CLINICAL GUIDELINES

Summary of Literature and Recommendations Concerning Immunization and Steroid Injections

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Several practices routinely delay steroid injections because of a recent immunization and instruct patients to delay immunizations until 10-14 days after steroid injections. First, there is concern that a steroid injection could blunt the patient's immunological response and decrease effectiveness. Second, there is concern that steroid injections could result in uninhibited replication of live attenuated viruses and increase the risk of complications. At times these policies delay therapy or result in significant inconvenience to the patient.

The CDC, AAP and ISIS each make the following statements:

- **Glucocorticoid therapy is generally not considered a contraindication to immunization with either live attenuated virus when the steroid therapy is short term (<14 days) or of low to moderate dose (< 40mg of prednisone of it equivalent).**
- **Injection of cortisone is not considered a contraindication to live virus immunization as long as low to moderate doses of glucocorticoid are administered.**

Neither the CDC, nor the American Academy of Pediatrics, nor the International Spine Injection Society states that cortisone injections are a contraindication to inactivated virus, toxoid or biosynthetic immunizations.

In summary, immunizations do not appear to be a contraindication to injection therapy. I have copied citations from the CDC, the American Academy of Pediatrics and the International Spine Injection Society for your reference.

Immunology and Vaccine-Preventable Diseases – Pink Book –General Recommendations
CDC/NCIRD

Certain drugs may cause immunosuppression. For instance, persons receiving cancer treatment with alkylating agents or antimetabolites, or radiation therapy should not be given live vaccines. Live vaccines can be given after chemotherapy has been discontinued for at least 3 months. Persons receiving large doses of corticosteroids should not receive live vaccines. For example, this would include persons receiving 20 milligrams or more of prednisone daily or 2 or more milligrams of prednisone per kilogram of body weight per day for 14 days or longer. See Varicella chapter for more information about administration of zoster vaccine to immunosuppressed persons.

Aerosolized steroids, such as inhalers for asthma, are not contraindications to vaccination, nor are alternate-day, rapidly tapering, and short (less than 14 days) high-dose schedules, topical formulations, and physiologic replacement schedules.

CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2011;60(No. RR-2):1–61.

Altered Immunocompetence: General Principles

Altered immunocompetence, a term often used synonymously with immunosuppression and immunocompromise, can be classified as primary or secondary. Primary immunodeficiencies generally are inherited and include conditions defined by an absence or quantitative deficiency of cellular or humoral components or both that provide immunity. Examples include congenital immunodeficiency diseases such as X-linked agammaglobulinemia, severe combined immunodeficiency disease, and chronic granulomatous disease. Secondary immunodeficiency generally is acquired and is defined by loss or qualitative deficiency in cellular or humoral immune components that occurs as a result of a disease process or its therapy. Examples of secondary immunodeficiency include HIV infection, hematopoietic malignancies, treatment with radiation, and treatment with immunosuppressive drugs including alkylating agents and antimetabolites. The degree to which immunosuppressive drugs cause clinically significant immunodeficiency generally is dose related and varies by drug. Primary and secondary immunodeficiencies might include a combination of deficits in both cellular and humoral immunity. In this report, the general term altered immunocompetence also is used to include conditions such as asplenia and chronic renal disease, and treatments with therapeutic monoclonal antibodies (specifically, the tumor necrosis factor inhibitors) (*127–132*) and prolonged administration of high-dose corticosteroids.

Determination of altered immunocompetence is important to the vaccine provider because incidence or severity of some vaccine-preventable diseases is higher in persons with altered immunocompetence; therefore, certain vaccines (e.g., inactivated influenza vaccine and pneumococcal vaccines) are recommended specifically for persons with these diseases (*28,68*). Vaccines might be less effective during the period of altered immunocompetence. Live vaccines might need to be deferred until immune function has improved. Inactivated vaccines administered during the period of altered immunocompetence might need to be repeated after immune function has improved. In addition, persons with altered immunocompetence might be at increased risk for an adverse reaction after administration of live, attenuated vaccines because of uninhibited replication.

The degree of altered immunocompetence in a patient should be determined by a physician. The challenge for clinicians and other health-care providers is assessing the safety and effectiveness of vaccines for conditions associated with primary or secondary immunodeficiency, especially when new therapeutic modalities are being used and information about the safety and effectiveness of vaccines has not been characterized fully in persons receiving these drugs (Table 13). Laboratory studies can be useful for assessing the effects of a disease or drug on the immune system. Tests useful to assess humoral immunity include immunoglobulin (and immunoglobulin subset) levels and specific antibody levels (e.g., tetanus and diphtheria). Tests that demonstrate the status of cellular immunity include lymphocyte numbers (i.e., a complete blood count with differential), a test that delineates concentrations and proportions of lymphocyte subsets (i.e., B

and T lymphocytes, CD4+ T versus CD8+ T lymphocytes), and tests that measure T-cell proliferation in response to specific or nonspecific stimuli (e.g., lymphocyte proliferation assays) (*133,134*). The ability to characterize a drug or disease condition as affecting cellular or humoral immunity is only the first step; using this information to draw inferences about whether particular vaccines are indicated or whether caution is advised with use of live or inactivated vaccines is more complicated and might require consultation with an infectious disease or immunology specialist.

Corticosteroids

The amount of systemically absorbed corticosteroids and the duration of administration needed to suppress the immune system of an otherwise immunocompetent person are not well defined. Corticosteroid therapy usually is not a contraindication to administering live-virus vaccine when administration is 1) short term (i.e., <14 days); 2) a low to moderate dose (<20 mg of prednisone or equivalent per day); 3) long-term, alternate-day treatment with short-acting preparations; 4) maintenance physiologic doses (replacement therapy); or 5) topical (skin or eyes), inhaled, or by intraarticular, bursal, or tendon injection (*154*). No evidence of more severe reactions to live, attenuated viral vaccines has been reported among persons receiving corticosteroid therapy by aerosol, and such Recommendations and Reports MMWR / January 28, 2011 / Vol. 60 / No. 2 23 therapy is not a reason to delay vaccination. Although the immunosuppressive effects of steroid treatment vary, the majority of clinicians consider a dose equivalent to either ≥2 mg/kg of body weight or ≥20 mg/day of prednisone or equivalent for persons who weigh >10 kg when administered for ≥14 days as sufficiently immunosuppressive to raise concern about the safety of vaccination with live-virus vaccines (*154*). Corticosteroids used in greater than physiologic doses also can reduce the immune response to vaccines. Vaccination providers should defer live-virus vaccination for at least 1 month after discontinuation of high-dose systemically absorbed corticos-teroid therapy administered for >14 days.

American Academy of Pediatrics. Immunization in special clinical circumstances. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS. eds. Red Book: 2009 Report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009.

Corticosteroids

Children who receive systemic corticosteroid therapy can become immunocompromised.
The minimal amount of systemic corticosteroids and duration of administration sufficient to cause immunosuppression in an otherwise healthy child are not well defined.
The frequency and route of administration of corticosteroids, the underlying disease, and concurrent therapies are additional factors affecting immunosuppression. Despite these uncertainties, sufficient experience exists to recommend empiric guidelines for administration of attenuated live-virus vaccines to previously healthy children receiving corticosteroid therapy. A dosage equivalent to ≥2 mg/kg per day of prednisone or equivalent to a total of ≥20 mg/day for children who weigh more than 10 kg, particularly when given for more than 14 days, is considered sufficient to raise concern about the safety of immunization with attenuated live-virus vaccines. Accordingly, guidelines for administration of attenuated live-virus vaccines to recipients of corticosteroids are as follows:

• Topical therapy, local injections, or aerosol use of corticosteroids.
Application of low-potency topical corticosteroids to focal areas on the skin; administration by aerosolization in the respiratory tract; application on conjunctiva; or intraarticular, bursal, or tendon injections of corticosteroids usually do not result in immunosuppression that would contraindicate administration of attenuated live-virus vaccines. However, attenuated live-virus vaccines should not be administered if clinical or laboratory evidence of systemic immunosuppression results from prolonged application until corticosteroid therapy has been discontinued for at least 1 month.

• ***Physiologic maintenance doses of corticosteroids.*** Children who are receiving only maintenance physiologic doses of corticosteroids can receive attenuated live-virus vaccines during corticosteroid treatment.

• ***Low or moderate doses of systemic corticosteroids given daily or on Alternate days.*** Children receiving <2 mg/kg per day of prednisone or its equivalent, or <20 mg/day if they weigh more than 10 kg, can receive attenuated live-virus vaccines during corticosteroid treatment.

• ***High doses of systemic corticosteroids given daily or on alternate days for fewer than 14 days.*** Children receiving ≥2 mg/kg per day of prednisone or its equivalent, or ≥20 mg/day if they weigh more than 10 kg, can receive attenuated live virus vaccines immediately after discontinuation of treatment. Some experts, however, would delay immunization until 2 weeks after corticosteroid therapy has been discontinued, if possible (i.e., if the patient's condition allows temporary cessation).

• ***High doses of systemic corticosteroids given daily or on alternate days for 14 days or more.*** Children receiving ≥2 mg/kg per day of prednisone or its equivalent, or ≥20 mg/day if they weigh more than 10 kg, should not receive attenuated live-virus vaccines until corticosteroid therapy has been discontinued for at least
1 month.

• ***Children who have a disease that, in itself, is considered to suppress the immune response and who are receiving systemic or locally administered corticosteroids.*** These children should not be given attenuated live-virus vaccines, except in special circumstances.
These guidelines are based on concerns about vaccine safety in recipients of high doses of corticosteroids. When deciding whether to administer attenuated live-virus vaccines, the potential benefits and risks of immunization for an individual patient and the specific circumstances should be considered.

The guidelines also are based on considerations of safety concerning attenuated live-virus vaccines and do not necessarily correlate with those for optimal vaccine immunogenicity. For example, some children receiving moderate doses of prednisone, such as 1.5 mg/kg per day for several weeks or longer, may have a less-than-optimal immune response to some vaccine antigens. In contrast, some children receiving relatively high doses of corticosteroids (e.g., 30 mg/day of prednisone) may respond adequately to immunization. Immunization can be deferred temporarily until corticosteroids are discontinued if timely return for immunization is ensured. Otherwise, children should be immunized despite corticosteroid use to enhance the likelihood of protection in the case of exposure to disease.

International Spine Injection Society (SIS)

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Myth: Glucocorticoid administration has minimal effect on immune response.

Fact: Systemic glucocorticoids have many effects upon innate and acquired immunity. These effects are dose dependent and increase the risk of infection with common bacterial, viral, and fungal pathogens.

Although there exist no specific data on immune system effects from epidural administration of glucocorticoids, data are available regarding systemic administration. With systemic high-dose glucocorticoid therapy (doses of 40mg or more of prednisone per day) there is an immediate risk of infection due to inhibition of phagocytic cell function, which abates after completion of therapy. In a study of patients with rheumatoid arthritis, the acute effects of 1 gram of intravenous methylprednisolone were evaluated.1 Patients were given either one or three daily doses of methylprednisolone (1 gram per dose). Leukopenia developed within two hours of the dose, peaked at six hours, and resolved by 24 hours (in both regimens). Patients were followed for 16 weeks, during which PPD testing was unaffected, primary antibody responses to antigens were normal, and serum immunoglobulin levels were unchanged.

Doses of less than 40 mg per day of prednisone in adults can be considered "low to moderate". In this range, T lymphocytes may be slightly reduced in circulation (CD4- positive cells > CD8 positive cells). Delayed-type hypersensitivity responses may be impaired, resulting in cutaneous anergy. With long-term "low-dose" use, the effects on phagocytic cell function are minimal, but some inhibition of immune responses may increase with duration of therapy.

In addition to the direct effects on the immune system, patient-specific factors may have significant influence on the risk of infection. Older patients, hospitalized patients, and those with lowered functional status are at greater risk of infection. Patients with pre-existing conditions such as rheumatoid arthritis (RA) may also have a greater risk of infection related to glucocorticoid use. In one large study of RA patients, current and recent glucocorticoid doses were most strongly associated with such risk, but the data also suggested a cumulative risk effect from doses taken during the preceding 2-3 years.2

Myth: Recent administration of systemic glucocorticoid is a contraindication to live virus vaccination.

Fact: Live-virus vaccination should be deferred for at least 1 month after discontinuation of high-dose systemically absorbed glucocorticoid therapy administered for >14 days.
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There are insufficient data to define either dose or duration of therapy of systemically absorbed glucocorticoid needed to suppress the immune system in an otherwise immunocompetent person. "Short term" therapy usually indicates less than 14 days of treatment. "Low to moderate" dosing usually means less than 40mg of prednisone (or equivalent) per day. Glucocorticoid therapy is generally not considered a contraindication to administering live-virus vaccine when the steroid

therapy is short-term or of low to moderate dose. Live-virus vaccination may also be performed when long-term therapy is administered in alternate-day treatment with short acting preparations. Replacement therapy (physiologic doses) is also not generally a contraindication to vaccination. Topical, inhaled, intra-articular, bursal, or tendon injections are also generally not viewed as contraindications to vaccination as long as low to moderate doses of glucocorticoid are administered. Live-virus vaccination should be deferred for at least 1 month after discontinuation of high-dose systemically absorbed glucocorticoid therapy administered for >14 days.

In most patients on glucocorticoid therapy for renal, pulmonary, or rheumatic diseases, pneumococcal vaccine is immunogenic, although antibody titers may be reduced. In one small study of asthmatics, 14 steroid-dependent patients had no difference in the strength of response compared to 14 control asthmatics.[3] The doses of glucocorticoids taken by these patients ranged from 10 mg to 35 mg daily or every other day. Similarly, patients receiving chronic glucocorticoid therapy for rheumatologic or pulmonary disorders generate an adequate antibody response to influenza vaccine, although some have lower antibody titer.[4,5] The significance of lower immunization-induced antibody titers with regard to infection prevention is unclear, and dose thresholds for glucocorticoid use with regard to vaccination success have not been established.