchange than after normal immunoglobulin.

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3. Hughes RAC, van der Meché FGA. Corticosteroids for Guillain-Barré syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 10/06/08).
4. Raphaël JC, *et al.* Plasma exchange for Guillain-Barré syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 29/03/05).
5. Hughes RAC, *et al.* Intravenous immunoglobulin for Guillain-Barré syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 10/09/08).
6. Irani DN, *et al.* Relapse in Guillain-Barré syndrome after treatment with human immune globulin. *Neurology* 1993; **43:** 872–5.
7. Castro LHM, Ropper AH. Human immune globulin infusion in Guillain-Barré syndrome: worsening during and after treatment. *Neurology* 1993; **43:** 1034–6.
8. Romano JG, *et al.* Relapses in the Guillain-Barré syndrome after treatment with intravenous immune globulin or plasma exchange. *Muscle Nerve* 1998; **21:** 1327–30.

MOTOR NEURONE DISEASE. Several studies and a systematic review have shown normal immunoglobulins to be of benefit in the treatment of multifocal motor neuropathy, a form of motor neurone disease (p.2380) associated with anti-GM_1 antibody formation.[1-7] In most patients, however, improvement has to

be maintained with periodic infusion and some become less responsive to therapy over time, requiring higher doses. A retrospective study[8] of 10 patients with multifocal motor neuropathy treated with normal immunoglobulins showed that while the initial response could be maintained for several years, efficacy decreased during prolonged treatment even when doses were progressively adjusted. During the first few years of therapy, increased dosage restored the effectiveness of normal immunoglobulins, but was found to be less able to do so later in follow up.

1. Van den Berg LH, *et al.* Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 1995; **59:** 248–52.
2. Meucci N, *et al.* Long term effect of intravenous immunoglobulins and oral cyclophosphamide in multifocal motor neuropathy. *J Neurol Neurosurg Psychiatry* 1997; **63:** 765–9.
3. Van den Berg LH, *et al.* The long-term effect of intravenous immunoglobulin treatment in multifocal motor neuropathy. *Brain* 1998; **121:** 421–8.
4. Ellis CM, *et al.* Use of human intravenous immunoglobulin in lower motor neuron syndromes. *J Neurol Neurosurg Psychiatry* 1999; **67:** 15–19.
5. Federico P, *et al.* Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study. *Neurology* 2000; **55:** 1256–62.
6. Léger JM, *et al.* Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. *Brain* 2001; **124:** 145–53.
7. van Schaik IN, *et al.* Intravenous immunoglobulin for multifocal motor neuropathy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 14/02/06).
8. Terenghi F, *et al.* How long is IVIg effective in multifocal motor neuropathy? *Neurology* 2004; **62:** 666–8.

Neonatal disorders. ***HAEMOLYTIC DISEASE OF THE NEWBORN.*** For a discussion of haemolytic disease of the newborn and its management, including the use of intravenous immunoglobulin as an alternative to exchange transfusions in affected pregnancies, see p.2204.

NEONATAL INFECTION. Sepsis is a serious problem in premature infants despite appropriate antimicrobial therapy. Preterm infants are born with low serum-immunoglobulin concentrations which decrease over the next several weeks of life. There is also a deficiency of antibodies to specific organisms such as group B streptococci, *Staphylococcus epidermidis*, and *Escherichia coli*.

Some, but not all, studies suggest that prophylactic use of intravenous normal immunoglobulin in premature infants shortly after birth can decrease the incidence of septicaemia.[1] Aspects of the methodology of these studies have, however, been criticised[2] and a systematic review[3] concluded that prophylactic use of intravenous immunoglobulin for prevention of infection in preterm or low birth-weight neonates was of at best marginal benefit only, and of no benefit in preventing sepsis, and did not recommend routine use. Some benefit has been seen after use of intravenous immunoglobulin to treat infants with suspected sepsis[1] and it may improve the response to antibacterials,[4] although a further systematic review[5] found insufficient evidence to support routine use in infants with suspected, or subsequently proved, neonatal infection.

The optimum dosage of intravenous immunoglobulin is not established. A prophylactic dose of 500 mg/kg on admission repeated every 1 to 2 weeks has been suggested for units where infection is common in very low birth-weight infants.[1] Others have suggested adjusting the dose to maintain a specified serum-immunoglobulin concentration. Alternatively, normal immunoglobulin could be given only to infants with immunoglobulin concentrations below a certain level, or be reserved for immediate use in those who become ill with suspected sepsis.[1]

Normal immunoglobulin cannot protect against all types of infection. Normal immunoglobulin preparations from different manufacturers may have, for a specific pathogen, differing levels of specific antibody and differing levels of functional activity or there may be lot-to-lot variability in functional activity for normal immunoglobulin from a specific manufacturer. Such variability, resulting in low concentrations of functional antibodies in the 4 batches of immunoglobulins used in the National Institute of Child Health Study,[6] was held responsible for the lack of demonstrable effectiveness of immunoglobulins in that study, one of the largest to date.

1. Whitelaw A. Treatment of sepsis with IgG in very low birthweight infants. *Arch Dis Child* 1990; **65:** 347–8.
2. Noya FJD, Baker CJ. Intravenously administered immune globulin for premature infants: a time to wait. *J Pediatr* 1989; **115:** 969–71.
3. Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 29/03/05).
4. Christensen RD, *et al.* Effect on neutrophil kinetics and serum opsonic capacity of intravenous administration of immune globulin to neonates with clinical signs of early-onset sepsis. *J Pediatr* 1991; **118:** 606–14.
5. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 29/03/05).
6. Fanaroff AA, *et al.* A controlled trial of intravenous immune globulin to reduce nosocomial infections in very-low-birthweight infants. *N Engl J Med* 1994; **330:** 1107–13.

Neuropsychiatric disorders. Benefit has been demonstrated from plasma exchange or intravenous immunoglobulin in children with exacerbations of obsessive-compulsive disorder or tic disorders including Tourette's syndrome associated with streptococcal infection.[1] These results suggested that these disorders may respond to immunomodulatory therapy in a subgroup of patients with paediatric auto-immune neuropsychiatric disorders associated with streptococcal infections (PANDAS), believed to be due to cross-reaction of antistreptococcal antibodies with neural tissue. In a double-blind, placebo-controlled study[2] of the use of normal immunoglobulins in 30 patients with tic disorders, despite initial improvement compared with placebo over 8 weeks no significant differences were found in the severity of obsessions and compulsions beyond this time.

1. Perlmutter SJ, *et al.* Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet* 1999; **354:** 1153–8.
2. Hoekstra PJ, *et al.* Lack of effect of intravenous immunoglobulins on tics: a double-blind placebo-controlled study. *J Clin Psychiatry* 2004; **65:** 537–42.

Passive immunisation. ***CMV INFECTION.*** See Bone Marrow Transplantation, under Immunocompromised Patients, above.

HEPATITIS C. In a randomised, placebo-controlled study[1] in seronegative sexual partners of patients positive for antibody to hepatitis C, normal immunoglobulin given intramuscularly every 2 months was found to significantly reduce the incidence of subsequent seroconversion. One of 450 subjects who received normal immunoglobulin became seropositive during follow-up compared with 6 of 449 who had received placebo.

1. Piazza M, *et al.* Sexual transmission of the hepatitis C virus and efficacy of prophylaxis with intramuscular immune serum globulin: a randomized controlled trial. *Arch Intern Med* 1997; **157:** 1537–44.

PARVOVIRUS B19 INFECTION. Persistent infection with human parvovirus B19 can cause red cell aplasia with resultant anaemia, particularly in immunocompromised patients. Normal immunoglobulins contain antibodies able to neutralise parvovirus B19 and have been used in various groups of infected patients.[1] Resolution of anaemia and clearance of parvovirus B19 from the circulation have been reported after use of normal immunoglobulin in a patient who had had red cell aplasia for 10 years.[2] Normal immunoglobulin was given by intravenous infusion in a dose of 400 mg/kg daily for 10 days and then periodically for several months. Successful treatment of anaemia due to parvovirus B19-induced red cell aplasia with plasmapheresis and intravenous immunoglobulin has been described in a liver transplant recipient.[3] Efficacy has also been found in recipients of other solid-organ transplants including heart, kidney, and lung.[1] Clearance of parvovirus B19 from the circulation has been reported in patients who also have AIDS, but the presence of concomitant opportunistic infections may prevent resolution of the anaemia.[4,5]

Normal immunoglobulin given to patients with parvovirus B19-associated chronic fatigue syndrome has also resulted in clearance of the virus from the circulation and resolution of symptoms.[6,7]

Beneficial responses to intravenous immunoglobulin have also been reported in a few patients with parvovirus B19 infections associated with vasculitic syndromes.[8,9]

1. Mouthon L, *et al.* Intravenous immunoglobulins in autoimmune- or parvovirus B19-mediated pure red-cell aplasia. *Autoimmun Rev* 2005; **4:** 264–9.
2. Kurtzman G, *et al.* Pure red-cell aplasia of 10 years' duration due to persistent parvovirus B19 infection and its cure with immunoglobulin therapy. *N Engl J Med* 1989; **321:** 519–23.
3. Ramage JK, *et al.* Parvovirus B19-induced red cell aplasia treated with plasmapheresis and immunoglobulin. *Lancet* 1994; **343:** 667–8.
4. Frickhofen N, *et al.* Persistent B19 parvovirus infection in patients infected with human immunodeficiency virus type 1 (HIV-1): a treatable cause of anemia in AIDS. *Ann Intern Med* 1990; **113:** 926–33.
5. Bowman CA, *et al.* Red cell aplasia associated with human parvovirus B19 and HIV infection: failure to respond clinically to intravenous immunoglobulin. *AIDS* 1990; **4:** 1038–9.
6. Kerr JR, *et al.* Successful intravenous immunoglobulin therapy in 3 cases of parvovirus B19-associated chronic fatigue syndrome. *Clin Infect Dis* 2003; **36:** e100–e106. Full version: http://www.journals.uchicago.edu/doi/pdf/10.1086/374666 (accessed 15/07/08)
7. McGhee SA, *et al.* Persistent parvovirus-associated chronic fatigue treated with high dose intravenous immunoglobulin. *Pediatr Infect Dis J* 2005; **24:** 272–4.
8. Finkel TH, *et al.* Chronic parvovirus B19 infection and systemic necrotising vasculitis: opportunistic infection or aetiological agent? *Lancet* 1994; **343:** 1255–8.
9. Viguier M, *et al.* Treatment of parvovirus B19-associated polyarteritis nodosa with intravenous immune globulin. *N Engl J Med* 2001; **344:** 1481–2.

TOXIC SHOCK SYNDROME. For a discussion of toxic shock syndrome and its treatment, including reference to clinical improvement after administration of intravenous normal immunoglobulins, see p.196.

Pregnancy. Fetal loss has been attributed in some cases to the presence of antiphospholipid antibodies (lupus anticoagulant and anticardiolipin) in the mother. Successful pregnancy outcome has been reported after use of intravenous normal immunoglobulin during pregnancy to a few such women.[1]

1. Triolo G, *et al.* IVIG in APS pregnancy. *Lupus* 2004; **13:** 731–5.

Skin disorders. Normal immunoglobulins have been tried in a few patients with blistering skin diseases.[1-3] The usual treatment for pemphigus and pemphigoid is with systemic corticosteroids; normal immunoglobulins in high doses have produced generally transient improvement when used alone,[4] although corticosteroid-sparing effects have been reported.[5,6] There have been case reports of patients with severe epidermolysis bullosa acquisita responding to therapy with high-dose intravenous immunoglobulins.[7,8] Studies have been conducted into the use of high-dose normal immunoglobulin for the treatment of other blistering conditions including Stevens-Johnson syndrome and toxic epidermal necrolysis.[9] One retrospective analysis[10] of 48 consecutive cases of toxic epidermal necrolysis found a beneficial effect with survival in 42 patients. In contrast, a prospective open study[11] in 34 consecutive patients admitted to hospital with Stevens-Johnson syndrome or toxic epidermal necrolysis suggested that normal immunoglobulin might actually be associated with an increase in mortality. Further retrospective analyses, however, did find a reduction in mortality in 16 consecutive patients admitted with toxic epidermal necrolysis[12] and in 7 children with Stevens-Johnson syndrome.[13] Normal immunoglobulin has also produced benefit in patients with pyoderma gangrenosum.[14-17]

Clinical benefit was noted in 9 of 10 patients with auto-immune chronic urticaria who were given a 5-day course of intravenous immunoglobulins, 2 of whom had prolonged remission over 3 years of follow-up.[18] Benefit has also occurred after intravenous immunoglobulin therapy for atopic dermatitis[19] and psoriasis.[20]

1. Harman KE, Black MM. High-dose intravenous immune globulin for the treatment of autoimmune blistering diseases: an evaluation of its use in 14 cases. *Br J Dermatol* 1999; **140:** 865–74.
2. Ahmed AR, Dahl MV. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. *Arch Dermatol* 2003; **139:** 1051–9.
3. Ahmed AR. Use of intravenous immunoglobulin therapy in autoimmune blistering diseases. *Int Immunopharmacol* 2006; **6:** 557–78.
4. Godard W, *et al.* Bullous pemphigoid and intravenous gammaglobulin. *Ann Intern Med* 1985; **103:** 965.
5. Beckers RCY, *et al.* Adjuvant high-dose intravenous gammaglobulin in the treatment of pemphigus and bullous pemphigoid: experience in six patients. *Br J Dermatol* 1995; **133:** 289–93.
6. Ahmed AR. Intravenous immunoglobulin therapy for patients with bullous pemphigoid unresponsive to conventional immunosuppressive treatment. *J Am Acad Dermatol* 2001; **45:** 825–35.
7. Mohr C, *et al.* Successful treatment of epidermolysis bullosa acquisita using intravenous immunoglobulins. *Br J Dermatol* 1995; **132:** 824–6.
8. Gourgiotou K, *et al.* Epidermolysis bullosa acquisita: treatment with intravenous immunoglobulins. *J Eur Acad Dermatol Venereol* 2002; **16:** 77–80.
9. Mittmann N, *et al.* Intravenous immunoglobulin use in patients with toxic epidermal necrolysis and Stevens-Johnson syndrome. *Am J Clin Dermatol* 2006; **7:** 359–68.
10. Prins C, *et al.* Treatment of toxic epidermal necrolysis with high-dose intravenous immunoglobulins: multicenter retrospective analysis of 48 consecutive cases. *Arch Dermatol* 2003; **139:** 26–32.
11. Bachot N, *et al.* Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. *Arch Dermatol* 2003; **139:** 33–6.
12. Trent JT, *et al.* Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: the University of Miami experience. *Arch Dermatol* 2003; **139:** 39–43.
13. Metry DW, *et al.* Use of intravenous immunoglobulin in children with Stevens-Johnson syndrome and toxic epidermal necrolysis: seven cases and review of the literature. *Pediatrics* 2003; **112:** 1430 6.
14. Dirschka T, *et al.* Successful treatment of pyoderma gangrenosum with intravenous human immunoglobulin. *J Am Acad Dermatol* 1998; **39:** 789–90.
15. Hagman JH, *et al.* The use of high-dose immunoglobulin in the treatment of pyoderma gangrenosum. *J Dermatol Treat* 2001; **12:** 19–22.
16. Dobson CM, *et al.* Superficial granulomatous pyoderma treated with intravenous immunoglobulin. *J Am Acad Dermatol* 2003; **48:** 456–60.
17. Cummins DL, *et al.* Treatment of pyoderma gangrenosum with intravenous immunoglobulin. *Br J Dermatol* 2007; **157:** 1235–9.
18. O'Donnell BF, *et al.* Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol* 1998; **138:** 101–6.
19. Jolles S. A review of high-dose intravenous immunoglobulin treatment for atopic dermatitis. *Clin Exp Dermatol* 2002; **27:** 3–7.
20. Gurmin V, *et al.* Psoriasis: response to high-dose intravenous immunoglobulin in three patients. *Br J Dermatol* 2002; **147:** 554–7.

Preparations

Ph. Eur.: Human Normal Immunoglobulin; Human Normal Immunoglobulin for Intravenous Administration;
USP 31: Immune Globulin.

Proprietary Preparations (details are given in Part 3)
Arg.: Beriglobina; Citax F; Endobulin; Flebogamma; Gamimune†; Gammaglobulina; IgG; Isiven†; Pentaglobin; Sandoglobulina†; Seroglubin; ***Austral.:*** Intragam; Intraglobin†; Octagam; Sandoglobulin; ***Austria:*** Beriglobin; Endobulin; Gamma-Venin†; Gammabulin; Gammagard; Gammanorm; Intraglobin; Octagam; Pentaglobin; Sandoglobulin†; Subcuvia; Venimmun N; ***Belg.:*** Gammagard SD; Multigam; Octagam; Sandoglobuline; Subcuvia; Vivaglobin; ***Braz.:*** Armoglobulina; Beriglobina; Blauimuno†; Gama Venina; Gamimune†; Octagam†; Sandoglobulina†; Venimmuna; Vigam†; ***Canad.:*** Baygam†; Gamastan; Gamimune N†; Gammagard; Gamunex; Iveegam; ***Chile:*** Beriglobina P; Flebogamma; Gamimune N†; Ig Vena N; Octagam†; Sandoglobulina†; ***Cz.:*** Biaven†; Endobulin; Flebogamma; Gamimune N†; Gamma-Venin†; Gammagard; Gammanorm; Gamunex; Intraglobin F†; Kiovig; Octagam; Pentaglobin; Subcuvia; Venimmun N; Vivaglobin; ***Denm.:*** Beriglobin; Endobulin; Gammagard; Gammaglobulin†; Gammanorm; Gammonativ†; Octagam; Sandoglobulin; Subcuvia; ***Fin.:*** Endobulin; Gammagard; Gammaglobulin†; Gammanorm; Nanogam; Octagam; Subcuvia; Venogamma†; ***Fr.:*** Endobuline; Gammagard; Octagam; Subcuvia; Tegeline; Vivaglobin; ***Ger.:*** Beriglobin; Endobulin; Flebogamma; Gamma-Venin†; Gammagard; Gammanorm; Gammonativ†; Gamunex; Intraglobin†; Intratect; Octagam; Pentaglobin; Polyglobin; Sandoglobulin; Subcuvia; Venimmun†; Vivaglobin; ***Gr.:*** Flebogamma; Gamma-Venin P; Gammagard; Intraglobin F; Kiovig; Octagam; Pentaglobin; Sandoglobuline; Subcuvia; Vivaglobin; ***Hong Kong:*** Flebogam-

ma; Gammagard; Globuman†; Intraglobin F; Octagam; Pentaglobin; Venoglobulin-S†; ***Hung.:*** Gammagard; Gammanorm; Humaglobin; Intratect; Octagam; Pentaglobin; Vivaglobin; ***India:*** Gamafine; ***Indon.:*** Gamimune N; Gammaraas; ***Irl.:*** Intraglobin; ***Israel:*** Beriglobin P; Endobulin†; Flebogamma; Gammagard†; Intraglobin F; Omr-IgG; Sandoglobulin; Venoglobulin; Vigam; ***Ital.:*** Biaven; Endobulin; Flebogamma; Gamma-Venin P†; Gammagard; Globuman†; Haimaven†; Ig Gamma†; Ig Vena; Intraglobin; Isiven; Pentaglobin; Sandoglobulina; Uman-Gamma†; Venimmun†; ***Jpn:*** Venilon; Venoglobulin; ***Malaysia:*** Flebogamma; Gammagard†; Globuman†; Intraglobin F†; IV-Globulin; Pentaglobin†; Venoglobulin-S†; Vigam; ***Mex.:*** Beriglobina P; Gamma-Venin P; Gammagard†; Isiven†; Octagam; Pentaglobin; Sandoglobulina; Seroglubin†; Vigam; ***Neth.:*** Endobuline†; Flebogamma; Gammagard; Gammanorm; GammaQuin; Ivegam; Octagam; Subcuvia; Vivaglobin; ***Norw.:*** Gammaglobulin†; Gammanorm; Octagam; ***NZ:*** Intragam; Octagam; Sandoglobulin; ***Philipp.:*** Gamimune N; Gammagard; IV-Globulin S; ***Pol.:*** Endobulin; Gamma-Globulina; Gammagard; Intraglobin F; Intratect; Kiovig; Pentaglobin; Sandoglobulin; Subcuvia; Venimmun; ***Port.:*** Flebogamma; Gammagard; Gammanorm; Gamunex; Globuman†; Ig Vena; Octagam; Sandoglobulina; Subcuvia; Vivaglobin; ***Rus.:*** Gamimune N (Гамимун Н); Humaglobin (Хумаглобин)†; Immunovenin (Иммуновенин)†; Octagam (Октагам); ***S.Afr.:*** Beriglobin; Endobulin†; Intragam; Intraglobin F; Pentaglobin; Polygam; ***Singapore:*** Flebogamma; Gammagard†; Intraglobin F; Pentaglobin; Venoglobulin†; Vigam†; ***Spain:*** Beriglobina P; Endobulin; Flebogamma; Gammagard; Gammaglobulina; Globuman†; Octagamocta; ***Swed.:*** Beriglobin; Endobulin; Gammagard; Gammanorm; Gammonativ; Octagam; Polyglobin†; Subcuvia; Xepol; ***Switz.:*** Beriglobin; Endobulin; Gammagard; Globuman; Intraglobin F; Octagam; Pentaglobin; Redimune; ***Thai.:*** Flebogamma; Gammaraas; Globuman†; Ig Vena; Intraglobin; Octagam; Pentaglobin; Venoglobulin-S†; Vigam; ***Turk.:*** Biseko; Endobulin; Flebogamma; Gamimune N; Gammar; Globuman; IG Vena NIV; Intraglobin; Isiven; Octagam; Pentaglobin; Subcuvia; Tegeline; Vigam; ***UK:*** Flebogamma; Gammabulin†; Gammagard; Kiovig; Octagam; Sandoglobulin; Subcuvia; Subgam; Vigam; Vivaglobin; ***USA:*** Carimune; Flebogamma; Gamastan; Gamimune N†; Gammagard; Gammar-P†; Gamunex; Iveegam†; Octagam; Panglobulin†; Polygam; Privigen; Venoglobulin†; Vivaglobin; ***Venez.:*** Flebogamma; Sandoglobulina†; Venoglobulina†.

Multi-ingredient: ***Arg.:*** Biotaer Gamma†; Histaglobin; ***Austria:*** Histaglobin; ***Chile:*** Pentaglobin; ***Cz.:*** Histaglobin†; ***Ger.:*** Histadestal; ***India:*** Histaglobulin; ***Pol.:*** Histaglobulina; ***S.Afr.:*** Histaglobin.

Pertussis Immunoglobulins

Inmunoglobulinas contra la tos ferina.

ATC — J06BB13.

Pharmacopoeias. Many pharmacopoeias, including *US*, have monographs.

USP 31 (Pertussis Immune Globulin). A sterile solution of globulins derived from the plasma of adult human donors who have been immunised with pertussis vaccine. It may contain glycine as a stabilising agent, and a suitable preservative. It should be stored at 2° to 8°.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201.

Interactions

As for immunoglobulins in general, p.2201.

Uses and Administration

Pertussis immunoglobulins have been used for passive immunisation against pertussis (whooping cough) and to prevent or modify pertussis in susceptible persons who have been exposed to infection.

Preparations

USP 31: Pertussis Immune Globulin.

Pertussis Vaccines

Vacunas de la tos ferina.

ATC — J07AJ01; J07AJ02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Pertussis Vaccine (Adsorbed); Vaccinum Pertussis Adsorbatum). A sterile suspension of inactivated whole cells of one or more strains of *Bordetella pertussis* in saline to which hydrated aluminium phosphate or aluminium hydroxide has been added. It may contain a suitable antimicrobial preservative. The estimated potency is not less than 4 units per dose. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that wP may be used on the label.

Ph. Eur. 6.2 (Pertussis Vaccine (Acellular, Component, Adsorbed); Vaccinum Pertussis sine Cellulis ex Elementis Praeparatum Adsorbatum). A preparation of individually prepared and purified antigenic components of *Bordetella pertussis* adsorbed on a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It contains either a suitably prepared pertussis toxoid or a pertussis toxin-like protein free from toxic properties produced by expression of a genetically modified form of the corresponding gene. It may also contain filamentous haemagglutinin, pertactin, and other defined antigens such as fimbrial-2 and fimbrial-3 antigens. The final vaccine contains not more than 100 units of bacterial endotoxin per dose. It may contain a suitable antimicrobial preservative. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that aP may be used on the label.

Ph. Eur. 6.2 (Pertussis Vaccine (Acellular, Co-purified, Adsorbed); Vaccinum Pertussis Sine Cellulis Copurificatum Adsorbatum). A preparation of antigenic components of *Bordetella pertussis* adsorbed on a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that aP may be used on the label.

Adverse Effects

As for vaccines in general, p.2201.

Local reactions may occur at the site of injection of pertussis vaccines or pertussis-containing vaccines and use may be followed by fever and irritability. Local reactions and fever occur less frequently with the acellular vaccine than with whole-cell vaccine, especially in children over 6 months of age and adults. However, booster doses of acellular pertussis-containing vaccines are associated with an increased risk of injection site reactions.

Severe reactions which have been reported include persistent screaming and generalised collapse but these effects were generally associated with an earlier type of vaccine and the reactions are stated to be rarely observed with the currently available vaccines.

Rare neurological adverse reactions have included convulsions and encephalopathy. There has been much debate, however, on the causal role of pertussis vaccine in such reactions (see below for detailed discussion). It should be remembered that neurological complications occur more frequently as a consequence of pertussis infection than from vaccination.

Asthma. A higher incidence of asthma was reported in 243 children who had received whole-cell pertussis vaccine than in 203 children who had not.[1] However, follow-up of a large Swedish study[2] showed no difference in the incidence of wheezing or allergic reactions between children who had received diphtheria, tetanus, and whole-cell pertussis vaccines and those who had not. A later prospective study[3] also found no evidence that whole-cell pertussis vaccination increased the risk of wheezing illness in young children. Furthermore, no association was found between pertussis vaccination in infancy and development of asthma in children aged up to 7 years in a later study of the same group of children.[4]

1. Odent MR, *et al.* Pertussis vaccination and asthma: is there a link? *JAMA* 1994; **272:** 592–3.
2. Nilsson L, *et al.* Lack of association between pertussis vaccination and symptoms of asthma and allergy. *JAMA* 1996; **275:** 760.
3. Henderson J, *et al.* Pertussis vaccination and wheezing illnesses in young children: prospective cohort study. *BMJ* 1999; **318:** 1173–6.
4. Maitra A, *et al.* Pertussis vaccination in infancy and asthma or allergy in later childhood: birth cohort study. *BMJ* 2004; **328:** 925–6.

Effects on the nervous system. There has been continuing debate over several decades concerning the perceived link between pertussis vaccination and brain damage. Anxiety among both the public and health care professionals in the UK in the mid-1970s over the safety of whole-cell pertussis vaccines led to a fall in the acceptance rates for infant vaccination and major epidemics of pertussis in 1977/79 and 1981/83. Since that time confidence has been restored and, with the introduction of acellular vaccines, the vast majority of infants now receive the vaccine before their second birthday. Comparison of whole-cell vaccines with acellular vaccines has since confirmed that the latter are associated with a greatly reduced incidence of serious neurological disorders.[1]

The consensus of opinion now seems to be that there is a temporal, but not necessarily causal, relationship between whole-cell pertussis vaccine and acute neurological illness that may occasionally lead to long-term dysfunction, and that risks of not immunising are greater than the potential risks associated with the vaccine.

The difficulty in ascertaining whether a causal relationship exists between whole-cell pertussis vaccine (usually given as diphtheria, tetanus, and pertussis (DTP) vaccine) and acute neurological reactions arises partly because primary vaccination is given at an age when neurological dysfunction with other causes is often first manifested. The observed temporal relationship may be entirely coincidental, may result from indirect factors such as pyrexia after vaccination, or may represent a direct effect of DTP vaccine. Much of the evidence is based on large epidemiological studies,[2-7] in particular the National Childhood Encephalopathy Study (NCES)[8] from the UK and its 10-year follow-up.[9] Serious acute neurological illnesses reported to the NCES[8] were found to be more common in infants immunised within 7 days (relative risk 2.4), and especially within 72 hours of onset, than in unimmunised children. For previously normal children, irrespective of outcome, the risk was estimated as 1 in 110 000 injections. In a subset of cases diagnosed as infantile spasms,[10] no link with vaccination was found overall, but there was a small excess of cases of infantile spasm in previously normal children who had received either DTP or diphtheria and tetanus vaccines during the previous 7 days (relative risk 2.0-2.5) followed by a corresponding deficit during the next 3 weeks. This suggested that vaccination may trigger the onset of spasms in a child with an underlying predisposition.

In 1991, the USA Institute of Medicine reviewed the available data, including the NCES results, and concluded that a causal relationship between the whole-cell pertussis component of DTP vaccine and acute encephalopathy probably existed, with an estimated excess risk of 0 to 10.5 per million vaccinations.[11] They concurred with the conclusion that a causal relationship between vaccination and infantile spasm was unlikely.

The NCES 10-year follow-up found that children who had had a serious acute neurological illness (excluding infantile spasms) had an increased risk of death or long-term dysfunction, but the risk was no greater in children given DTP vaccine in the 7 days before the original acute illness.[9] The National Vaccines Advisory Committee concluded that the results were insufficient to determine whether DTP vaccine influenced the development of chronic neurological dysfunction, and this conclusion has been accepted by both the Advisory Committee on Immunization Practices[12] and the American Academy of Pediatrics.[13]

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Precautions

As for vaccines in general, p.2202. The precautions and contra-indications to the use of pertussis vaccines have sometimes been more stringent than is now considered necessary because of the controversy about their potential adverse effects, especially neurotoxicity (see under Adverse Effects, above). In the UK it is now recommended that immunisation should continue with acellular pertussis vaccine even when episodes of fever (irrespective of severity), hypotonic-hyporesponsive episodes, persistent crying or screaming, or severe local reactions (irrespective of extent) have occurred after a preceding dose. Children who have had a local or general reaction to a whole-cell pertussis vaccine should complete their immunisation with acellular pertussis vaccine.

Whether or not children with a personal or family history of convulsions or epilepsy or who have suffered cerebral damage in the neonatal period should receive pertussis vaccines appears to have been the most difficult question to resolve in the past. In the UK it is now considered that a family history of seizures is not a contra-indication to immunisation. When a child has a history of seizures associated with fever, but no evidence of neurological deterioration, immunisation should proceed as normal; advice on the prevention of fever should be given at the time of immunisation (see Fever and Hyperthermia, p.10 for comments on the prevention of fever after immunisation). Similarly when there is a history of seizures not associated with fever, but no evidence of neurological deterioration, immunisation should proceed as normal. If a seizure associated with fever occurs within 72 hours of immunisation, further immunisation should be deferred until the condition is stable if no underlying cause is found and the child has not recovered completely within 24 hours. Immunisation should also be carried out in children with a history of cerebral damage in the neonatal period unless there is evidence of an evolving neurological abnormality. In children with a neurological problem that is still evolving it is recommended that immunisation should be deferred until the condition is stable. If a child develops encephalopathy or encephalitis within 7 days of immunisation, further immunisation should be deferred until the condition is stable if no underlying cause is found and the child has not recovered completely within 7 days.