Clinical Policy Bulletin:
Immune Globulins for Post-exposure Prophylaxis

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Policy

Hepatitis A Immune Globulin:
Aetna considers hepatitis A immune globulin medically necessary for members who are exposed or likely to be ex A virus (HAV). Risk groups include household and sexual contacts of persons with hepatitis A, newborn infants of mothers, staff* and children at child-care centers and schools with HAV outbreaks, staff* of custodial care institutional outbreaks, and individuals exposed to HAV through food or waterborne outbreaks.

Aetna considers hepatitis A immune globulin experimental and investigational for other indications because of insu of safety and effectiveness.

Hepatitis B Immune Globulin:
Aetna considers hepatitis B immune globulin medically necessary for members who have had contact with an individ with hepatitis B virus (HBV). Risk groups include infants born to hepatitis B surface antigen (HBsAg)-positive moth percutaneous or permucosal exposure to HbsAg-positive blood, sexual contacts of HbsAg-positive persons, and h exposure of infants less than 1 year of age to a primary caregiver with acute HBV infection.

Aetna considers prolonged use of hepatitis B immune globulin medically necessary for prophylaxis of recurrent hep in HbsAg-positive liver transplant recipients.

Aetna considers hepatitis B immune globulin experimental and investigational for other indications because of insu of safety and effectiveness.

Cytomegalovirus Immune Globulin:
Aetna considers cytomegalovirus (CMV) immune globulin (e.g., Cytogam) medically necessary for members who h symptoms or exposure to cytomegalovirus. Cytomegalovirus immune globulin is also considered medically necess
prophylaxis or treatment of CMV disease in CMV-negative renal transplant members receiving a CMV-positive donor prophylaxis and treatment of CMV disease in other transplant recipients.

Aetna considers the use of CMV immune globulin experimental and investigational for all other indications, including prophylaxis of persons with IgA deficiency or Waldenstrom's macroglobulinemia, prevention of congenital cytomegalovirus treatment of in-utero cytomegalovirus infection because of insufficient evidence of its safety and effectiveness.

See also CPB 0206 - Parenteral Immunoglobulins.

Rho-D Immune Globulin:

Aetna considers Rho-D Immune Globulin (e.g., Gamulin Rh, HypRho-D Full Dose, HypRho-D Mini-Dose, MICRh Gamulin Rh, Rhogam, and WinRho SDF) medically necessary for preventing hemolytic disease of the newborn. R globulin is considered medically necessary for all unsensitized Rh-negative women at 24 to 28 weeks gestation, known to be Rh-negative. A repeat post-partum dose is considered medically necessary if a Rh-positive infant is delivered. Administration of Rho-D immune globulin is considered medically necessary in unsensitized Rh-negative women, known to be Rh-negative, after other obstetric complications such as amniocentesis, chorionic villus sampling, elective pregnancy termination (including elective abortion), cordocentesis, fetal surgery or manipulation (including external antepartum placental hemorrhage, ante-partum fetal death, miscarriage and stillbirth. Rho-D immune globulin is also medically necessary for treatment of Rho-D positive persons with idiopathic thrombocytopenic purpura.

Aetna considers Rho-D immune globulin experimental and investigational for other indications because of insufficient safety and effectiveness. Rho-D immunoglobulin is also indicated in Rh incompatibility reaction post transfusion.

Rabies Immune Globulin:

Aetna considers rabies immune globulin medically necessary for treatment of rabies exposure where the animal has been known to be rabid at the time of direct exposure or attack.

Aetna considers rabies immune globulin experimental and investigational for other indications because of insufficient safety and effectiveness.

Varicella Zoster (Chickenpox) Immune Globulin:

Aetna considers varicella zoster immune globulin (VZIG) medically necessary for prevention of varicella (chickenpox) in high-risk individuals who have significant exposure to the disease due to contact with an individual who is infected according to recommendations of the American Academy of Pediatrics. High-risk individuals include immunocompetent without a history of chickenpox, susceptible pregnant women, newborn infants whose mother had onset of chickenpox before delivery or within 48 hours after delivery, hospitalized premature infants 28 or more weeks gestation with no history of chickenpox, and hospitalized premature infants less than 28 weeks gestation regardless of maternal illness. Significant exposures include household contacts of infected persons, face-to-face indoor play with infected person contact with infected persons, and newborn infants whose mothers had onset of chickenpox near time of delivery (above).

Aetna considers post-exposure prophylaxis with varicella zoster immune globulin (VarizIG) as soon as possible with exposure to a person with varicella or shingles medically necessary for HIV positive individuals who are susceptible zoster virus (those who have not been vaccinated, have no history of varicella or herpes zoster, or are seronegative zoster virus).

Aetna considers VZIG experimental and investigational for other indications because of insufficient evidence of its effectiveness.

Tetanus Immune Globulin:

Aetna considers intra-muscular injection of tetanus immune gamma globulin medically necessary for prevention of
immunized persons, incompletely immunized persons (who have not completed the 3-dose primary vaccination set remotely immunized persons (last complete vaccination more than 10 years ago) with neglected or tetanus-prone (contaminated, necrotizing, or puncture wounds)*.

Aetna considers tetanus immune globulin experimental and investigational for other indications because of insufficient safety and effectiveness.

Rubeola (Measles) Immune Globulin:

Aetna considers intramuscular injection of measles (rubeola) immune globulin medically necessary for unvaccinated exposed to the disease.

Aetna considers rubeola immune globulin experimental and investigational for other indications because of insufficient safety and effectiveness.

Immune Globulin (IVIG) for German Measles (Rubella):

Aetna considers non-specific intravenous immune globulin (IVIG) medically necessary for non-immune women with exposure to rubella during the first trimester (3 months) of pregnancy.

Aetna considers IVIG for rubella experimental and investigational when these criteria are not met because of insufficient safety and effectiveness.

Respiratory Syncytial Virus (RSV) Immune Globulin or Palivizumab:

See CPB 0318 - Synagis (palivizumab).

Vaccinia (Smallpox) Immune Globulin:

Aetna considers vaccinia vaccine medically necessary for treatment of vaccine complications with severe clinical manifestations (e.g., eczema vaccinatum, progressive vaccinia, severe generalized vaccinia, and severe ocular viral implantation).

Aetna considers vaccinia immune globulin experimental and investigational for other indications because of insufficient safety and effectiveness. See also CPB 0644 - Smallpox Vaccine.

Infantile Botulism Immune Globulin:

Aetna considers human-derived botulinum immune globulin (BabyBIG or BIG-IV) for the treatment of infant botulism types A or B in members below 1 year of age medically necessary.

Aetna considers human-derived botulinum immune globulin (BabyBIG or BIG-IV) experimental and investigational indications because of insufficient evidence of its safety and effectiveness.

Immune Globulin IM (GamaSTAN S/D (formerly BayGam))

Aetna considers immune globulin IM (IGIM) medically necessary for the following indications:

I. Hepatitis A. The prophylactic value of IGIM is greatest when given before or soon after exposure to hepatitis considered experimental and investigational for individuals with clinical manifestations of hepatitis A or in those exposed more than 2 weeks previously; or

II. Measles (rubeola), for the prevention or modification of measles in susceptible contacts (one who has not been and has not had measles previously) exposed less than 6 days previously. Note: IGIM should not be given with vaccine.

III. Immunoglobulin deficiency, to prevent serious infection if circulating IgG levels of approximately 200 mg/dL maintained; or

IV. Varicella, prevention in immunosuppressed persons, if varicella zoster immune globulin is unavailable. Not immunization against varicella in immunosuppressed persons is best accomplished with varicella-zoster imm
Aetna considers IGIM experimental and investigational for rubella prophylaxis. The routine use of IGIM for rubella early pregnancy is of dubious value and cannot be justified.

*Note:* Treatment of work-related injuries is excluded from coverage under some benefit plans. Please check benefit descriptions. Work-related injuries may be covered by the employer's workman's compensation benefit plan.

**Background**

*Cytomegalovirus Immune Globulin*

Cytomegalovirus Immune Globulin IV (CMV-Ig) is an injectable product that contains antibodies directed specificaly cytomegalovirus (CMV), which is generally present in persons who have been exposed to the virus. While CMV is adults and is typically benign in healthy people, it is a significant cause of morbidity and mortality in people who are immunosuppressed due to organ transplantation or AIDS.

Cytomegalovirus Immune Globulin IV is currently approved by the Food and Drug Administration (FDA) for use in attenuation of CMV disease in renal transplant patients. It also has been shown to be beneficial in prevention and CMV disease in patients who have received an orthotopic liver transplant. There is also evidence for use of CMV- organ transplants (such as heart and lung) and in bone marrow transplants.

Studies in renal transplantation have generally been limited to patients who are CMV sero-negative; use in sero-po therefore remains investigational. This is not the case with other transplants; in fact, results in liver transplant patie decrease in severe CMV-associated syndromes.

In a retrospective analysis, Buxmann et al (2012) examined the current prenatal "off-label use" of CMV-hyperimmune -HIG) in the prevention and treatment of congenital CMV (cCMV) infection, including the long-term outcome of the retrospective observational study comprised mothers and their children, born between January 1, 2006, and Octob. Prenatal CMV-HIG was administered after diagnosis of primary CMV infection of the mother. Clinical and virologic collected from maternal and pediatric medical and laboratory reports. Follow-up was 12 to 36 months after birth. women and 43 children met the study criteria. In total, 40 mothers and 6 unourn infants received 115 doses of CM treatment group (TG; CMV-DNA polymerase chain reaction-positive amniotic fluid) included 4 mothers; the multi-n CMV-positive mother and unknown CMV status of fetus) included 38 mothers (39 infants). For the 4 unorn children HIG was administered either intra-umbilically or into the amniotic fluid; 3 of the 4 mothers received intravenous CM children in TG remained CMV-positive and were asymptomatic at birth and during follow-up. One infant in TG had cCMV infection in-utero, at birth, and during follow-up. In MG, 37 of 38 women received intravenous CM-HIG and received CMV-HIG in-utero. In total, 9 (23.1 %) of 39 children in MG were positive for cCMV (including a terminate 8 instances of cCMV infection at birth in MG were asymptomatic at birth and during follow-up. The fetus from the t pregnancy showed no sonographic symptoms of cCMV infection. No severe side effect occurred in 115 CMV-HIG The authors concluded that CMV-HIG was well-tolerated. Compared with published untreated mother-child pairs, t observed a trend toward a smaller risk for intrauterine CMV transmission following CMV-HIG application. Signs of disease were not reversed after CMV-HIG.

Simioni et al (2013) stated that primary CMV infection during pregnancy is the leading infectious cause of congenit disabilities. Diagnosis of maternal primary CMV infection and fetal compromise can be difficult, as well as the fact child are asymptomatic at birth, which makes binomial CMV and pregnancy challenging. The treatment of pregna CMV-HIG has shown promising results. However, as far as the authors knew, no randomized trials of immunoglob CMV-infected fetuses are ongoing.

An UpToDate review on “Cytomegalovirus infection in pregnancy” (Sheffield and Boppana, 2013) states that “Hype therapy of pregnant women with primary CMV infection in early pregnancy is a promising, but investigational, appro
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symptomatic infection in offspring. Data are limited to the following studies .... There are several limitations to inte data. These include the lack of randomization, the absence of a control group that received placebo, the use of his small number of adverse events, and use of interventions that differed in the therapy and prevention groups and in controls. None of the studies addressed the financial and logistical issues associated with screening large obstetri for CMV infection and the expense of pursuing false positive results. Until data from randomized trials are available
should emphasize the simple preventive measures noted below (see 'Prevention' below and 'Precautions to preve below). Although hyperimmunoglobulin therapy is not generally recommended, the use of this therapy should be in Some pregnant women with primary CMV infection may choose to undergo this therapy after a discussion of the at he efficacy of hyperimmunoglobulin and the limitations of the few published studies, as well as potential side effec It is currently being evaluated in a large multicenter National Institutes of Health (NIH) trial and the results of this guide recommendations. A second randomized European trial has just been completed and final data are being a

In a phase II, randomized, placebo-controlled, double-blind study, Revello et al (2014) evaluated the effectiveness globulin in the prevention of congenital cytomegalovirus. A total of 124 pregnant women with primary CMV infectio weeks of gestation were randomly assigned within 6 weeks after the presumed onset of infection to receive hyperim or placebo every 4 weeks until 36 weeks of gestation or until detection of CMV in amniotic fluid. The primary end-congenital infection diagnosed at birth or by means of amniocentesis. A total of 123 women could be evaluated in analysis (1 woman in the placebo group withdrew). The rate of congenital infection was 30 % (18 fetuses or infant the hyperimmune globulin group and 44 % (27 fetuses or infants of 62 women) in the placebo group (a difference o points; 95 % CI: -3 to 31; p = 0.13). There was no significant difference between the 2 groups or, within each gr women who transmitted the virus and those who did not, with respect to levels of virus-specific antibodies, T-cell-m response, or viral DNA in the blood. The clinical outcome of congenital infection at birth was similar in the 2 groups obstetrical adverse events was higher in the hyperimmune globulin group than in the placebo group (13 % versus authors concluded that in this study involving 123 women who could be evaluated, treatment with hyperimmune glo significantly modify the course of primary CMV infection during pregnancy. Moreover, they stated that “From the c point of view, our results (a 32 % relative decrease in the transmission rate and no significant difference in the clinibirth) represent less than the 47 % reduction in congenital CMV that has been considered by some to be the thresh recommending screening for and treatment of primary maternal infection in pregnancy as a cost-effective strategy. randomized, phase 3 studies of the prevention of congenital infection are under way. One, sponsored by Biotest, i conducted in Europe, and the second, sponsored by the Enunce Kennedy Shriver National Institute of Child Health Development, is ongoing in the United States (ClinicalTrials.gov number, NCT01376778). The hope is that the res studies will further our understanding of the efficacy and safety of hyperimmune globulin administration as a means congenital CMV infection”.

Hepatitis B Immune Globulin

Hepatitis B immune globulin is appropriate when used to provide passive immunization to hepatitis B as prophylax exposed individuals. The Advisory Committee on Immunization Practices (ACIP) states that combined passive and immunization is preferred to passive immunization with HBlg alone in neonates born to HBSAb-positive women, in exposed percutaneously or by ingestion or mucous membrane contact, and in individuals bitten by human carriers combined treatment is recommended for patients exposed through sexual contact. Hepatitis B immune globulin is promptly after exposure and again in 1 month.

Hepatitis B immune globulin is also indicated for prophylaxis of recurrent hepatitis B infection in HBsAg-positive liv recipients. Hepatitis B immune globulin prophylaxis is administered on a lifelong or indefinite basis for this indicatio

The manufacturers state that the intra-muscular (IM) product is not to be used in an intravenous (IV0 fashion. This because "serious systemic allergic reactions could occur following inadvertent IV administration of HBlg, since suc occurred following IV administration of immune globulin". Since it appears that the contraindication to IV use is the IV use is occurring without safety problems, it is appropriate to allow IV use when IM is not an option.
Rao and colleagues (2009) performed a systematic review and a meta-analysis to evaluate lamivudine monotherap
ty of lamivudine and HBIG in HBV infected liver recipients. A fixed effects model was used for statistical pool
risks (RR) for the different outcomes. Six articles (n = 551) fulfilled the inclusion criteria. Statistically significant dif
observed between lamivudine monotherapy and lamivudine + HBIG therapy in hepatitis B recurrence (p < 0.0001; R
confidence interval [CI]: 0.25 to 0.58), YMDD mutant (p = 0.002; RR = 0.40; 95% CI: 0.23 to 0.72) and hepatitis B
HBV-DNA positive patients before orthotopic liver transplantation (p < 0.00001; RR = 0.31; 95% CI: 0.21 to 0.45).
differences were observed in patient survival (p = 0.59; RR = 1.02; 95% CI: 0.95 to 1.09), graft survival (p = 0.56;
CI: 0.95 to 1.09) and diseases leading to death between the 2 groups (HBV recurrence leading to death: p = 0.05;
CI: 0.22 to 1.02); hepatocellular carcinoma recurrence leading to death: p = 0.13; RR = 0.34; 95% CI: 0.09 to 1.36
concluded that combination of lamivudine and HBIG can effectively decrease the recurrence rate of HBV and the in
mutant, but it can not improve patient survival and graft survival significantly. They stated that well-designed, large
needed to evaluate the efficiency of combined therapy of lamivudine and HBIG in prophylaxis of HBV recurrence in
recipients.

**Hepatitis A Immune Globulin**

Hepatitis A immune globulin is indicated for persons who are exposed or likely to be exposed to hepatitis A virus (gr
groups include household and sexual contacts of persons with hepatitis A, newborn infants of HAV-infected mothe
children at child-care centers and schools with HAV outbreaks, staff of custodial care institutions with HAV outbrea
individuals exposed to HAV through food or water-borne outbreaks. The usual dose is a single IM injection adminin
weeks of exposure.

**Rho-D Immune Globulin**

Rhogam is a specially prepared immune globulin injected into an Rh-negative mother to prevent Rh hemolytic dise
children. Rho-D immune globulin may be indicated for prevention of Rh hemolytic disease in neonates by administer
pre-menopausal, Rho-D-negative females; and for treatment of selected Rho-D-positive patients with ITP.

Administration of Rhogam is recommended under generally accepted guidelines for all unsensitized Rh-negative w
weeks gestation, unless the father is known to be Rh-negative. If a Rh-positive infant is delivered, accepted guidel
dose should be repeated post-partum, preferably within 72 hours of delivery. The American College of Obstetricia
Gynecologists recommends administration of Rhogam after other obstetric complications such as amniocentesis, c
sampling, ectopic pregnancy, pregnancy termination, cordocentesis, fetal surgery or manipulation (including extern
partum placental hemorrhage, ante-partum fetal death, miscarriage and stillbirth. The literature indicates this immu
also be used for treatment of selected Rho-D-positive persons with idiopathic thrombocytopenic purpura. Under g
Guidelines, Rhogam is recommended for all unsensitized Rh-negative women after elective abortion, unless the fat
be Rh-negative.

WinRho may be administered intramuscularly or intravenously over 3 to 5 mins. Other brands are indicated for IM
Intramuscular injection is a relative contraindication in patients with ITP; however, has been used with some succ
feel that use of this product for treatment of ITP may not be effective in splenectomized patients, others provide ev
contrary. When given in conjunction with pregnancy, Rho-D immune globulin does not provide benefit for the infa
pregnancy. Its use is intended to prevent Rh hemolytic disease in future infants born to that mother.

**Varicella Zoster Immune Globulin**

Varicella zoster immune globulin (VZIG) is considered appropriate when used to prevent varicella (chickenpox) inf
recommended by the ACIP. According to the ACIP, VZIG is necessary, provided that significant exposure has occ
immunocompromised children without a history of chickenpox. Immunocompromised adolescents and adults are lik
but if susceptible, should also receive VZIG. Varicella zoster immune globulin is also necessary, provided that sign
has occurred, for the following groups; susceptible pregnant women; newborn infants whose mother had onset of c
the 5 days before delivery or within the 48 hours after delivery; hospitalized premature infants (greater than or equa
gestation) whose mother has no history of chickenpox; and hospitalized premature infants (less than 28 weeks of gestation or equal to 1,000 grams) regardless of maternal history.

Varicella zoster immune globulin may be indicated in the above listed susceptible groups if significant exposure to occurred in the hospital: in the same 2- to 4-bed room, or adjacent beds in a large ward; face-to-face contact with memeb or patient, or visit by a person deemed contagious. Experts differ in the duration of face-to-face contact administration of VZIG. Some experts suggest a contact of 5 or more mins as constituting significant exposure for others define close contact as more than 1 hour. In any case, the face-to-face contact should be non-transient to b significant.

Other types of exposure for which VZIG is indicated in the above listed susceptible groups include: household exp the same household); exposure from playmates (face-to-face indoor play); and intimate contact with zoster lesions hugging a person deemed contagious; and exposure of newborn infant (onset of varicella in the mother 5 days or delivery or within 48 hours after delivery; VZIG is not indicated if the mother has zoster). The ACIP recommends th administered within 96 hours of exposure

Laboratory determination of susceptibility to varicella is sometimes impractical. Because of this, the ACIP recomm determination of susceptibility be based on a carefully obtained history of prior infection or exposure. However, in pregnant women, serologic status should be determined through immunofluorescent assay or ELISA test if results within 96 hours of exposure. If this test is feasible and negative, immune globulin need not be given. Otherwise, p should be considered susceptible.

Varicella zoster immune globulin is not necessary in individuals who are considered to be immune to varicella zost exception of bone marrow transplant recipients, individuals considered to be immune to varicella zoster include tho of prior varicella infection, or negative or uncertain exposure if they are at least 15 years of age and immunocompete patients with a history of infection with varicella or herpes zoster subsequent to bone marrow transplant are consid immune.

There is currently no evidence that administration of VZIG to pregnant women during the first or second trimester o prevent congenital varicella syndrome or that administration during the third trimester will prevent neonatal varicell post-exposure administration of VZIG in susceptible, pregnant women may prevent or suppress clinical disease in without preventing fetal infection or disease. For this reason, administration of VZIG for pregnant women who do n listed above is not considered to be necessary.

VariZIG (Cangene Corporation, Winnipeg, Canada) is the only VZIG preparation available in the United States for prophylaxis of varicella in persons at high-risk for severe disease who lack evidence of immunity to varicella and ar varicella vaccine. VariZIG is available in the United States through an investigational new drug (IND) application e protocol. It is a purified immune globulin preparation made from human plasma containing high levels of anti-varic antibodies (immunoglobulin G). In May 2011, the FDA approved an extended period for administering VariZIG. Th exposure to varicella zoster virus during which a patient may receive VariZIG, which had been 96 hours (4 days), i VariZIG should be administered as soon as possible after exposure (CDC, 2012).

Aberg et al (2014) reported on the 2013 update on primary care guidelines for management of HIV infected person Medicine Association of the Infectious Diseases Society of America. New information based on literature publishe 2013 was incorporated into this updated version of the guidelines. The guidelines make a strong recommendation moderate quality evidence, that HIV positive patients who have not been vaccinated, have no history of varicella or are sero-negative for varicella zoster virus, and are thus susceptible to varicella zoster virus should receive post-ex prophylaxis. The post-exposure prophylaxis should consist of varicella zoster immune globulin (VariZIG) as soon a within 10 days) after exposure to a person with varicella or shingles. The recommendations further noted that vari vaccination may be considered in HIV-infected, varicella zoster virus seronegative persons aged > 8 years with CD 200 cells / microliter and in HIV-infected children aged 1 to 8 years with CD4 cell percentages > 15% due to moder evidence in the peer-reviewed literature.


**Vaccinia (Smallpox) Immune Globulin**

Vaccinia vaccine is indicated for treatment of vaccine complications with severe clinical manifestations (e.g., eczema progressing vaccinia, severe generalized vaccinia, and severe ocular viral implantation). The only product currently treatment of complications of vaccinia vaccination is vaccinia immunoglobulin, which is an isotonic sterile solution of vaccinia immunoglobulin fraction of plasma from persons vaccinated with vaccinia vaccine. It is effective for treatment of ec vaccinatum and certain cases of progressive vaccinia; it might be useful also in the treatment of ocular vaccinia re-inadvertent implantation. However, vaccinia immunoglobulin is contraindicated for the treatment of vaccinial keratitis immunoglobulin is recommended for severe generalized vaccinia if the individual is extremely ill or has a serious underlying disease. Vaccinia immunoglobulin provides no benefit in the treatment of post-vaccinial encephalitis and has no role in treatment of smallpox. The Centers for Disease Control and Prevention (CDC) (2001) states that current supplies of immunoglobulin are limited, and its use should be reserved for treatment of vaccine complications with serious clinical manifestations. According to the CDC (2001), vaccinia immunoglobulin should be administered as early as possible. Doses can be repeated, usually at intervals of 2 to 3 days, until recovery begins (e.g., no new lesion CDC is currently the only source of vaccinia immunoglobulin for civilians.

**Rabies Immune Globulin**

Rabies immune globulin is indicated for treatment of rabies exposure where the animal has escaped or is known to have time of direct exposure or attack. Treatment of rabies exposure is comprised of a series of rabies vaccine (human vaccine, HDCV) and a single rabies immune globulin injection (Rabies Immune Globulin, RIG). For persons not previously vaccinated with HDCV, the usual frequency is a single IM injection of RIG and a series of HDCV consisting of 1-mL doses on days 0, 3, 7, and 14. For persons previously vaccinated with HDCV, 2 HDCV IM injections are given within 7 days of exposure. The literature indicates rabies immune globulin should not be administered to previously vaccinated individuals.

**Tetanus Immune Globulin**

Intramuscular injection of tetanus immune globulin is indicated for prevention of tetanus in immunized or previously vaccinated persons for neglected or tetanus-prone wounds (contaminated, necrotizing, or puncture wounds). Post-exposure treatment tetanus toxoid is recommended under accepted guidelines for wounded persons who have not completed the 3-dose vaccine series, and those who have completed vaccination more than 10 years ago. In addition, accepted guidelines recommend incompletely vaccinated persons with serious or contaminated wounds should receive human tetanus immune globulin in a single IM injection repeated at 4-week intervals, if necessary.

**Rubeola (Measles) Immune Globulin**

Intramuscular injection of measles (rubeola) immune globulin is indicated for unvaccinated individuals exposed to measles. Accepted guidelines recommend that the immune globulin should be administered within 6 days of exposure.

**Immune Globulin for Rubella (German Measles)**

The use of immune globulin for pregnant women with acute infection is controversial. There are no data to suggest that immune globulin will have any beneficial effect on the fetal response to disease. Thus, the CDC recommends limiting the use of immune globulin to women with known rubella exposure who decline pregnancy termination. The usual dose of immune globulin is a single IM injection.

**Infant Botulism Immune Globulin**

Arnon et al (2006) created the orphan drug Human Botulism Immune Globulin Intravenous (Human) (BIG-Iv), which contains botulinum toxin, and evaluated its safety and efficacy in treating infant botulism, the intestinal-toxemia form of human botulism. These investigators performed a 5-year, randomized, double-blind, placebo-controlled trial statewide, in California, infants with suspected (and subsequently laboratory-confirmed) infant botulism (75% caused by type A Clostridium botulinum and 47% by type B toxin); treatment was given within 3 days after hospital admission. These researchers subsequently
-year nationwide, open-label study of 382 laboratory-confirmed cases of infant botulism treated within 18 days after admission. As compared with the control group in the randomized trial, infants treated with BIG-IV had a reduction in the hospital stay, the primary efficacy outcome measure, from 5.7 weeks to 2.6 weeks (p < 0.001). BIG-I reduced the mean duration of intensive care by 3.2 weeks (p < 0.001), the mean duration of mechanical ventilation = 0.01), the mean duration of tube or intravenous feeding by 6.4 weeks (p < 0.001), and the mean hospital charge 88,600 dollars (in 2004 U.S. dollars; p < 0.001). There were no serious adverse events attributable to BIG-IV. In the study, infants treated with BIG-IV within 7 days of admission had a mean length of hospital stay of 2.2 weeks, and with BIG-IV shortened the mean length of stay significantly more than did later treatment. The authors concluded that treatment of infant botulism type A or type B with BIG-IV was safe and effective in shortening the length and cost of the hospitalization and the severity of illness.

Underwood et al (2007) reported a tertiary care hospital's 30-year experience with the diagnosis, treatment, and outcome of infant botulism in the PICU before and after the availability of Botulism Immune Globulin Intravenous. This was a retrospective chart review of the 67 patients who had received a diagnosis of infant botulism and were admitted to the ICU from the ages on presentation, length of hospital stay, length of ICU stay, length of mechanical ventilation, and type of were recorded and compared for patients who had received Botulism Immune Globulin Intravenous and those who basis of these results, conclusions were drawn regarding the effect of Botulism Immune Globulin Intravenous on 7 infant botulism. A total of 67 patients' charts were reviewed; 23 male and 29 female patients did not receive Botulis Globulin Intravenous. Of patients who did not receive Botulism Immune Globulin Intravenous, the median age at p 71 days, median length of hospital stay was 35 days, ICU stay was 24 days, and duration of mechanical ventilation total of 40% had type A toxin, and 60% had type B toxin. There was a significant difference between patients with and B in length of hospital stay but not length of ICU stay or mechanical ventilation. Patients with type A toxin were older than patients with type B toxin. Fifteen children received Botulism Immune Globulin Intravenous. There were significant differences in length of hospital stay, length of ICU stay, and length of mechanical ventilation between patients who received Botulism Immune Globulin Intravenous and those who did not. The authors concluded that the use of Botulin Intravenous significantly decreased the length of ICU stay, length of mechanical ventilation, and overall hospitalization in children with infant botulism.

Vanella de Cueros et al (2011) stated that infant botulism is the most common form of human botulism in Argentina States. BabyBIG (botulism immune globulin intravenous [human]) is the antitoxin of choice for specific treatment in the United States. However, its high cost limits its use in many countries. These investigators reported the efficacies of equine botulinum antitoxin (EqBA) as an alternative treatment. They conducted an analytical, observational, and longitudinal study on cases of infant botulism registered in Mendoza, Argentina, from 1993 to 2007. They analyzed records of laboratory-confirmed cases and evaluated the safety and efficacy of treatment with EqBA. Forty-nine cases of infant botulism demanding admission in ICUs and mechanical ventilation included 31 treated within 5 days after the onset of signs and 18 untreated with EqBA. EqBA-treated patients had a reduction in the mean hospital stay of 23.9 days (p = 0.0007). For infants treated with EqBA, the ICU stay was shortened by 11.2 days (p = 0.0155), and tube feeding was reduced by 24.4 days (p = 0). Incidence of sepsis in EqBA-treated patients was 47.3% lower (p = 0.0017) than in the untreated ones. Neither severe adverse effects attributable to EqBA were noticed, except for 1 infant who developed a transient erythematous rash that was observed. The authors suggested that prompt treatment of infant botulism with EqBA is safe and effective and be considered an alternative specific treatment for infant botulism when BabyBIG is not available.

Also, an UpToDate review on "Botulism" (Pegram and Stone, 2012) states that "Human-derived botulinum immune Human-derived botulinum immune globulin (called BIG-IV or BabyBIG) is available for intravenous use in infants of age who are diagnosed with infant botulism. BIG-IV should be administered as early as possible in the illness."

BabyBIG, botulism immune globulin intravenous (human) (BIG-IV), is an orphan drug that consists of human-derivative antitoxin antibodies that is approved by the FDA for the treatment of infant botulism types A and B.

BabyBIG is given as a single IV infusion. Recommended dose is 1.5 mL/kg (75 mg/kg) given as a single intravenous infusion slowly (0.5 mL/kg/h); if no untoward reaction in 15 minutes, increase rate to 1.0 mL/kg/h (2.2, 2.3).
recommended rates, infusion of the indicated dose should take 97.5 minutes total elapsed time).


CPT Codes / ICD-9 Codes / HCPCS Codes

**Hepatitis A Immune Globulin:**

CPT codes covered if selection criteria are met [no specific code]:

90399

96372

HCPCS codes covered if selection criteria are met:

J1460 Injection, gamma globulin, intramuscular, 1 cc [GamaSTAN S/D (formerly BayGam) no individuals with clinical manifestations of hepatitis A or in those exposed more than 2 w previously]

J1560 Injection, gamma globulin, intramuscular, over 10 cc [GamaSTAN S/D (formerly BayGa for individuals with clinical manifestations of hepatitis A or in those exposed more than previously]

ICD-9 codes covered if selection criteria are met:

V01.79 Contact with or exposure to other viral diseases

V15.85 Exposure to potentially hazardous body fluids

ICD-9 codes not covered for indications listed in the CPB:

070.0 Viral hepatitis A with hepatic coma

070.1 Viral hepatitis A without mention of hepatic coma

Other ICD-9 codes related to the CPB:

V05.3 Need for prophylactic vaccination and inoculation against viral hepatitis

V07.2 Prophylactic immunotherapy

V70.5 Health examination of defined subpopulations

**Hepatitis B Immune Globulin:**

CPT codes covered if selection criteria are met:

90371

HCPCS codes covered if selection criteria are met:

J1571 Injection, hepatitis B immune globulin (Hepagam B), intramuscular, 0.5 ml
Immune Globulins for Post-exposure Prophylaxis

J1573 Injection, hepatitis B immune globulin (Hepagam B), intravenous, 0.5 ml

**ICD-9 codes covered if selection criteria are met:**

V01.79 Contact with or exposure to other viral diseases
V15.85 Exposure to potentially hazardous body fluids
V42.7 Liver replaced by transplant

**ICD-9 codes not covered for indications listed in the CPB:**

070.20 - 070.23 Viral hepatitis B with hepatic coma
070.30 - 070.33 Viral hepatitis B without mention of hepatic coma

**Other ICD-9 codes related to the CPB:**

V05.3 Need for prophylactic vaccination and inoculation against viral hepatitis
V07.2 Prophylactic immunotherapy

**Cytomegalovirus Immune Globulin:**

**CPT codes covered if selection criteria are met:**

90291

**HCPCS codes covered if selection criteria are met:**

J0850 Injection, cytomegalovirus immune globulin intravenous (human), per vial

**ICD-9 codes covered if selection criteria are met:**

078.5 Cytomegaloviral disease
484.1 Pneumonia in cytomegalic inclusion disease
771.1 Congenital cytomegalovirus infection
996.80 - 996.89 Complications of transplanted organs
V01.79 Contact with or exposure to other viral diseases
V42.0 - V42.9 Organ or tissue replaced by transplant

**ICD-9 codes not covered for indications listed in the CPB:**

273.3 Macroglobulinemia
279.01 Selective IgA immunodeficiency
647.80 - 647.83 Other specified infectious and parasitic diseases [cytomegalovirus infection] [in utero]

**Rho-D immune Globulin:**

**CPT codes covered if selection criteria are met:**
Other CPT codes related to the CPB:

59000
59012
59015
59072
59074
59076
59412
59812 - 59857

HCPCS codes covered if selection criteria are met:

J2788 Injection, Rho D immune globulin, human, minidose, 50 mcg
J2790 Injection, Rho D immune globulin, human, full dose, 300 mcg
J2791 Injection, Rho D immune globulin, human (Rhophylac), intramuscular or intravenous, 1
J2792 Injection, Rho D immune globulin, intravenous, human, solvent detergent, 100 IU

ICD-9 codes covered if selection criteria are met:

287.31 Immune thrombocytopenia purpura
632 Missed abortion
633.00 - 633.91 Ectopic pregnancy
634.00 - 634.92 Spontaneous abortion
641.10 - 641.13 Hemorrhage from placenta previa
641.20 - 641.23 Premature separation of placenta
656.40 - 656.43 Intrauterine death

Other ICD-9 codes related to the CPB:

656.10 - 656.13 Rhesus isoimmunization complicating pregnancy, childbirth, and the puerperium
656.20 - 656.23 Isoimmunization from other and unspecified blood-group incompatibility, complicating p childbirth, and the puerperium
Rabies Immune Globulin:

CPT codes covered if selection criteria are met:

90375
90376

ICD-9 codes covered if selection criteria are met:

V01.5 Contact with or exposure to rabies

Other ICD-9 codes related to the CPB:

071 Rabies

Varicella Zoster Immune Globulin:

CPT codes covered if selection criteria are met:

90396
96372

HCPCS codes covered if selection criteria are met:

J1460 Injection, gamma globulin, intramuscular, 1 cc [GamaSTAN S/D (formerly BayGam)] for prevention in immunosuppressed persons, if varicella zoster immune globulin is unavailable

J1470 Injection, gamma globulin, intramuscular, 2 cc

J1480 Injection, gamma globulin, intramuscular, 3 cc

J1490 Injection, gamma globulin, intramuscular, 4 cc

J1500 Injection, gamma globulin, intramuscular, 5 cc

J1510 Injection, gamma globulin, intramuscular, 6 cc

J1520 Injection, gamma globulin, intramuscular, 7 cc

J1530 Injection, gamma globulin, intramuscular, 8 cc

J1540 Injection, gamma globulin, intramuscular, 9 cc

J1550 Injection, gamma globulin, intramuscular, 10 cc

J1560 Injection, gamma globulin, intramuscular, over 10 cc [GamaSTAN S/D (formerly BayGam)] for prevention in immunosuppressed persons, if varicella zoster immune globulin is unavailable

ICD-9 codes covered if selection criteria are met:

765.00 - 765.28 Prematurity [maternal exposure to chickenpox]
Other ICD-9 codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>052.0 - 052.9</td>
<td>Chickenpox</td>
</tr>
<tr>
<td>279.00 - 279.9</td>
<td>Disorders of the immune mechanism</td>
</tr>
<tr>
<td>647.60 - 647.64</td>
<td>Other viral diseases in the mother classifiable elsewhere, but complicating pregnancy, puerperium</td>
</tr>
<tr>
<td>765.00 - 765.19</td>
<td>Extreme immaturity and other preterm infants</td>
</tr>
<tr>
<td>771.2</td>
<td>Other congenital infections</td>
</tr>
<tr>
<td>771.89</td>
<td>Other infections specific to the perinatal period</td>
</tr>
<tr>
<td>V05.4</td>
<td>Need for prophylactic vaccination and inoculation against varicella</td>
</tr>
<tr>
<td>V07.2</td>
<td>Prophylactic immunotherapy</td>
</tr>
</tbody>
</table>

**Tetanus Immune Globulin:**

**CPT codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>90389</td>
<td>Injection tetanus immune globulin, human, up to 250 units</td>
</tr>
</tbody>
</table>

**HCPCS codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1670</td>
<td>Injection tetanus immune globulin, human, up to 250 units</td>
</tr>
</tbody>
</table>

**ICD-9 codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>728.86</td>
<td>Necrotizing fasciitis</td>
</tr>
<tr>
<td>870.0 - 897.7</td>
<td>Open wound [complicated only] [contaminated, necrotizing, puncture]</td>
</tr>
<tr>
<td>910.0 - 919.9</td>
<td>Superficial injury [infected only] [contaminated, necrotizing, puncture]</td>
</tr>
<tr>
<td>940.0 - 949.5</td>
<td>Burns [contaminated, necrotizing]</td>
</tr>
</tbody>
</table>

Other ICD-9 codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>037</td>
<td>Tetanus</td>
</tr>
<tr>
<td>771.3</td>
<td>Tetanus neonatorum</td>
</tr>
<tr>
<td>V03.7</td>
<td>Need for prophylactic vaccination and inoculation against bacterial disease, tetanus tox</td>
</tr>
<tr>
<td>V06.1</td>
<td>Need for prophylactic vaccination and inoculation against combinations of diseases, diphtheria, pertussis, combined [DTP] [DTaP]</td>
</tr>
<tr>
<td>V07.2</td>
<td>Prophylactic immunotherapy</td>
</tr>
</tbody>
</table>

**Rubeola (Measles) Immune Globulin:**

**CPT codes covered if selection criteria are met [no specific code]:**
HCPCS codes covered if selection criteria are met:

J1460 Injection, gamma globulin, intramuscular, 1 cc [GamaSTAN S/D (formerly BayGam) co
prevention in immunosuppressed persons, if varicella zoster immune globulin is unava
J1470 Injection, gamma globulin, intramuscular, 2 cc
J1480 Injection, gamma globulin, intramuscular, 3 cc
J1490 Injection, gamma globulin, intramuscular, 4 cc
J1500 Injection, gamma globulin, intramuscular, 5 cc
J1510 Injection, gamma globulin, intramuscular, 6 cc
J1520 Injection, gamma globulin, intramuscular, 7 cc
J1530 Injection, gamma globulin, intramuscular, 8 cc
J1540 Injection, gamma globulin, intramuscular, 9 cc
J1550 Injection, gamma globulin, intramuscular, 10 cc
J1560 Injection, gamma globulin, intramuscular, over 10 cc [GamaSTAN S/D (formerly BayGa
prevention in immunosuppressed persons, if varicella zoster immune globulin is unava

ICD-9 codes covered if selection criteria are met:

V01.79 Contact with or exposure to other viral diseases

Other ICD-9 codes related to the CPB:

055.0 - 055.9 Measles
V04.2 Need for prophylactic vaccination and inoculation against measles
V07.2 Prophylactic immunotherapy

Immune Globulin (IVIG) for German Measles (Rubella):

CPT codes covered if selection criteria are met [no specific code]:

90399

HCPCS codes covered if selection criteria are met:

J1460 Injection, gamma globulin, intramuscular, 1 cc
J1470 Injection, gamma globulin, intramuscular, 2 cc
J1480 Injection, gamma globulin, intramuscular, 3 cc
J1490 Injection, gamma globulin, intramuscular, 4 cc
J1500 Injection, gamma globulin, intramuscular, 5 cc
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1510</td>
<td>Injection, gamma globulin, intramuscular, 6 cc</td>
</tr>
<tr>
<td>J1520</td>
<td>Injection, gamma globulin, intramuscular, 7 cc</td>
</tr>
<tr>
<td>J1530</td>
<td>Injection, gamma globulin, intramuscular, 8 cc</td>
</tr>
<tr>
<td>J1540</td>
<td>Injection, gamma globulin, intramuscular, 9 cc</td>
</tr>
<tr>
<td>J1550</td>
<td>Injection, gamma globulin, intramuscular, 10 cc</td>
</tr>
<tr>
<td>J1560</td>
<td>Injection, gamma globulin, intramuscular, over 10 cc</td>
</tr>
</tbody>
</table>

**ICD-9 codes covered if selection criteria are met:**

- 647.50 - 647.54 Rubella, complicating pregnancy, childbirth, and the puerperium
- V01.4 Contact with or exposure to rubella

**Other ICD-9 codes related to the CPB:**

- 056.0 - 056.9 Rubella
- V07.2 Prophylactic immunotherapy

**Imune Globulin (IGIM) for German Measles (Rubella):**

**HCPCS codes not covered for conditions listed in the CPB:**

- J1460 Injection, gamma globulin, intramuscular, 1 cc [GamaSTAN S/D (formerly BayGam) no Rubella prophylaxis]
- J1560 Injection, gamma globulin, intramuscular, over 10 cc [GamaSTAN S/D (formerly BayG for Rubella prophylaxis]

**ICD-9 codes not covered for conditions listed in the CPB:**

- 647.50 - 647.54 Rubella, complicating pregnancy, childbirth, and the puerperium

**Other ICD-9 codes related to the CPB:**

- V01.4 Contact with or exposure to rubella
- V07.2 Need for prophylactic immunotherapy

**Vaccinia (Smallpox) Immune Globulin:**

**CPT codes covered if selection criteria are met:**

- 90393

**ICD-9 codes covered if selection criteria are met:**

- 999.0 Generalized vaccinia
- V01.3 Contact with or exposure to smallpox

**Other ICD-9 codes related to the CPB:**
Immune Globulins for Post-exposure Prophylaxis

050.0 - 050.9  Smallpox
323.51  Encephalitis following immunization procedures
V04.1  Need for prophylactic vaccination and inoculation against smallpox
V07.2  Prophylactic immunotherapy

ICD-9 codes contraindicated for this CPB:
370.0 - 370.9  Keratitis

Infantile Botulism Immune Globulin:
CPT codes covered if selection criteria are met:
90288

Other CPT codes related to the CPB:
96365
96366

ICD-9 codes covered if selection criteria are met::
040.41  Infant botulism

Immune Globulin Deficiency (IgG):
CPT codes covered if selection criteria are met: :
96372

HCPC codes covered if selection criteria are met: :
J1460  Injection, gamma globulin, intramuscular, 1 cc [GamaSTAN S/D (formerly BayGam) co
Immunoglobulin deficiency, to prevent serious infection if circulating IgG levels of appr
mg/dL plasma are maintained]
J1560  Injection, gamma globulin, intramuscular, over 10 cc [GamaSTAN S/D (formerly BayGa
for Rubella prophylaxis.]

ICD-9 codes covered if selection criteria are met: :
279.03  Other selective immunoglobulin deficiencies [IgG]

Other ICD-9 codes related to the CPB:
V07.2  Need for prophylactic immunotherapy

The above policy is based on the following references:


50. Pegram PS, Stone SM. Botulism. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed June 2012.


54. Sheffield JS, Boppana SB. Cytomegalovirus infection in pregnancy. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed April 2013.

