



Serum sickness and serum sickness-like reactions

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INTRODUCTION

The cardinal features of serum sickness are rash, fever, and polyarthralgias or polyarthritis, which begin one to two weeks after the first exposure to the responsible agent and resolve within a few weeks of discontinuation. Although patients may appear very ill and uncomfortable during the acute febrile stage, the disease is self-limited, and prognosis is excellent once the responsible drug is stopped.

This topic review will discuss serum sickness and serum sickness-like reactions (SSLRs), with an emphasis upon the biology and clinical features of serum sickness. A detailed discussion of hypersensitivity vasculitis, which has features similar to serum sickness, is presented separately. (See "[Overview of cutaneous small vessel vasculitis](#)" and "[Hypersensitivity vasculitis in children](#)".)

BACKGROUND

The term "serum sickness" was introduced by von Pirquet and Schick, who published a book with that title (*Die Serumkrankheit*) in 1905 [1]. The authors described an illness that developed in some patients after administration of horse serum that had been given as an anti-toxin for the treatment of diphtheria and scarlet fever. They noted that there was a delay between administration of the horse serum and the development of the symptoms of serum sickness, and the delay was shorter if horse serum was administered again at a later time.

TERMINOLOGY

The classic clinical syndrome of serum sickness is caused by immunization of the host (human) by heterologous (nonhuman) serum proteins and subsequent illness caused by formation of immune complexes. However, the term "serum sickness" has also been applied to a variety of different but related syndromes of rash, arthritis, and fever beginning several days to weeks following administration of other types of drugs or in association with some infections. In this topic, we will refer to these related syndromes as "serum sickness-like reactions" and reserve "serum sickness" for the syndrome caused by immune reaction to a heterologous or chimeric protein therapeutic.

PATHOPHYSIOLOGY

Serum sickness — Serum sickness is the prototypic example of the Gell and Coombs "type III" or immune complex-mediated hypersensitivity disease ([table 1](#)) [2]. The reaction requires the presence of the antigen, coincident with antibodies directed against the antigen, leading to the formation of antigen-antibody or immune complexes. These should normally be cleared by the mononuclear phagocyte system, although if this system is not functioning well or is saturated by the immune complex load, then excess immune complexes may form in the circulation and deposit in tissues or form directly in the involved tissues. Immune complexes may deposit preferentially in joints because the synovial endothelium is fenestrated (with more permeable pores or slits) and thus is more accessible to proteins and protein complexes, although the reason that immune complexes target specific tissues is not well-understood. Once deposited, the presence of immune complexes in parenchymal tissues triggers an inflammatory response.

Immune complex formation — Following primary immunization with a protein antigen, immunoglobulin M (IgM) antibodies typically begin to develop 7 to 14 days later, and immunoglobulin G (IgG) antibodies appear a few days after IgM [3]. If the foreign protein is still present in the circulation when these antibodies appear, the antigen and antibodies may combine to form immune complexes. The traditional teaching about serum sickness implicated IgG as the predominant immunoglobulin in immune complex formation, although all immunoglobulin classes may be involved. The timing of the development of serum sickness suggests involvement of IgM-containing immune complexes after initial exposure to an antigen. Biopsies of lesional skin in patients with serum sickness from equine anti-thymocyte globulin (ATG) demonstrated IgM, immunoglobulin A (IgA), and immunoglobulin E (IgE), although not IgG, supporting the role of immune complexes containing immunoglobulin classes other than IgG in some cases [4,5].

The ratio of antigen to antibody is critical to the type of immune complex formed. The Heidelberger precipitin curve for the formation of antigen-antibody complexes demonstrates that intermediate-sized or large immune complexes (eg, Ag5Ab5) form in the zone of

equivalence, when the ratio of antibody to antigen is optimal ([figure 1](#)). These complexes deposit in tissues and are able to activate complement and recruit inflammatory cells more efficiently than small immune complexes. Small immune complexes form under conditions of either excess antigen (Ag) or excess antibody (Ab) (eg, Ag1Ab1, Ag2Ab1, or Ag1Ab2). These small complexes are inefficient at activating complement or binding to low-affinity Fc receptors and cause minimal or no damage if deposited in the tissues.

Complement activation leads to the formation of complement fragments, including C3a, a potent "anaphylatoxin" that causes mast cell degranulation, resulting in histamine release, vasodilation, enhanced vascular permeability, and the development of urticarial lesions. The complement fragment C5a is a potent chemoattractant for neutrophils. (See "[Complement pathways](#)".)

Complement activation also facilitates clearance of the immune complexes by coating soluble immune complexes with complement fragments. The complement-coated immune complexes then bind to erythrocytes, which express the receptor for fragments of C3 (complement component 3), on their surfaces. Erythrocyte-bound immune complexes are subsequently cleared by the mononuclear phagocyte system (primarily in the spleen and Kupffer cells of the liver). (See "[Regulators and receptors of the complement system](#)".)

Soluble immune complexes, both with and without complement fragments, are also cleared from the circulation by binding to receptors for the Fc portion of IgG (Fc-gamma-R) on cells of the mononuclear phagocyte system. Serum sickness resolves when there is antibody excess or when the antigen is entirely removed from the serum.

Complement-independent mechanisms — Subsequent studies suggested that complement-independent mechanisms were also involved in the pathophysiology of serum sickness. Studies of experimental serum sickness and other immune complex diseases have been performed in mice that were genetically manipulated to disable the complement system and/or remove cellular receptors for the Fc portion of IgG (Fc-gamma-R) [6-9]. These studies revealed that in mice, a functioning complement system is not necessary to generate serum sickness, although intact Fc-gamma-receptors are. Immune complexes in tissues can react directly with Fc-gamma-receptors on neutrophils, mast cells, and phagocytes, leading to release of cytokines, histamine, and other inflammatory mediators and formation of characteristic pathologic lesions, even in the absence of complement. Additional studies have shown that immune complexes acting via the related Fc-gamma-receptor, Fc-gamma-RII, can have an inhibitory and immunomodulatory function [10].

Serum sickness-like reactions — Reactions to a variety of drugs (especially [cefaclor](#) and anti-seizure medications) can clinically resemble classic serum sickness but are believed to be caused by different mechanisms. These are called serum sickness-like reactions (SSLRs).

SSLRs also occur following infections (especially streptococcal and some viral infections, such as hepatitis B) and some vaccines [11,12]. The pathogenesis is not well-understood, although it may **not** depend upon high titers of antibodies and circulating immune complexes, as in classic serum sickness.

- **Cefaclor** – The antibiotic, cefaclor, can cause an SSLR with fever, rash, arthralgias, and possibly other symptoms, typically beginning one to three weeks after initial administration. One study demonstrated that metabolites of cefaclor produced in vitro were found to be toxic for lymphocytes and that the predisposing drug metabolism has a familial distribution and is thus presumptively genetically influenced [13]. This type of reaction in which drug metabolites may have a direct toxic effect on cells and lead to idiosyncratic, delayed drug reactions has been described for other medications, such as trimethoprim-sulfamethoxazole [14,15]. Increased intestinal permeability may contribute to the pathogenesis of SSLRs due to cefaclor [16].

It has been suggested that the term "serum sickness-like disease" should be replaced by "urticaria with arthritis" to describe this drug-induced syndrome [17], although this terminology has not become common. Other terms proposed include "benign iatrogenic vasculitis" and "urticaria-arthralgia syndrome" [18]. (See "[Overview of cutaneous small vessel vasculitis](#)".)

- **Penicillin** – An SSLR that occurs days after drug administration may be seen in some patients who receive prolonged, high-dose intravenous **penicillin G**. This may be caused by drug-specific immune complexes, rather than complexes containing heterologous serum proteins. Small drug molecules or their reactive metabolites may serve as haptens that bind covalently to serum proteins, such as albumin, and result in an antibody response either to the hapten or the hapten-protein conjugate [14]. Note that the same patients may develop immediate hypersensitivity, which could be mediated by IgE or IgG, and present with acute urticaria or an anaphylactic/anaphylactoid reaction, as well as a later SSLR. (See "[Drug eruptions](#)" and "[Overview of cutaneous small vessel vasculitis](#)".)
- **Hepatitis B** – The term "serum sickness" is also used occasionally to describe an immune complex disease associated with infectious agents. As an example, acute hepatitis B infection may present with serum sickness-like features of rash, polyarthritis, and fever in the preicteric phase [19].

ETIOLOGY AND EPIDEMIOLOGY

Serum sickness is more common in adults, while SSLRs are more common in children. Medications and other therapeutic agents are the most common cause of both serum

sickness and SSLRs. However, the overall incidence of these reactions is not well-documented and varies considerably depending upon the medication in question.

Agents causing serum sickness — Classic serum sickness is caused by administration of a protein antigen from a nonhuman species. Other types of medications and exposures are uncommonly implicated.

- The various heterologous proteins that have been associated with serum sickness are shown in the table ([table 2](#)). Equine or rabbit anti-thymocyte globulin (ATG) has been implicated in transplant patients [2,20]. In the United States, use of heterologous anti-toxins is relatively infrequent, although still central to the treatment of snakebite or rabies exposure. A meta-analysis reported that serum sickness occurs in 13 percent of patients receiving the sheep hyperimmune Fab anti-venom used in the United States after pit viper snakebites [21]. Series have reported serum sickness after administration of anti-snake venoms to develop in 5.6 to 29 percent of patients [22,23].
- Serum sickness has also been reported with several therapeutic murine monoclonal antibodies and chimeric antibodies (made by molecular engineering to combine some protein domains from human immunoglobulins and some of murine derivation) [24,25]. [Rituximab](#) (an anti-B cell chimeric mouse monoclonal antibody) has been implicated repeatedly [25-28]. A 2015 literature review identified 33 reported cases associated with rituximab [25].

[Infliximab](#), a chimeric mouse monoclonal antibody against tumor necrosis factor-alpha (TNF-alpha) that is used for Crohn disease or rheumatoid arthritis has also been associated with an immune-mediated rash, sometimes with features typical of serum sickness, in up to 3 percent of patients [24,29,30].

- A small number of case reports have implicated humanized or fully human monoclonal antibodies, including [omalizumab](#) [31,32], [alemtuzumab](#) [33], [natalizumab](#) [34], [adalimumab](#) [35], and [obinutuzumab](#) [36].
- Rarely, recurrent exposure to allogeneic human plasma during blood transfusions [37], insect stings [38], mosquito bites [39], vaccinations [40-43], or allergy immunotherapy extracts [44,45] may cause SSLRs.

Risk factors — Apparent risk factors include the dose, duration, and nature of the heterologous protein, as well as the age of the patient. Hypergammaglobulinemia may also be a risk factor, although this is based upon small numbers of cases.

- **Dose** – Higher doses of the administered agent are more likely than lower doses to result in serum sickness. This observation was made in the original description by von Pirquet, who noted that serum sickness developed in over 80 percent of patients

receiving doses greater than 100 mL of anti-serum, while only 10 to 15 percent of patients receiving less than 20 mL of anti-serum were afflicted. Similarly, higher doses of equine botulinum anti-toxin and anti-snake venom were found to be more likely than lower doses to lead to serum sickness [46,47]. The influence of dose was not found in another study of serum sickness due to snakebite anti-venom serum [23]. (See "Snakebites worldwide: Clinical manifestations and diagnosis" and "Bites by Crotalinae snakes (rattlesnakes, cottonmouths [water moccasins], or copperheads) in the United States: Clinical manifestations, evaluation, and diagnosis".)

Nevertheless, even small doses of foreign protein may lead to the development of serum sickness in some situations. Some patients, for example, exposed to small amounts of bovine serum albumin administered during embryo transfer in the process of in vitro fertilization have been found to develop a serum sickness reaction to the bovine serum used for in vitro culture of the ova [48]. Similarly, it has been postulated that some of the reactions to human diploid cell **rabies vaccine** may arise from reactions to the fetal bovine serum used to grow the cells in tissue culture (table 2) [41].

- **Dosing schedule** – Serum sickness can develop after a patient's initial exposure to a drug or after subsequent exposures [49].

Intermittent exposure to a heterologous protein is associated with higher rates of SSLRs compared with continuous exposure, as illustrated by the following reports [24,50]:

- Twenty-five percent (10 of 40) of patients reinfused with **infliximab** following a long dosing hiatus developed a severe delayed reaction requiring glucocorticoid therapy [24]. These reactions typically occurred 3 to 12 days following the second or third infusion.
- Delayed SSLRs (arthralgias and fevers) developed in 15 percent of 52 adults given intermittent courses of **infliximab** therapy for Crohn disease [50]. Delayed administration (greater than 20 weeks) of a second dose was associated with a higher risk of reactions. In this study, reactions were more likely to occur after a second dose than after subsequent doses of infliximab and were less likely to occur if the time between administration of the first and second doses was less than 20 weeks. (See "Overview of biologic agents in the rheumatic diseases" and "Treatment of Crohn disease in adults: Dosing and monitoring of tumor necrosis factor-alpha inhibitors".)
- **Properties of the causative agent** – Some agents are more likely to cause serum sickness than others. As examples, 85 percent of patients developed serum sickness in

response to ATG administered daily for 10 to 14 days for bone marrow failure in one series [5]. Forty to 80 percent of patients given anti-venoms for snakebite may develop serum sickness [51-54]. In contrast, a report from the Ukraine stated that anti-diphtheria serum caused serum sickness in only 1.5 percent of 2247 patients [55].

- **Age of patient** – For some etiologies, adults may be at higher risk for serum sickness than children. Serum sickness in response to human and equine anti-rabies globulins was found in fewer than 0.5 percent of children under the age of 10 years in a series of 72,000 patients (adults and children) receiving these preparations [56]. Although unusual in children overall, SSLRs have been reported as a relatively common etiology of acute arthritis in children under 16 years of age [17]. (See "[Evaluation of the child with joint pain and/or swelling](#)".)
- **Hypergammaglobulinemia and cryoglobulinemia** – The development of serum sickness following treatment with [rituximab](#) may be more likely in patients with hypergammaglobulinemia [49]. Patients with hepatitis C-related mixed cryoglobulinemia vasculitis are at risk for serum sickness after rituximab infusion [57].
- **Previous animal and insect exposure** – Patients with prior exposure to rabbits may be at an increased risk of developing serum sickness after receiving rabbit ATG [20], and multiple repeated insect stings and bites may predispose to the rare phenomenon of serum sickness after stings [39].

Factors that reduce risk — Chemical modifications of the heterologous protein can decrease the risk of serum sickness reactions to some agents:

- The risk of serum sickness reactions after administration of Fab fragments of sheep anti-digoxin to treat a digitalis overdose is very small because Fab fragments rather than intact antibodies are administered and because the dose administered tends to be very low.
- Purification and enzymatic partial digestion of equine rabies anti-toxin (hyperimmunoglobulin) appear to decrease the risk of a reaction to that agent [58].
- Use of Fab fragments of sheep anti-venom to treat Crotalidae snakebites is associated with lower rates of serum sickness and milder symptoms when reactions do occur, although the risk is not completely eliminated [59-61]. These fragments do not activate complement or bind to the Fc-gamma-receptor, because they lack the Fc fragment, which contains the binding sites for complement and Fc-gamma-receptors.

Another factor that may reduce the risk of serum sickness reactions is the concomitant administration of immunosuppressant drugs. It has been reported that administration of [methotrexate](#) prevents development of cutaneous vasculitis in treating rheumatoid arthritis

patients with repeated doses of [infliximab](#). However, the mechanism of this interaction has not been characterized, and the safety of this approach in general is not known. (See "[Overview of biologic agents in the rheumatic diseases](#)" and '[Preventing recurrence](#)' below.)

Agents causing serum sickness-like reactions — Drugs and vaccines are the leading causes of serum sickness-like reactions (SSLRs).

Drugs — Drugs, particularly antibiotics, are the leading cause of SSLRs. Penicillin, [amoxicillin](#), [cefaclor](#), and [trimethoprim-sulfamethoxazole](#) are most commonly implicated, although many drugs have been associated with these reactions ([table 3](#)) [[27,62-67](#)] (see "[Drug eruptions](#)"). Viral infections can cause fever, rash, and arthralgias that mimic SSLRs.

In children, SSLRs are about 15-fold more likely with [cefaclor](#) than with other cephalosporins or [amoxicillin](#), even though all are structurally similar beta-lactam antibiotics [[68-70](#)]. Among children under five years of age treated with cefaclor, SSLRs have been reported to occur in 0.024 to 0.2 percent of courses [[18](#)]. About 50 percent of patients were hospitalized, although the outcomes were universally favorable.

Vaccines — Administration of [rabies vaccine](#) preparations have been associated with SSLRs [[71-74](#)]. Rarely, commonly administered immunizations, such as influenza, tetanus, and pneumococcal vaccines, have been reported to cause SSLRs [[40,75,76](#)]. A review of vaccine side effects from the Institute of Medicine concluded that "the evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and serum sickness" [[77](#)].

CLINICAL MANIFESTATIONS

Serum sickness — The most common signs and symptoms of serum sickness are dermatitis (rash), fever, malaise, and polyarthralgias or polyarthritis.

Temporal course — Signs and symptoms of serum sickness begin one to two weeks after the first exposure to the responsible agent. In patients who have been previously exposed to the causative drug, the syndrome starts earlier (ie, within one to seven days of receiving the inciting agent), and the illness has a more severe and "explosive" onset. If the patient still has IgG or IgE antibodies resulting from a previous exposure when that drug or serum is given again, an immediate reaction (such as an acute anaphylactoid reaction) may occur, giving rise to a mixed clinical picture that has features of both anaphylaxis and serum sickness. In theory, this could result from activation of mast cells or leukocytes by complement split products (ie, the anaphylatoxins C3a and C5a) via IgG immune complexes or direct mast cell activation via IgE cross-linking. (See "[Anaphylaxis: Emergency treatment](#)" and "[Complement pathways](#)".)

Serum sickness resolves when the causative agent is removed from the system. Typically, fever resolves within a few days of removal of the responsible agent, followed by resolution of rheumatic symptoms. Previous skin lesions may linger for longer periods. Symptoms typically resolve within two weeks of removal of the offending agent, although in unusual cases, symptoms can persist for as long as two to three months [1]. The course of illness may be protracted if the culprit agent has been administered as a depot or sustained release form [62].

Fever — Virtually all patients diagnosed with serum sickness develop fever, which is usually $>38.5^{\circ}\text{C}$ ($>101.3^{\circ}\text{F}$). The fever of serum sickness is characterized by high spikes that return to normal within the same day. Rigors are unusual. The fever is remittent but has no predictable temporal pattern. Malaise preceding and during the fever is common.

Dermatologic findings — The cutaneous manifestations of serum sickness are variable. Almost all patients diagnosed with serum sickness develop a pruritic rash, which is often the earliest clinical feature. The dermatitis generally lasts a few days to two weeks after the causative agent is stopped. The mucous membranes are not involved, which can be a useful feature in distinguishing serum sickness from clinically similar conditions, especially Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). There may be urticarial lesions, which are typically longer-lasting than hives from other causes ([picture 1](#) and [picture 2](#) and [picture 3](#) and [picture 4](#)). Individual lesions may last days to weeks.

The rash often starts in the region around the injection site if a drug was administered locally by intramuscular or subcutaneous injection (as was typical for equine diphtheria anti-toxin described by von Pirquet). This was first described in patients receiving horse anti-thymocyte globulin (ATG) administered as part of an immunosuppressive regimen used to treat aplastic anemia and other forms of bone marrow failure [2,4,5]. It may also start in the anterior lower trunk, groin, periumbilical, or axillary regions and spread to involve the back, upper trunk, and extremities. Skin changes may be prominent at the lateral aspect of the feet and hands, at the junction of the sole and side of the foot, or the border between the palm and dorsal skin of the fingers and hands ([picture 5](#) and [picture 6](#)).

Other skin manifestations may include palpable purpura, morbilliform eruptions, papules, or maculopapular lesions. Palmar erythema, livedo reticularis, and periungual hemorrhages have also been described. Frank vasculitis is uncommon. Ulcers, secondary infection, or scarring do not occur. (See '[Differential diagnosis](#)' below.)

Rheumatic features — Arthralgias are a characteristic but inconsistent feature of serum sickness, appearing in approximately two-thirds of patients. The joints commonly involved include the metacarpophalangeal joints, knees, wrists, ankles, and shoulders, although pain in the spine is also described. Pain in the jaw and temporomandibular joints is reported,

particularly with serum sickness caused by ATG [20,57]. Myalgias in the arms and thighs may also occur.

While tenderness to palpation and movement are common and may be severe, swelling and erythema due to arthritis occur in only a minority of patients. The joint involvement tends to occur after the rash has started and resolves before the rash has cleared.

Less common features — Other less common features of serum sickness include [5]:

- Nonspecific headache and blurred vision
- Edema (including facial or peripheral edema)
- Lymphadenopathy (particularly in regional lymph nodes draining the site of injection of the protein antigen/immunogen)
- Splenomegaly
- Gastrointestinal symptoms, including bloating, cramps, nausea, and diarrhea and occasionally melena
- Anterior uveitis
- Peripheral neuropathy, including Guillain-Barré syndrome – Rarely, the inflammatory process of serum sickness may be sufficiently intense to lead to long-term sequelae, such as persistent neuropathy, but the inflammatory process itself is self-limited if the offending antigen is removed
- Nephropathy, including glomerulonephritis
- Vasculitis

Serum sickness-like reactions — Serum sickness-like reactions (SSLRs) are generally less severe than classic serum sickness and can include arthralgias, lymphadenopathy, and urticarial rash, with or without fever [78]. When fever is present, it is typically low-grade. In a prospective study of children treated with [cefaclor](#), 42 developed SSLRs, with symptoms beginning 5 to 10 days following oral administration in 90 percent [16]. Symptoms frequently resolve within 3 to 4 days but may last for two weeks, even with glucocorticoid treatment [78].

Patients with SSLRs usually present with urticarial lesions that often start in the flexures that then become generalized. These eruptions are frequently initially mistaken for acute urticaria, but in contrast to acute urticaria, individual lesions remain for greater than 24 hours. The skin lesions typically gradually expand, leaving central clearing or central faint purpura, which are usually most evident on the abdomen or lower legs ([picture 7A-C](#)).

Other signs include erythema and edema of the hands and feet, although this is not common. Children with SSLRs may present with acute onset of joint pain, leading to inability to walk.

EVALUATION

Laboratory tests — We suggest that all patients who appear moderately or severely ill and patients with any severity of illness who are not taking a medication that can be readily implicated as the culprit, be evaluated with the following laboratory tests:

- **Complete blood count and differential** – In serum sickness, complete blood count (CBC) with differential frequently demonstrates neutropenia, with development of reactive, plasmacytoid lymphocytes. Mild thrombocytopenia may occur. Eosinophilia may be present but is not prominent.
- **Erythrocyte sedimentation rate and C-reactive protein** – These acute-phase reactants are elevated during active serum sickness.
- **Urinalysis** – During serum sickness, urinalysis demonstrates mild proteinuria in about one-half of patients. Those with proteinuria may also develop transient mild hematuria without cellular casts. In contrast, urinalysis is usually normal in SSLRs [16].
- **Serum chemistries, including blood urea nitrogen, creatinine, and liver function tests** – Occasionally in serum sickness, the serum creatinine is elevated up to about twice the baseline value, but renal dysfunction tends to resolve within a few days. Overt glomerulonephritis is rare. Hypoalbuminemia may be present in patients with edema. In contrast, renal and other systemic organ involvement is unusual in SSLRs due to medications.

Testing to exclude infection — An important early goal of the evaluation is the exclusion of infectious causes, such as hepatitis B. Testing for specific infectious diseases should be performed if indicated by the history or physical examination or if a patient has an unusually long disease course that persists after stopping the medication suspected of causing serum sickness. (See '[Differential diagnosis](#)' below.)

Other laboratory findings — Other tests, such as complement studies and skin biopsy, are sometimes performed in patients suspected of having serum sickness or SSLRs, although these are not recommended as part of the routine evaluation.

- **Complement studies, including CH50, C3, and C4** – During severe episodes, complement measurements, including C3, C4, and total hemolytic complement (CH50), are depressed, reflecting complement consumption. Measures of circulating immune

complexes, including the fluid-phase C1q-binding test and the Raji cell assay, are typically elevated [5,19]. The changes in complement and immune complex levels do not closely parallel the clinical course of serum sickness, and these tests are not routinely recommended as part of the laboratory evaluation. (See "[Overview and clinical assessment of the complement system](#)".)

- **Skin biopsy** – Skin biopsies are not usually necessary or helpful in confirming the diagnosis, since the findings are variable and not specific for serum sickness. In most cases, findings are similar to those seen in patients with urticaria:
 - Mild perivascular infiltrates consisting of lymphocytes and histiocytes, in the absence of vessel necrosis, were the most typical findings in skin biopsies of patients who developed serum sickness from equine anti-thymocyte globulin (ATG) [4]. Immunofluorescence microscopy demonstrated IgM and C3, although no IgG. It is possible that patients receiving ATG are not representative of all patients with serum sickness, because they are immunosuppressed by both ATG and glucocorticoids and often are neutropenic because of their underlying hematologic problem.
 - Leukocytoclastic vasculitis with neutrophilic involvement and fibrinoid necrosis has been reported in a minority of patients with serum sickness. Immunohistochemical or immunofluorescence staining with specific antibodies may reveal the presence of IgG and C3 within the walls of small arterioles and capillaries. (See "[Overview of cutaneous small vessel vasculitis](#)".)
 - A neutrophil-rich urticarial pattern has been reported with SSLRs [79,80].

DIAGNOSIS

The diagnosis of serum sickness is usually made clinically, based upon the characteristic pattern of acute or subacute onset of a compatible rash, fever, and severe arthralgias and myalgias disproportionate to the degree of swelling, all occurring one to two weeks after exposure (for a first occurrence) to a potentially causative agent. Laboratory findings should be consistent with the diagnosis.

The diagnosis of SSLRs is made in the same manner. Identification of the offending agent can be difficult if patients are on multiple medications that can be associated with SSLRs.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of serum sickness and SSLRs includes viral illnesses with exanthems, hypersensitivity vasculitis, acute rheumatic fever, acute meningococcal or

gonococcal infection, systemic juvenile idiopathic arthritis (formerly called Still's disease), and other types of drug reactions. In children, Kawasaki disease and acute annular urticaria are additional possibilities.

In patients of any age

- **Viral exanthematous infections** – Viral infections can cause fever, rash, malaise, myalgias, and arthralgias, although joint complaints are usually not as prominent as in serum sickness. Viral infections that cause exanthems or urticaria can be particularly difficult to differentiate from serum sickness. The presence of mucosal lesions or pharyngeal lesions, which may be seen with viral infections, is atypical of serum sickness. Increasing transaminases suggest the possibility of preicteric hepatitis B infection, which can be confirmed by specific tests for hepatitis B virus. (See "[Hepatitis B virus: Clinical manifestations and natural history](#)".)

The emerging viral disease, chikungunya may be confused with serum sickness. Typically, the pain associated with the arthritis of chikungunya is more severe and disabling than the arthralgias in serum sickness, and headache is typical in chikungunya but not common in serum sickness. (See "[Chikungunya fever: Epidemiology, clinical manifestations, and diagnosis](#)".)

Dengue fever also may present with fever, arthralgia, and rash, but the cutaneous finding are more hemorrhagic and petechial than in serum sickness, and myalgias are more prominent than arthralgias. Zika virus infection may present with fever, rash, and arthralgias, but conjunctivitis is more likely in Zika infection. Travelers or residents of areas with these disorders should have appropriate serologic or nucleic acid-based testing to rule out these infections. (See "[Dengue virus infection: Clinical manifestations and diagnosis](#)" and "[Zika virus infection: An overview](#)".)

- **Hypersensitivity vasculitis and urticarial vasculitis** – The pathogenesis of hypersensitivity vasculitis, urticarial vasculitis, and serum sickness all involve pathogenic formation of immune complexes, and both clinical and pathogenic overlap occurs between these conditions. A number of drugs (eg, penicillins) can cause both SSLRs and hypersensitivity vasculitis. Most patients with serum sickness do not develop frankly vasculitic rashes. Arthralgias and arthritis are typically more prominent in serum sickness than in primary vasculitis, although they may be present in both.
 - Urticarial vasculitis can be associated with systemic lupus erythematosus or can be a primary disorder, often associated with hypocomplementemia and autoantibodies to the complement component C1q as part of the hypocomplementemic urticarial vasculitis syndrome. (See "[Urticarial vasculitis](#)".)

- Children with immunoglobulin A vasculitis (IgA vasculitis; formerly called Henoch-Schönlein purpura) typically have prominent bloody diarrhea, a petechial rash, proteinuria, and arthritis, with IgA deposits present in the skin and renal biopsies. (See "[Hypersensitivity vasculitis in children](#)" and "[IgA vasculitis \(Henoch-Schönlein purpura\): Clinical manifestations and diagnosis](#)".)
- Patients with chronic hepatitis C may have the mixed cryoglobulinemia syndrome, but those patients typically have recurrent vasculitic palpable purpura and frequently have overt findings of glomerulonephritis. (See "[Mixed cryoglobulinemia syndrome: Clinical manifestations and diagnosis](#)".)
- **Acute rheumatic fever** – Patients with acute rheumatic fever typically have migratory arthritis with prominent joint swelling, in contrast to the simple arthralgias that characterize serum sickness. Cardiac murmurs, carditis, and elevated serologic tests consistent with a recent streptococcal infection also suggest acute rheumatic fever. (See "[Acute rheumatic fever: Clinical manifestations and diagnosis](#)".)
- **Scarlet fever** – The characteristic scarlatiniform rash of scarlet fever is rarely associated with serum sickness, and the "strawberry tongue" of scarlet fever is not seen in serum sickness ([picture 8](#)). In scarlet fever, the rash occurs along with the acute streptococcal infection on the second or third day of illness, whereas the onset of the rash and fever of serum sickness occurs at least several days after exposure to the inciting drug. (See "[Complications of streptococcal tonsillopharyngitis](#)".)
- **Lyme disease** – The erythema migrans rash of Lyme disease is distinct from the rash of serum sickness ([picture 9](#)). The typical monoarthritis of the knee seen in Lyme disease is not typical of serum sickness. A history of tick exposure would suggest the diagnosis of Lyme disease. (See "[Lyme disease: Clinical manifestations in children](#)", section on 'Erythema migrans' and "[Clinical manifestations of Lyme disease in adults](#)", section on 'Early localized disease').
- **Disseminated gonococcemia or meningococcemia** – Patients with meningococcemia are usually acutely ill with findings of meningitis. The skin findings of patients with these conditions often include cutaneous pustules or purpuric lesions containing the organism, whereas pustules are not seen in serum sickness ([picture 10](#)). Patients with disseminated gonococcal infection can have a localized septic arthritis with swelling atypical of serum sickness but can also have polyarthritis with painful periarticular swelling that can be confused with the findings of serum sickness. (See "[Clinical manifestations of meningococcal infection](#)" and "[Disseminated gonococcal infection](#)".)

- **Reactive arthritis** – Both reactive arthritis (formerly known as Reiter syndrome) and serum-sickness patients develop fever and joint pain. Mucosal involvement (urethritis, stomatitis) and eye inflammation are common in reactive arthritis and not in serum sickness. The skin lesions associated with reactive arthritis, such as circinate balanitis, are distinct from the typical skin findings of serum sickness. Joint swelling and the development of chronic or recurrent arthritis are prominent in reactive arthritis, although not in serum sickness. (See "[Reactive arthritis](#)".)
- **Drug reaction with eosinophilia and systemic symptoms** – In both drug reaction with eosinophilia and systemic symptoms (DRESS) and serum sickness, fever and rash are characteristic, and lymphadenopathy may be prominent. The typical urticarial rash of serum sickness is not seen in DRESS. A morbilliform rash present in the early phases of DRESS may be similar to the morbilliform pattern sometimes seen in serum sickness, but the rash of DRESS usually becomes confluent and very red and results in sloughing and peeling that are not seen in serum sickness. Arthralgias, typical of serum sickness, are not seen in DRESS. The prominent eosinophilia and elevated transaminases that are characteristic of DRESS are not seen in serum sickness. (See "[Drug reaction with eosinophilia and systemic symptoms \(DRESS\)](#)".)
- **Other drug reactions** – Other drug reactions that may mimic serum sickness or SSLRs include nonspecific exanthems, urticaria, and generalized hypersensitivity reactions. The development of an IgE-mediated drug allergy can cause the onset of urticaria during a course of therapy. The concomitant presence of other allergic symptoms (such as throat tightness, wheezing, or acute anaphylaxis) may help elucidate the underlying process. If the culprit drug was penicillin or another beta-lactam drug, then skin testing for IgE-mediated drug allergy may be possible after the reaction has resolved. (See "[Penicillin allergy: Immediate reactions](#)".)
- **Erythema multiforme** – The presence of target skin lesions and involvement of the palms, soles, and mucosal surfaces are characteristic features of erythema multiforme ([picture 11](#)). None of these are typical of serum sickness. White blood cell counts and liver enzymes may be elevated in erythema multiforme but are not in serum sickness or SSLRs. Arthralgias are generally not prominent in erythema multiforme. (See "[Erythema multiforme: Pathogenesis, clinical features, and diagnosis](#)" and "[Fever and rash in the immunocompetent patient](#)".)
- **Stevens-Johnson syndrome** – Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are potentially fatal drug hypersensitivity reactions that typically begin suddenly, with high fever, vesicular or bullous lesions on an erythematous background, and systemic illness ([picture 12](#)). In the earliest stages, these reactions could be confused with SSLRs, although the later lesions of these severe reactions are distinct,

and the mucous membranes are not involved in serum sickness or SSLRs. Prompt discontinuation of possible culprit drugs is the most important immediate intervention in SJS and TEN. (See "[Stevens-Johnson syndrome and toxic epidermal necrolysis: Pathogenesis, clinical manifestations, and diagnosis](#)".)

- **Systemic juvenile idiopathic arthritis** – Systemic juvenile idiopathic arthritis (formerly called Still's disease) may present with fever, arthralgias, oligoarthritis or periarthritis, and rashes. The rash of systemic juvenile idiopathic arthritis is classically evanescent, appearing during the febrile phase of the circadian variations in body temperature associated with systemic juvenile idiopathic arthritis and then fading within a few hours ([picture 13](#)). In contrast, the rash of serum sickness is morphologically different and is usually more persistent. Systemic juvenile idiopathic arthritis is likely to continue or recur without treatment, whereas serum sickness resolves within a few weeks of discontinuing the offending agent. The extreme elevations in serum ferritin that are characteristic of systemic juvenile idiopathic arthritis are not seen in serum sickness. (See "[Systemic juvenile idiopathic arthritis: Clinical manifestations and diagnosis](#)" and "[Clinical manifestations and diagnosis of adult-onset Still's disease](#)".)
- **Sweet syndrome** – Sweet syndrome (acute febrile neutrophilic dermatosis) presents with high fevers and skin rash, and arthralgias and myalgias may also be prominent. The skin lesions of Sweet syndrome are painful or associated with a burning sensation and are vesicular, nodular, or plaque-like, which are all features that differ from the usual pruritic rash of serum sickness. The drugs that trigger Sweet syndrome in some cases are not those typically responsible for serum sickness or SSLRs. Skin biopsies, often used to diagnosis Sweet syndrome, demonstrate prominent neutrophilic infiltrate that differs from findings typically seen in serum sickness. (See "[Sweet syndrome \(acute febrile neutrophilic dermatosis\): Pathogenesis, clinical manifestations, and diagnosis](#)" and "[Sweet syndrome \(acute febrile neutrophilic dermatosis\): Management and prognosis](#)".)

Other considerations in children

- **Autoinflammatory syndromes** – Autoinflammatory syndromes (such as familial Mediterranean fever, chronic infantile neurologic, cutaneous, and articular [CINCA] syndrome, and neonatal-onset multisystem inflammatory disorder [NOMID]) present with fever, rashes, and arthritis. However, these are recurrent disorders, rather than the acute self-limited reaction of serum sickness. (See "[The autoinflammatory diseases: An overview](#)".)
- **Kawasaki disease** – The presentation of fever, rash, and hand edema in children with Kawasaki disease can mimic serum sickness. However, Kawasaki disease can involve peripheral extremity changes, including erythema of palms or soles or edema of hands

or feet (during the acute phase) and periungual desquamation (during the convalescent phase), which are different from the polyarthritides and arthralgias of serum sickness. In addition, prominent mucosal disease in the mouth and conjunctiva are typical of Kawasaki disease and unusual in serum sickness. (See "[Kawasaki disease: Clinical features and diagnosis](#)".)

- **Acute annular urticaria (urticaria multiforme)** – Acute annular urticaria, also known as urticaria multiforme, is a self-limited urticarial hypersensitivity eruption that primarily occurs in infants and very young children [81-83]. Lesions appear on the face, trunk, and extremities as annular erythematous plaques with central clearing or dusky blue centers. Unlike SSLRs and erythema multiforme, the duration of individual lesions does not exceed 24 hours. Myalgias and arthralgias are absent. Pruritus is typically present. Other associated findings may include angioedema of the face or acral areas, dermatographism, and low-grade fever. Viral or bacterial infections, antibiotics, and vaccinations have been proposed as potential triggers. The disorder is treated with antihistamines and discontinuation of a triggering medication, if present. (See "[Approach to the patient with annular skin lesions](#)".)

TREATMENT

There are no evidence-based guidelines or controlled trials upon which to base therapy recommendations. The approach here is based upon the author's experience, as well as case reports and series in the literature [18,49,51,84,85].

To determine common practices, a retrospective chart review examined the management of children presenting with reactions to [cefaclor](#) by emergency department pediatricians [84]. The most common treatment for SSLRs was discontinuation of the culprit drug, combined with the prescription of both antihistamines and glucocorticoids.

Withdrawal of culprit agent — Many patients with minimal disease do not require treatment other than discontinuing the offending agent. Typically, fever and arthralgias resolve and new skin lesions stop forming within 48 hours of this intervention. Clinical symptoms may last longer for drugs with delayed clearance, although clearance of drugs is usually accelerated by the antibodies that also cause the serum-sickness reaction.

Mild to moderate symptoms — For patients with mild serum sickness or SSLRs, withdrawal of the suspect agent is usually all that is required. Arthralgias and low-grade fever can be treated with analgesics and nonsteroidal anti-inflammatory agents. Antihistamines may be sufficient for patients with pruritus and mild rash. Antihistamine dosing is discussed separately. (See "[New-onset urticaria](#)", section on '[H1 antihistamines](#)').

Severe symptoms — Glucocorticoids are helpful for patients with more severe signs and symptoms, such as higher fever (eg, temperature $>38.5^{\circ}\text{C}$ [$>101.3^{\circ}\text{F}$]), more severe arthritis and arthralgias, or more extensive rashes, including extensive vasculitic eruptions. The utility of glucocorticoids in the treatment of serum sickness and SSLRs is based upon case reports and small observational series. These agents are usually administered orally (eg, [prednisone](#) at 0.5 to 1 mg/kg per day) [27,62,64]. Sometimes even higher doses are used. Occasionally, patients who are very uncomfortable or who appear acutely ill may be treated with intravenous [methylprednisolone](#) in the range of 1 to 2 mg/kg per day in one or two divided doses [49,86]. Glucocorticoids can frequently be rapidly tapered, with a total duration of therapy of less than one week. However, withdrawal will occasionally result in recurrence of the symptoms, in which case glucocorticoids should be restarted and tapered more slowly.

Special circumstances — Occasionally, a medication that caused serum sickness and for which there is no reasonable alternative either cannot be discontinued or is needed again in the future.

Agents that cannot be stopped — In rare situations, the offending agent is lifesaving and may need to be continued while serum sickness is treated symptomatically. In animal models of chronic serum sickness, in which intermittent injections of foreign proteins were repeated over time, fatal renal failure developed in some animals [87]. However, favorable outcomes have been reported in humans in this situation. As an example, anti-thymocyte globulin (ATG) is used in the treatment of patients with aplastic anemia, and it is sometimes continued in the setting of serum sickness because the therapy is potentially curative. (See "[Treatment of aplastic anemia in adults](#)", section on '[Triple IST \(hATG, CsA, EPAG\)](#)').

In other situations, plasmapheresis has been used to treat or prevent recurrent serum-sickness attacks when implicating agents could not be discontinued, although this approach would be appropriate only if the therapeutic agent is not primarily present in the circulation, since apheresis would also remove the therapy [88].

Retreatment protocols — Retreatment protocols based on gradual dose escalation in combination with glucocorticoids have been reported for the management of oncology patients who developed SSLRs in response to monoclonal antibody treatments but required ongoing therapy [25,89-91]. Best documented are cases involving retreatment with [rituximab](#), an anti-B cell monoclonal antibody, in patients with lymphomas and other B cell disorders [89-91]. Most reactive patients had a broad hypersensitivity syndrome, which included signs and symptoms of mast cell activation, in many cases associated with positive IgE skin testing, a type of reaction that should be amenable to desensitization. Slow administration with gradually increasing infusion rates and concentrations, as is typically used in desensitization protocols, together with pretreatment and additional doses of glucocorticoids during and after infusion, as needed, may allow for successful retreatment.

This combination approach was successful in two patients who did not tolerate retreatment with either gradual dose escalation or high-dose glucocorticoids alone [90,92]. Whether patients with isolated SSLRs to rituximab or other foreign proteins can be truly immunologically "desensitized" remains to be demonstrated. Referral to an allergy specialist with expertise in drug desensitization is suggested if this approach were under consideration [90].

PREVENTING RECURRENCE

Once serum sickness or SSLRs develop, the drug that is responsible should be avoided, if possible. This should be recorded in the patient's medical record, and the patient should be educated about the various names the culprit drug might have. If the drug is commonly encountered, the patient should obtain a medical identification bracelet or necklace. After an episode of serum sickness, re-exposure to the same drug may lead to a more rapid and more severe serum-sickness reaction. (See '[Temporal course](#)' above.)

If no alternative agents are available and retreating with a drug that previously caused serum sickness is absolutely required, treatment with antihistamines or glucocorticoids may help prevent future episodes of serum sickness upon re-exposure [50].

Future use of related drugs — There is some controversy about whether related drugs can be used safely in a patient with a past serum sickness or SSLR to a specific agent. As an example, after cefaclor-induced SSLRs, administration of another cephalosporin is usually well-tolerated, and there are case reports of patients tolerating [cefazolin](#) following a SSLR to [nafcillin](#) [93]. However, some authorities recommend that all beta-lactam drugs be avoided when possible [18,85].

In patients with previous serum sickness to a vaccine, we know of no reports of repeat serum sickness to different vaccines. The most likely cause would be the protein components of vaccines, although it would be prudent to avoid vaccines with similar vehicles to the culprit vaccine as well, when possible.

Neither skin tests nor any in vitro studies are able to predict initial or recurrent episodes of serum sickness [58,94].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "[Society guideline links: Drug allergy and hypersensitivity](#)".)

SUMMARY AND RECOMMENDATIONS

- **Terminology and pathophysiology**

- **Serum sickness** – Classic serum sickness describes the clinical syndrome in which foreign (heterologous, nonhuman) serum proteins are recognized by host (human) immunoglobulins and immune complexes form. If the immune complexes are not adequately cleared by the mononuclear phagocyte system, they precipitate in tissues, activate complement, and trigger an inflammatory response. It is a Gell and Coombs "type III" or immune complex-mediated hypersensitivity disease ([table 1](#)). (See '[Terminology](#)' above and '[Serum sickness](#)' above.)
- **Serum sickness-like reactions** – Serum sickness-like reactions (SSLRs) are generally similar to but less severe than classic serum sickness and the pathophysiology is less well-characterized. (See '[Terminology](#)' above and '[Serum sickness-like reactions](#)' above.)
- **Etiology** – Serum sickness can be caused by a variety of foreign proteins, including equine anti-thymocyte globulin (ATG), monoclonal and chimeric antibodies, such as [rituximab](#) and [infliximab](#), and even fully humanized monoclonals, such as [omalizumab](#) ([table 2](#)). In contrast, SSLRs are most commonly caused by antibiotics, such as penicillin, [cefaclor](#), [amoxicillin](#), and [trimethoprim-sulfamethoxazole](#), as well as vaccines, although a variety of medications have been uncommonly associated with SSLRs ([table 3](#)). (See '[Etiology and epidemiology](#)' above.)

- **Clinical presentation**

- **Serum sickness** – SS most commonly presents with rash, fever, malaise, and polyarthralgias or polyarthritis, developing one to two weeks after first exposure to the responsible agent and resolving within a few weeks of discontinuing the drug. In patients who have been previously exposed to the agent, the syndrome starts earlier (ie, within one to seven days), and the illness has a more severe and "explosive" onset. The rash is a pruritic urticarial and/or morbilliform eruption, and individual lesions last days to weeks. The first lesions often appear at the site of injection. The mucosal membranes are not involved. Laboratory findings are variable. (See '[Serum sickness](#)' above.)
- **SSLRs** – SSLRs present with arthralgias, lymphadenopathy, and urticarial rash, with or without low-grade fever, typically beginning 5 to 10 days following oral administration of the culprit drug. The urticarial lesions of SSLRs often start in the flexures and become generalized. Individual lesions remain for greater than 24

hours and can leave residual faint purpura, which are usually most evident on the abdomen. (See '[Serum sickness-like reactions](#)' above.)

- **Diagnosis** – The diagnosis of serum sickness and SSLRs is made clinically, based upon the characteristic pattern of physical and laboratory findings occurring after exposure to a potential offending agent. (See '[Diagnosis](#)' above.)
- **Differential diagnosis** – The differential diagnosis of SS and SSLRs is extensive and includes acute viral infections (ie, hepatitis B, Dengue, chikungunya, and Zika), vasculitic syndromes, DRESS, and erythema multiforme, among other disorders. In children, Kawasaki and urticaria multiforme are additional considerations. (See '[Differential diagnosis](#)' above.)
- **Management** – The management of these reactions involves discontinuation of possible culprit agents in all cases. Typically, fever and arthralgias resolve and new skin lesions stop forming within 48 hours of this intervention. This is often all that is required for patients with mild symptoms. Further treatments depend upon the discomfort of the individual patient. (See '[Withdrawal of culprit agent](#)' above.)
 - **Mild to moderate** – Antihistamines may be helpful for pruritus. Nonsteroidal anti-inflammatory agents and analgesics may be given for low-grade fever and arthralgias. (See '[Mild to moderate symptoms](#)' above.)
 - **More severe** – For patients with higher fever (eg, temperature $>38.5^{\circ}\text{C}$ [$>101.3^{\circ}\text{F}$]), more severe arthritis and arthralgias, or extensive rashes, we suggest short courses of glucocorticoids (**Grade 2C**). These are usually administered orally (eg, [prednisone](#) at 0.5 to 1 mg/kg per day), although intravenous administration ([methylprednisolone](#) in the range of 1 to 2 mg/kg per day in one or two divided doses) may be considered in patients who appear acutely ill. This treatment can usually be tapered within the course of one week. (See '[Severe symptoms](#)' above.)
- **Special circumstances** – If retreatment or continued treatment is absolutely required because the causative drug is lifesaving and no equivalent alternative exists, successful administration by slow, gradually-escalating infusions and concomitant administration of glucocorticoids has been described. Supervision by a drug allergy expert is advised. (See '[Special circumstances](#)' above.)
- **Future avoidance of the culprit drug** – Once serum sickness or SSLRs develop, the responsible drug should be avoided in the future, if possible. Recurrent reactions can be more severe and develop more quickly. It is not clear that similar drugs must also be avoided, although that is the safest approach if there are alternative drugs that could be used instead. (See '[Preventing recurrence](#)' above.)

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Topic 2078 Version 26.0

GRAPHICS

Gell and Coombs classification of immunologic drug reactions

Type	Description	Mechanism	Clinical features
I Immediate reaction (within one hour)	IgE-mediated, immediate-type hypersensitivity	Antigen exposure causes IgE-mediated activation of mast cells and basophils, with release of vasoactive substances, such as histamine, prostaglandins, and leukotrienes.	Anaphylaxis Angioedema Bronchospasm Urticaria (hives) Hypotension
II	Antibody-dependent cytotoxicity	An antigen or hapten that is intimately associated with a cell binds to antibody, leading to cell or tissue injury.	Hemolytic anemia Thrombocytopenia Neutropenia
III	Immune complex disease	Damage is caused by formation or deposition of antigen-antibody complexes in vessels or tissue. Deposition of immune complexes causes complement activation and/or recruitment of neutrophils by interaction of immune complexes with Fc IgG receptors.	Serum sickness Arthus reaction
IV	Cell-mediated or delayed hypersensitivity	Antigen exposure activates T cells, which then mediate tissue injury. Depending upon the type of T cell activation and the other effector cells recruited, different subtypes can be differentiated (ie, types IVa to IVd).	Contact dermatitis Some morbilliform reactions Severe exfoliative dermatoses (eg, SJS/TEN) AGEP DRESS/DiHS Interstitial nephritis Drug-induced hepatitis Other presentations

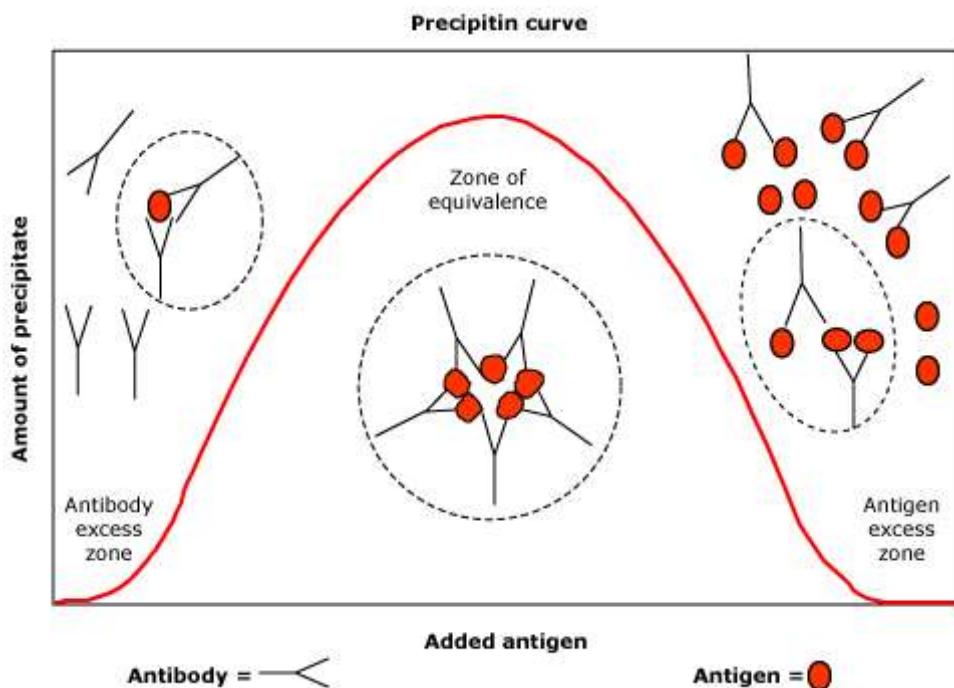
IgE: immunoglobulin E; Fc IgG: Fc portion of immunoglobulin G; SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis; AGEP: acute generalized exanthematous pustulosis;

DRESS/DiHS: drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome.

Adapted from: Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. Clin Allergy 1988; 18:515.

Graphic 80466 Version 18.0

Precipitin curve: Influence of antigen to antibody ratio



The Heidelberger precipitin curve demonstrates the influence of antigen:antibody ratios on the size of immune complexes and amount of precipitated immune complexes. The antigens and antibodies circled with dashed lines are in precipitates. Other antigens and antibodies remain in solution.

Graphic 68456 Version 3.0

Heterologous proteins causing serum sickness

Microbial anti-toxins

Equine anti-diphtheria

Equine or ovine anti-rabies

Equine anti-botulinum toxin

Venom anti-toxins

Equine, rabbit, ovine anti-snake venom (*Crotalidae* [pit vipers, rattlesnakes] anti-venin, *Micrurus* [coral snake] anti-venin)

Equine anti-spider venom (*Lactrodetus*) anti-venin

Immune and cell metabolism modulators

Equine or rabbit anti-thymocyte globulin

Murine anti-CD3 (OKT3)

Rituximab (murine/human chimeric anti-CD20)

Infliximab (murine/human chimeric anti-TNF-alpha)

Adalimumab (recombinant human anti-TNF-alpha) (?)

Alemtuzumab (humanized anti-CD52) (?)

Omalizumab (humanized anti-IgE) (?)

Natalizumab (humanized anti-alpha-4 integrin) (?)

Dalotuzumab (anti-insulin growth factor 1) (?)

Obinutuzumab (anti-CD20)

Immunizations

Rabies antigens (human diploid cell rabies vaccine)

Pneumococcal vaccine (?)

Hemophilus B vaccine (?)

Tissue culture protein

Bovine serum albumin (tissue culture media) (?)

Therapeutic fibrinolytic proteins

Streptokinase

Insect protein

Mosquito salivary proteins (?)

Insect stings

(?): case reports; causality is unclear.

TNF: tumor necrosis factor; IgE immunoglobulin E.

Graphic 51122 Version 13.0

Drugs implicated in serum sickness and serum sickness-like reactions

Commonly implicated drugs	Uncommonly implicated drugs (continued)
Cefaclor	6-mercaptopurine
Penicillins	Methimazole
Trimethoprim-sulfamethoxazole	Metronidazole
Uncommonly implicated drugs	Minocycline
Aspirin/salicylates	N-acetyl cysteine
Barbiturates	Naproxen
Bupropion	Novobiocin
Captopril	Pamabrom
Carbamazepine	Penicillamine
Cefatrizine	Phenylbutazone
Cefditoren	Phenytoin
Cholecystographic dyes	Propranolol
Ciprofloxacin	Propylthiouracil
Clarithromycin	Rifampin
Fluoxetine	Streptomycin
Furazolidone	Sulfasalazine
Hair straightener	Sulfonamides
Heparin	Tinidazole
Indomethacin	Verapamil
Insulin (in type 1 diabetes)	
Iron-dextran	
Itraconazole	

Urticular rash as a consequence of a serum sickness reaction



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Graphic 52352 Version 2.0

Serum sickness lesions



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Graphic 91345 Version 2.0

Serum sickness lesions detail



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Graphic 91346 Version 2.0

Serum sickness lesions on the chest



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Graphic 91344 Version 2.0

Foot serum sickness



Courtesy of Mark H Wener, MD.

Graphic 78783 Version 1.0

Serum sickness of the hands and feet



Reproduced with permission from: Bielory L, Gascon P, Lawley TJ, et al. Human serum sickness: A prospective analysis of 35 patients treated with equine anti-thymocyte globulin for bone marrow failure. Medicine 1988; 67:40. Copyright © 1988 Lippincott Williams and Wilkins.

Graphic 61556 Version 12.0

Serum sickness-like reaction



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Annular erythematous plaques are present.

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Graphic 78466 Version 4.0

Serum sickness-like reaction



Multiple annular, edematous plaques are present.

Graphic 78100 Version 1.0

Serum sickness-like reaction



Multiple inflammatory plaques, some with an annular configuration, are present in this child with serum sickness-like reaction. Purpuric lesions are present on the abdomen. Edema is present in the hands.

Graphic 54053 Version 1.0

Scarlet fever rash - Trunk and extremities



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The rash of scarlet fever is a diffuse erythema that blanches with pressure, with numerous small (1 to 2 mm) papular elevations, giving a "sandpaper" quality to the skin.

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Graphic 82757 Version 6.0

Early disseminated Lyme disease



Multiple lesions of erythema migrans are present.

Graphic 64784 Version 2.0

Acute meningococcemia



Skin lesions in acute meningococcemia can begin as papules but quickly progress to petechiae and purpura. As seen here, the purpuric lesions can coalesce.

Courtesy of Charles V Sanders. (The Skin and Infection: A Color Atlas and Text, Sanders CV, Nesbitt, LT Jr [Eds], Williams & Wilkins, Baltimore, 1995).

Graphic 52107 Version 6.0

Erythema multiforme



Characteristic target lesions of the palm in erythema multiforme begin with a central vesicle.

Courtesy of Nesbitt LT Jr. The Skin and Infection: A Color Atlas and Text, Sanders CV, Nesbitt LT Jr (Eds), Williams & Wilkins, Baltimore 1995.

Graphic 74095 Version 6.0

Cutaneous changes of Stevens-Johnson syndrome (SJS)



Generalized eruption of lesions that initially had a target-like appearance but then became confluent, brightly erythematous, and bullous. The patient had extensive mucous membrane involvement and tracheobronchitis.

Reproduced with permission from: Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. In: Color Atlas and Synopsis of Clinical Dermatology: Common and Serious Diseases, 3rd edition, Fitzpatrick TB, Johnson RA, Wolff K, et al (Eds), McGraw-Hill, New York 1997. Copyright © 1997 McGraw-Hill.

Graphic 67632 Version 18.0

Systemic juvenile idiopathic arthritis rash



A salmon-pink rash is characteristic of this juvenile idiopathic arthritis (JIA) subtype. The rash is brought out by heat and often can be found in the axillae and around the waist but may be present anywhere on the body.

Courtesy of Robert Sundel, MD.

Graphic 62959 Version 9.0

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