potentially severe haemolytic disease of the newborn, although other blood group antibodies may also cause the disease. The use of anti-D immunoglobulin to suppress the production of anti-D antibodies in a Rh(D)-negative mother in response to leakage of red blood cells across the placenta from a Rh(D)-positive fetus has produced a major reduction in the incidence of this disorder.

Prophylaxis. Postnatal prophylaxis of Rh(D)-negative mothers after the birth of a Rh(D)-positive infant is well established. In 1971, WHO[1] suggested a standard intramuscular dose of 200 to 300 micrograms but stated that a 100-microgram dose was likely to have a success rate only slightly inferior to that of a 200-microgram dose, thus allowing optimum use to be made of a limited resource. Clinical experience in the UK has confirmed the efficacy of the 100-microgram (500 units) intramuscular dose and this is the amount officially recommended in the UK in such situations.[2,3] Doses do, however, vary considerably in other countries: 200 to 300 micrograms (1000 to 1500 units) is given in the USA and in many European countries, and 125 micrograms (625 units) is used in Australia.

Despite the success of anti-D immunoglobulin prophylaxis, sensitisations have continued to occur. There are several possible reasons for this, the main one being immunisation during pregnancy where there has been no overt sensitising event. Postpartum doses may be omitted due to oversight or loss to follow-up. Assessment of the volume of any transplacental haemorrhage is essential to avoid inadequate dosing. Significantly large feto-maternal haemorrhage is likely to occur after traumatic deliveries including caesarean section, manual removal of the placenta, still-birth or intra-uterine death, abdominal trauma during the third trimester, delivery of twins, or unexplained hydrops fetalis.

The efficacy of postpartum prophylaxis is not in question but opinions differ on the need for prophylaxis during pregnancy. It is generally agreed that prophylaxis is necessary in all non-sensitised Rh(D)-negative women after therapeutic terminations at any stage of pregnancy, including medical termination utilising mifepristone, after ectopic pregnancy, spontaneous complete or incomplete miscarriage after 12 weeks' gestation, or threatened miscarriage after 12 weeks' gestation as evidenced by abnormal bleeding or abdominal pain. Recommendations have been made by the British Committee for Standards in Haematology for the management of these sensitising events.[3]

Prophylaxis should also be given to all non-sensitised Rh(D)-negative women after the following sensitising events during pregnancy: invasive prenatal diagnosis including amniocentesis, chorion villus sampling, or fetal blood sampling; other intra-uterine procedures such as insertion of shunts or embryo reduction; antepartum haemorrhage; external cephalic version of the fetus; closed abdominal injury; or intra-uterine death.[2,3] A dose of 50 micrograms (250 units) is recommended for prophylaxis after these events up to 20 weeks of pregnancy, and at least 100 micrograms (500 units) thereafter.

In the UK routine antenatal prophylaxis at 28 and 34 weeks' gestation is recommended for all Rh(D)-negative women[2-4] and should be given irrespective of whether anti-D prophylaxis had been given for other sensitising events during the same pregnancy or previous pregnancies.[3]

Treatment. In mild cases, the resultant hyperbilirubinaemia can be managed with phototherapy. In severe cases, exchange transfusions may be necessary and intra-uterine transfusions may be considered in pregnancies of less than about 34 weeks' gestation; beyond this, premature delivery is often preferable.[5] Some clinicians have reported treatment failures with intra-uterine transfusions but have found intravenous normal immunoglobulin 400 mg/kg daily for 5 days every 2 to 3 weeks to the mother to be effective. There are several case reports[6,7] of beneficial responses using similar doses, but no benefit was seen in 4 patients receiving 1000 mg/kg once a week.[8] This dose, however, appeared to reduce the severity of the disease in a patient with Kell sensitisation.[8] Reductions in bilirubin concentrations have been reported with intravenous normal immunoglobulin 500 mg/kg as a single dose in newborn infants,[9] and a systematic review[10] found that such treatment reduced the number of infants requiring exchange transfusion and the duration of hospital stay and phototherapy needed. Reports in small numbers of infants[11-15] suggest that epoetins may be of value in controlling anaemia which develops 2 to 8 weeks after birth.

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Idiopathic thrombocytopenic purpura. Normal immunoglobulin is used for chronic idiopathic thrombocytopenic purpura (p.1505), and anti-D immunoglobulin has been found to have similar properties. The potential role of anti-D immunoglobulin in the treatment of idiopathic thrombocytopenic purpura has been discussed in several reviews.[1-3] In general, despite many studies showing the clinical efficacy and low toxicity of intravenous anti-D immunoglobulin, its precise role has not been defined for a number of reasons. Firstly, the optimal dose has not been established: doses used have ranged from 12.5 to 25 micrograms/kg daily, given for at least 2 days, in early studies to later more promising single doses of 50 to 75 micrograms/kg. Secondly, no study has shown anti-D immunoglobulin to be as effective as corticosteroid therapy for initial treatment. Furthermore, despite suggestions that anti-D immunoglobulin may be safer and easier to give than normal immunoglobulin, good comparative data is scanty. Clinical studies have, however, shown the safety and efficacy of intravenous anti-D immunoglobulin in Rh(D)-positive, non-splenectomised patients with idiopathic thrombocytopenic purpura.[1] A prospective, randomised clinical study[4] in Rh(D)-positive children with idiopathic thrombocytopenic purpura found that a single intravenous dose of 75 micrograms/kg raised the platelet count more rapidly than a single intravenous dose of 50 micrograms/kg, and was as effective as a single intravenous dose of 800 mg/kg of normal immunoglobulin.

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Preparations

Ph. Eur.: Human Anti-D Immunoglobulin; Human Anti-D Immunoglobulin for Intravenous Administration;
USP 31: Rh (D) Immune Globulin.

Proprietary Preparations (details are given in Part 3)

Arg.: BayRho-D†; Igantid; Immunorho; Kam Rho-D; Partoben; Partogamma; Rhesogamma; ***Austral.:*** WinRho; ***Austria:*** Partobulin; Rhesogam; ***Belg.:*** RhoGAM; ***Braz.:*** Matergam; Partogama†; WinRho†; ***Canad.:*** BayRho-D†; Hyperrho S/D; WinRho; ***Chile:*** BayRho-D†; Igamad; Immunorho; Rhesogamma P; ***Cz.:*** Igamad; Partobulin; Rhesonativ; Rhophylac; ***Denm.:*** Rhesogamma P; Rhophylac; ***Fin.:*** Rhophylac; ***Fr.:*** Rhophylac; ***Ger.:*** Partobulin; Rhesogam; Rhophylac; ***Gr.:*** Rhesogamma P; Rhophylac; WinRho; ***Hong Kong:*** BayRho-D; Partobulin; RhoGAM; WinRho; ***Hung.:*** Rhesonativ; RhoGAM; ***India:*** Matergam-P; ***Indon.:*** HyperRho S/D; ***Irl.:*** Rhesonativ†; ***Israel:*** BayRho-D; KamRho-D; Rhophylac; WinRho; ***Ital.:*** Haima-D†; Igamad; Immunorho; Parto-Gamma†; Partobulin; Rhophylac; ***Malaysia:*** Rhesonativ†; ***Mex.:*** BayRho-D†; Octaglob D; Probi-Rho D†; Rhesogamma P; Rhophylac; ***Neth.:*** RheDQuin; Rhophylac; ***Norw.:*** Rhesogamma†; Rhophylac; ***NZ:*** RhoGAM; WinRho; ***Philipp.:*** WinRho; ***Pol.:*** Gamma Anty D; Partobulin; ***Port.:*** Igantid†; Rhesonativ; Rhesuman†; Rhophylac; WinRho; ***Rus.:*** HyperRHO S/D (ГиперРОУ С/Д); ***S.Afr.:*** Rhesugam; ***Singapore:*** BayRho-D†; ***Spain:*** Gamma Anti D; Rhesogamma; Rhesuman†; ***Swed.:*** Rhesogamma†; Rhesonativ; Rhophylac; ***Switz.:*** Rhophylac; ***Thai.:*** Igamad; Rhesuman†; ***Turk.:*** BayRho-D; Partobulin; Rhesogamma P; Rhesuman; RhoGAM; ***UK:*** D-Gam; Partobulin; Rhophylac; WinRho; ***USA:*** HyperRho S/D; MICRhoGAM; RhoGAM; Rhophylac; WinRho; ***Venez.:*** RhoGAM†.

Argentine Haemorrhagic Fever Vaccines

Junin Haemorrhagic Fever Vaccines; Vacunas de la fiebre hemorrágica argentina.

Profile

A live attenuated vaccine is being investigated for active immunisation against Argentine haemorrhagic fever.

◊ References.

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BCG Vaccines

Bacillus Calmette-Guérin Vaccines; Vacunas BCG.

Вакцины БЦЖ

ATC — J07AN01; L03AX03.

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

Ph. Eur. 6.2 (BCG Vaccine, Freeze-dried; Vaccinum Tuberculosis (BCG) Cryodesiccatum; Bacillus Calmette-Guérin Vaccine BP 2008). A freeze-dried preparation containing live bacteria obtained from a strain derived from the bacillus of Calmette and Guérin (*Mycobacterium bovis* BCG) whose capacity to protect against tuberculosis has been established. It may contain a stabiliser. The dried vaccine should be stored at 2° to 8° and be protected from direct sunlight.
The BP 2008 states that BCG may be used on the label.
The BP 2008 gives BCG Vaccine as an approved synonym.

BP 2008 (Percutaneous Bacillus Calmette-Guérin Vaccine). A suspension of living cells of an authentic strain of the bacillus of Calmette and Guérin with a higher viable bacterial count than Bacillus Calmette-Guérin Vaccine. It is supplied as a dried vaccine and is reconstituted immediately before use by the addition of a suitable sterile liquid. The dried vaccine should be stored at a temperature below –20° and be protected from light.
The BP 2008 states that Tub/Vac/BCG (Perc) may be used on the label.
The BP 2008 gives Percut. BCG Vaccine as an approved synonym.

USP 31 (BCG Vaccine). A dried living culture of the bacillus Calmette-Guérin strain of *Mycobacterium tuberculosis* var. *bovis*; it is grown from a strain that has been maintained to preserve its capacity for conferring immunity. It contains an amount of viable bacteria such that inoculation, in the recommended dose, of tuberculin-negative persons results in an acceptable tuberculin conversion rate. It contains a suitable stabiliser and no antimicrobial agent. The dried vaccine should be stored in hermetically sealed containers at 2° to 8°. The reconstituted vaccine should be used immediately after preparation and any portion not used within 2 hours should be discarded.

Ph. Eur. 6.2 (BCG for Immunotherapy; BCG ad Immunocurationem). A freeze-dried preparation of live bacteria derived from a culture of the bacillus of Calmette and Guérin (*Mycobacterium bovis* BCG) whose capacity for treatment has been established. It may contain a stabiliser. It is for intravesical use only. The product should be stored at 2° to 8° and be protected from direct sunlight.

USP 31 (BCG Live). A freeze-dried preparation of attenuated live bacteria derived from a culture of Bacillus Calmette-Guérin (*Mycobacterium bovis*, var. BCG) for intravesical use only. It is reconstituted and further diluted aseptically with a sterile diluent before use. A reconstituted dose contains 1.0–19.2 × 10^8 colony-forming units (cfu). It does not contain a preservative.
BCG Live is sensitive to light and must be stored in a glass container, protected from direct light, and at 2° to 8°.

Adverse Effects and Treatment

As for vaccines in general, p.2201.

Serious adverse reactions to BCG vaccines used *for immunisation* against tuberculosis are rare, although the incidence may vary between strains. The normal therapeutic response involves induration and development of a lesion at the injection site, possibly with enlargement of local lymph nodes; this lesion may later ulcerate and heal over some months leaving a scar. In a few patients an exaggerated reaction, usually associated with overdose, inadvertent subcutaneous injection, or use in persons who are already tuberculin positive, may result in an abscess or discharging ulcer, or suppurative lymphadenitis. Nonspecific systemic reactions may include fever and headache. Generalised reactions, possibly due to hypersensitivity, have been reported with a few fatalities. Disseminated BCG infection may occur and has also led to fatalities, particularly in immunocompromised patients. Disseminated BCG complications such as osteitis have been reported with some BCG vaccines. Very rarely, a lupoid type of reaction has occurred, mostly after multiple revaccination.

Intravesical use of BCG in the treatment and prophylaxis of bladder cancer is associated with an inflammatory response; transient dysuria and urinary frequency, sometimes with fever or a flu-like syndrome, and haematuria, are common, especially with repeated treatment (as in maintenance therapy). Rarely bladder contracture and epididymo-orchitis have been reported. As with vaccination, disseminated BCG infection has occurred rarely and may potentially be fatal. Fever lasting