

# Prednis-OH NO! – A Case of Anaphylaxis Induced by Prednisone

Nicholas Chapman (✉ [Nicholas.chapman@rvu.edu](mailto:Nicholas.chapman@rvu.edu))

Rocky Vista University College of Osteopathic Medicine <https://orcid.org/0000-0001-8200-8177>

Taylor Caddell

Rocky Vista University College of Osteopathic Medicine

Rage Geringer

Sky Ridge Medical Center

Greg Hicks

Sky Ridge Medical Center

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## Case report

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# **Abstract**

## **Background:**

Anaphylaxis is a potentially life-threatening condition caused by the sudden release of inflammatory mediators into the systemic circulation. Among this condition's etiologies, corticosteroid-induced anaphylaxis, despite being uncommon, should receive due consideration given the frequency of steroid use in various settings. Any patient that presents with shortness of breath, wheezing, hypotension, urticaria, or other characteristic signs of anaphylaxis following the administration of steroids should be promptly evaluated. Because of the potentially fatal nature of anaphylaxis, clinicians must be familiar with the presentation, diagnosis, and management of the reaction.

## **Case Report:**

The primary objective of this case report is to discuss an example of such a reaction in a 21-year-old female with a past medical history of anxiety, depression, and alcoholism who presented with anaphylaxis following prednisone use, as well as the proposed pathophysiology and management thereafter. She was managed with intravenous epinephrine and diphenhydramine with complete resolution of her symptoms. She was subsequently discharged with an EpiPen, cetirizine, and advised to establish care with an allergist for follow up and additional allergy testing. To complete this case report, we performed a review of current primary literature on the subject.

## **Conclusions:**

Though uncertain, many potential mechanisms of sensitization to corticosteroids were identified, including haptization, preservatives, excipients, and conjugated esters. Various means exist to aid in diagnosis, such as skin testing, immunoCAP assays, lymphocyte transformation tests, basophil activation tests, and graded drug challenges, though these tests are associated with a high false negative rate. Accurate identification of the causative agent is crucial in facilitating avoidance or rapid desensitization prior to future corticosteroid use.

## **Cover Letter**

This manuscript is ideal for publication in AACI journal because it raises awareness about an important yet often overlooked condition that may result from a commonly used medication. Lives may be saved given adequate clinical suspicion, diagnostic capabilities, and management of anaphylaxis induced by corticosteroids. The goals and passions for the field that AACI demonstrates most closely mirrors that of the authors of this manuscript and our hope is to elevate the field in partnership with AACI. This manuscript has not been published or submitted for publication elsewhere.

# Background

Corticosteroids are one of the most frequently administered medications available. They have a wide variety of uses due to their immunosuppressive, anti-proliferative, anti-inflammatory, and anti-allergic properties. As such, they are commonly used in the maintenance of a plethora of conditions such as malignancy, transplantation, autoimmune conditions, and allergic diseases. Given their anti-inflammatory and immunosuppressive effects, corticosteroids are also often used to prevent late-phase anaphylactic reactions [1]. However, corticosteroids may also be associated with many adverse effects such as hypertension, cataracts, hyperglycemia, hypothalamus-pituitary-adrenal axis suppression, immunosuppression, growth retardation, osteonecrosis, osteoporosis, and immediate-type hypersensitivity reactions including anaphylaxis [2, 3]. This propensity to cause anaphylaxis is uniquely contradictory to the anti-inflammatory nature of corticosteroids.

Anaphylaxis is an allergic response involving urticaria, wheezing, shortness of breath, angioedema, hypotension, and/or abdominal pain [2]. This reaction is IgE mediated, most often as a result of mast cell activation. Anaphylaxis induced by corticosteroids may be difficult to recognize due to the overlapping and camouflaging effects of the underlying condition being treated. Therefore, clinicians must remain vigilant when utilizing corticosteroid therapy, as subsequent anaphylaxis may be life-threatening. It has been demonstrated that up to two percent of anaphylaxis cases may be fatal, though this number is obscured by the fact that many cases that result in death are unobserved [4]. Furthermore, corticosteroids are often necessary in the treatment of other life-threatening conditions. Recognizing sensitivity to a specific corticosteroid or additive can allow for either desensitization or avoidance of a specific allergen in the future. Failure to recognize the responsible allergen may result in a significant reaction, potentially culminating in death.

Given the low prevalence of cases, there are no standardized methods to determine the specific component of corticosteroid responsible for the induction of a hypersensitivity reaction. One study demonstrated that the majority of patients who developed a hypersensitivity reaction to a specific corticosteroid were later able to tolerate an alternative corticosteroid [5]. Despite the small sample size, this finding may be promising for future management. More research is required to determine the cross-reactivity of corticosteroid in patients who have displayed sensitivity in the past. In this paper, we present a case of anaphylaxis secondary to prednisone use in a 21-year-old female and discuss the progression, outcome, and current literature regarding this topic.

## Case Report

A 21-year-old female with a past medical history significant for anxiety, depression, and alcoholism presented to her primary care physician after swimming in a local lake several days prior. She had since developed a painful, burning, red rash on her right posterior thigh. Her primary care physician prescribed her a prednisone burst in addition to a topical steroid cream. Thirty minutes after the ingestion of

prednisone, the patient began to develop shortness of breath and the sensation of her throat swelling, prompting her to seek evaluation at the emergency department.

Upon arrival at Sky Ridge Medical Center, her symptoms had worsened and she was experiencing severe and progressive shortness of breath, hypotension, nausea, flushing, and throat swelling. Her symptoms were consistent with anaphylactic shock and she was subsequently given intravenous diphenhydramine and epinephrine. This treatment resulted in a swift and complete resolution of her symptoms.

She was subsequently admitted overnight for observation on telemetry and continuous pulse oximeter with a plan to administer dexamethasone as an alternative rescue corticosteroid if she further deteriorated. The following day, a complete blood count and basic metabolic panel were unremarkable. The patient remained in the hospital for an additional night secondary to temporarily increased pruritus and lightheadedness.

The patient had no prior history of anaphylaxis or hypersensitivity reactions and had an unknown history of previous exposure to corticosteroids. She was counseled on avoidance of prednisone and other steroids in the future to prevent similar anaphylactic reactions. The patient was discharged with an EpiPen, cetirizine, and advised to establish care with an allergist for follow up and additional allergy testing.

## Discussion

The prevalence of hypersensitivity reactions to corticosteroids is reported to be between 0.3 and 0.5 percent based on various studies, with only a small portion of these hypersensitivities resulting in anaphylaxis [2, 3]. These reactions have been reported in patients as young as 18 months. A patch testing study of 2000 patients demonstrated a female predominance, with a 3:1 female to male ratio of reactivity to steroids [6]. The most common corticosteroids that cause anaphylactic reactions are hydrocortisone, prednisone, and methylprednisolone [2]. It is unclear if this is due to the relatively increased administration of these drugs, or whether these particular corticosteroids truly have a higher propensity for inducing anaphylaxis. Many risk factors for hypersensitivity to corticosteroids have been identified, including allergies, asthma, eczema, NSAID hypersensitivity, organ transplant, and past high dose applications of corticosteroids [7].

To what degree the epidemiology and risk factors of hypersensitivity to corticosteroids are influenced by selection bias is unclear. This uncertainty of causation versus correlation is a recurring theme throughout the literature, given the limited research that has been performed on the subject. There is evidence that suggests selection bias is indeed a confounding factor, as demonstrated by the increased incidence of hypersensitivity in populations who frequently receive steroids, such as patients with multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus [8].

Surprisingly, cases have been reported in both patients with a prior history of exposure to corticosteroids and in patients without such a history [1]. There have also been cases reported of sensitization occurring

through a specific route of exposure, followed by a reaction to administration of a corticosteroid through a different route. For example, one case report demonstrated a hypersensitivity reaction following the administration of systemic corticosteroids in a patient whose only prior route of exposure had been through topical means. Another reported case described an anaphylactic reaction to intravenous methylprednisolone succinate following an isolated episode of sensitization through ocular administration [2, 9]. A diagram depicting sensitization is illustrated below in Fig. 1. Sensitization has been demonstrated through various different routes of administration, including nasal, aerosol, parenteral, oral, cutaneous, and even intra-articular [2]. There have also been recorded cases of cross-reactivity between different types of corticosteroids. For example, a patient who is sensitized to prednisone may later develop a reaction in response to methylprednisolone [1].

The exact cause of sensitization to corticosteroids is unknown, although several hypotheses exist. One such hypothesis suggests that the structural component of corticosteroids responsible for the induction of allergic reactions may be the native molecule itself or a metabolite that acts as a hapten to form an allergic complex [1]. This interaction is demonstrated below in Fig. 1. Thus, the interaction may be due to the small molecular weight of corticosteroids, which allows haptenization with a larger carrier protein. This combination of molecules may elicit a reaction, while the drug in its native form fails to produce such a response.

Figure 2: Demonstrates the mechanism resulting in immunogenic complexes through the formation of haptens.

Corticosteroids are also routinely conjugated to esters in order to increase their solubility for intravenous administration [3]. While this increases the solubility of corticosteroids, it also produces another potential source for a hypersensitivity reaction. Succinate esters in particular appear to have a higher propensity to induce sensitization compared to conjugation with other esters [7]. Of note, patients may tolerate a previously intolerable corticosteroid once it has been conjugated to an alternative ester [3, 10]. For instance, Angel-Pereira and colleagues demonstrated that a patient was unable to tolerate sodium-succinate hydrocortisone, but was able to tolerate sodium-phosphate hydrocortisone. In contrast, there are also reports of positive skin testing to corticosteroids uniquely in the absence of ester conjugation [1]. Figure 3 shows the classification of corticosteroids based on their chemical conjugation. Identification of the agent responsible for induction of anaphylactic reaction may allow for avoidance of corticosteroids with identical conjugations, thus preventing a reaction.

Figure 3. Classification of corticosteroids based on chemical composition [2]. May inform the choice of alternative corticosteroids available for administration during emergent situations in the setting of anaphylactic shock to prior corticosteroid use.

Alternatively, corticosteroids may also contain preservatives or excipients which may result in sensitization and subsequent hypersensitivity reaction [7]. Some such examples include lactose, carboxymethylcellulose, polyethylene glycol, and hexylene glycol. Such preservatives serve to increase the shelf life of the drug, while excipients bind to the active drug to facilitate entry and metabolism

systemically. Possible sensitization to these compounds amplifies the difficulty practitioners experience when attempting to identify the causative agent [2]. This concept may be responsible for the surprisingly common false negative skin prick test results in some patients with a definitive history of anaphylaxis in response to corticosteroids [10].

Reactions may also be due to non-immunologic means. For example, reactions similar to those associated with acetylsalicylic acid have been observed. In such a case, steroid-induced inhibition of cyclooxygenase blocks prostaglandin production, resulting in increased leukotriene production and the presentation of an aspirin-like asthma clinical picture that resembles anaphylaxis. Furthermore, reactions may also be due to mimicry of anaphylaxis due to rapid infusion of large amounts of corticosteroids. In this scenario,  $\alpha$ -adrenergic blockade and negative inotropy leads to cardiovascular collapse due to decreased cardiac output, resulting in clinical manifestations similar to those of anaphylaxis [7].

Classically, the diagnosis of corticosteroid induced anaphylaxis is based on the clinical history and physical exam [2]. However, as allergy testing has evolved, additional methods have been developed to further support this diagnosis. An algorithm of a diagnostic approach in patients with suspected corticosteroid hypersensitivity is included below in Fig. 4. In patients with a suspected immediate-type hypersensitivity reaction, it is recommended to utilize skin prick testing with a preparation of 15 mg/5 mL. A negative result should prompt follow up with a drug challenge at increasing concentrations. In patients with a suspected delayed phase hypersensitivity reaction, evaluation should begin with patch testing. A negative result should then be followed up with an incremental drug challenge [1, 2]. Other methods of diagnostic confirmation include the serial measurement of mast cell tryptase, immunoCAP assays, skin patch testing, lymphocyte transformation testing, and basophil activation testing [2, 11].

Despite the varying degrees of success, it is important to understand the various tests available to confirm anaphylactic response to corticosteroids. The immunoCAP assay measures IgE specific antigen levels [12]. Alternatively, lymphocyte transformation testing measures T-cell proliferation in response to an allergen with the goal of identifying delayed-phase allergic responses [13]. Basophil activation testing uses flow cytometry to measure IgE function, quantifying the body's ability to stimulate the activation of basophils following exposure to an allergen [14]. Given the rapidly evolving nature of allergy and immunology, any of these tests may see further improvement and subsequent prominence. Unfortunately, the current variant of these tests have an unacceptably high false negative rate [10]. This inaccuracy demonstrates the need for improvement in testing quality, which appears inevitable given the rapid rate of evolution of allergy testing. Thus, methods to accurately identify the causative agent of anaphylactic response to corticosteroids is essential in order to facilitate avoidance or rapid desensitization of corticosteroids for times of future use.

The management of corticosteroid-induced anaphylaxis is similar to the management of any other type of anaphylactic reaction. The most important component of treatment is epinephrine injection or infusion [2]. Epinephrine works as an agonist at both  $\alpha$ -1 and  $\beta$ -2 adrenergic receptors, leading to vasoconstriction with a decrease in mucosal edema and enhanced bronchodilation respectively [15]. This treatment

addresses two of the most severe issues in anaphylaxis: hypotension and bronchoconstriction. However, one study suggests that out of 200 deaths associated with anaphylaxis, as many as two and a half percent were a direct consequence of epinephrine overdose [16]. While this is important to recognize, the benefits of epinephrine use in the setting of anaphylaxis far outweigh the risks, making it the cornerstone of treatment.

Epinephrine administration in and of itself is insufficient in the treatment of anaphylaxis. Another critical component of treatment is early and aggressive volume resuscitation. Volume resuscitation addresses hypotension and can prevent vascular collapse. Vascular collapse can also be managed through altering body position. Supine or Trendelenburg positions are the preferred positions for patients in anaphylactic shock [11]. One article hypothesized that a patient in anaphylactic shock who sits up or stands may have decreased venous return and subsequent vascular collapse due to the increased capacity of veins and capillaries in the lower body. Furthermore, in this scenario, any amount of epinephrine given will not effectively circulate and will therefore be rendered inert [16]. Patients in anaphylaxis should also be maintained at a high oxygen saturation in case airway compromise occurs. In situations of refractory bradycardia, atropine or potent vasoconstrictors may be utilized [15].

Non-emergent management of anaphylaxis patients should include avoidance of the inciting agent if such an agent can be determined. However, corticosteroids may be necessary in certain circumstances. In these cases, we can manage the patient with rapid desensitization, though sensitivity returns almost immediately after desensitization ceases. One example of such a case is illustrated by the use of intravenous methylprednisolone hypersensitivity in a patient with multiple sclerosis. This corticosteroid is the first line treatment for a multiple sclerosis exacerbation. Due to the critical nature of the exacerbation, Angel-Pereira and colleagues successfully demonstrated rapid desensitization to the drug, and successfully treated the exacerbation [10].

Considering our case, we identified several limitations in evaluating our patient due to our setting. Given the nature of hospital medicine, we were unable to perform the majority of the preferred diagnostic testing. Additionally, patient follow up with the care team was non-existent. While we successfully managed the patient at the time of presentation, the opportunity to perform more testing may have elucidated the exact cause of our patients' anaphylaxis. In context to the discussion, our case raised awareness about the existence of anaphylaxis induced by corticosteroids. Prior to evaluating this patient, our team was completely unaware of this possibility. In the future, we will remain diligent in our evaluation of such patients and ensure that they receive appropriate treatment and counseling on the topics of future testing and management.

The field would benefit tremendously from additional studies focused on the development of tests with a higher degree of accuracy in identification of the causative agent of sensitization to corticosteroids. These tests would allow us to differentiate whether the responsible component is the native molecule itself or some other structural component. Additionally, further studies on the cross-reactivity between different classes of corticosteroids would also enhance our understanding of this condition. By accruing

more knowledge and data on the exact causes and diagnostic interventions, we could more efficiently identify and manage corticosteroid-induced anaphylaxis.

## Conclusion

This case report demonstrates an uncommon yet extremely important clinical condition. Corticosteroids are given as treatment and maintenance for a vast array of diseases, and as such, physicians should be wary of possible anaphylactic shock in any patient displaying the appropriate clinical signs. While of questionable accuracy, several tests are available to support this diagnosis in the background of an appropriate clinical picture. Management of this condition includes the use of epinephrine, volume resuscitation, supplemental oxygen, postural manipulation, rapid desensitization, and future avoidance of the inciting substance. Identification of the causative corticosteroid is also essential for the purpose of alternative corticosteroid use. While avoidance of corticosteroids is ideal following an anaphylactic reaction, rapid desensitization is a viable and safe alternative when necessary. Most importantly, clinicians should be aware that anaphylaxis may result following corticosteroid use and must be knowledgeable of the diagnosis and management of this potentially fatal condition.

## Declarations

### Ethics Approval and Consent to Participate

Not applicable.

### Consent for Publication

Consent was obtained and this manuscript was cleared by HCA HealthONE PubClear.

### Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the production of this manuscript.

### Competing Interests

The authors declare that they have no competing interests.

### Funding

The authors declare that they received no funding for the production of this manuscript.

### Authors Contributions

RG was the resident physician overseeing the patient discussed in this manuscript and made substantial contributions to its conception and editing. GH was the attending physician and oversaw the compilation



of this case report. NC was the first author of the manuscript, analyzed and interpreted patient data, compiled literature evidence, and edited the case report. TC was the second author of the paper, compiled literature for analysis for this manuscript, and participated in editing. All authors read and approved the final manuscript.

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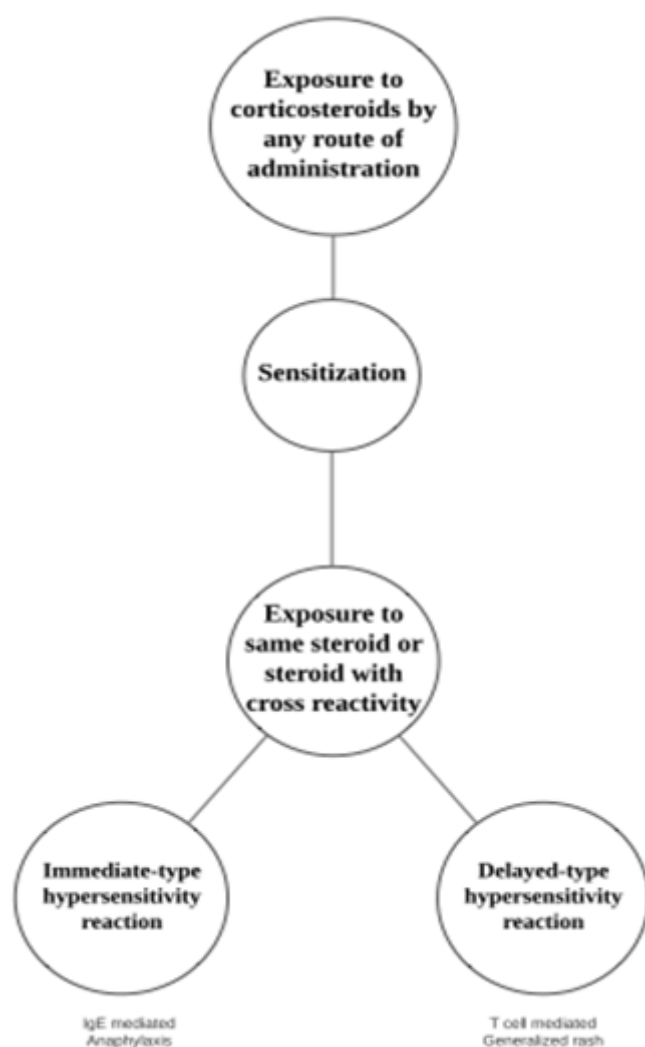
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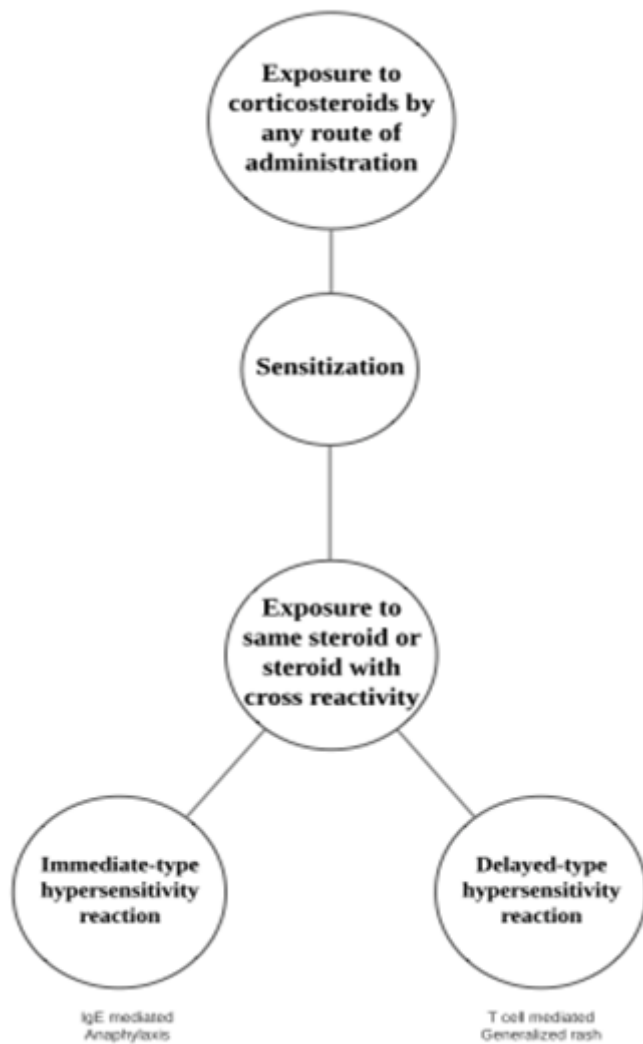
## Figures



**Figure 1**

**Figure 1**

Mechanism of hypersensitivity to corticosteroids. Adapted from [2].



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Mechanism of hypersensitivity to corticosteroids. Adapted from [2].



Figure 2

Figure 2

Demonstrates the mechanism resulting in immunogenic complexes through the formation of haptens.



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Demonstrates the mechanism resulting in immunogenic complexes through the formation of haptens.

Classification	A	B	C	D	
				D1	D2
Characteristics	No substitution on the D ring except a short chain ester or thioester on C21	Acetonides	Methylation on C16	Methylation on C16  Halogen substitution	No methylation on C16  No halogen substitution Side chain ester on C17 Possibly side chain ester on C21
Examples	Hydrocortisone  Prednisolone Methylprednisolone  And their ester acetates, sodium phosphates, and succinated Cortisone acetate  Prednisone  Tixocortol pivalate <sup>a</sup>	Triamcinolone acetonide  Fluocinolone acetonide Halcinonide Desonide  Fluocinonide  Budesonide <sup>a</sup>	Betamethasone  Dexamethasone Desoximetasone  Fluocortolone	Clobetasone-17-butyrate  Clobetasol-17-propionate Beclomethasone dipropionate Betamethasone valerate Betamethasone dipropionate	HC-17-propionate HC-17-butyrate Methylprednisolone aceponate Prednicarbate Difluprednate

<sup>a</sup> Used in patch tests

**Figure 3**

Classification of corticosteroids based on chemical composition [2]. May inform the choice of alternative corticosteroids available for administration during emergent situations in the setting of anaphylactic shock to prior corticosteroid use

Classification	A	B	C	D	
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Characteristics	No substitution on the D ring except a short chain ester or thioester on C21	Acetonides	Methylation on C16	Methylation on C16  Halogen substitution	No methylation on C16  No halogen substitution Side chain ester on C17 Possibly side chain ester on C21
Examples	Hydrocortisone  Prednisolone Methylprednisolone  And their ester acetates, sodium phosphates, and succinated Cortisone acetate  Prednisone  Tixocortol pivalate <sup>a</sup>	Triamcinolone acetonide  Fluocinolone acetonide Halcinonide Desonide  Fluocinonide  Budesonide <sup>a</sup>	Betamethasone  Dexamethasone Desoximetasone  Fluocortolone	Clobetasone-17-butyrate  Clobetasol-17-propionate Beclomethasone dipropionate Betamethasone valerate Betamethasone dipropionate	HC-17-propionate HC-17-butyrate Methylprednisolone aceponate Prednicarbate Difluprednate

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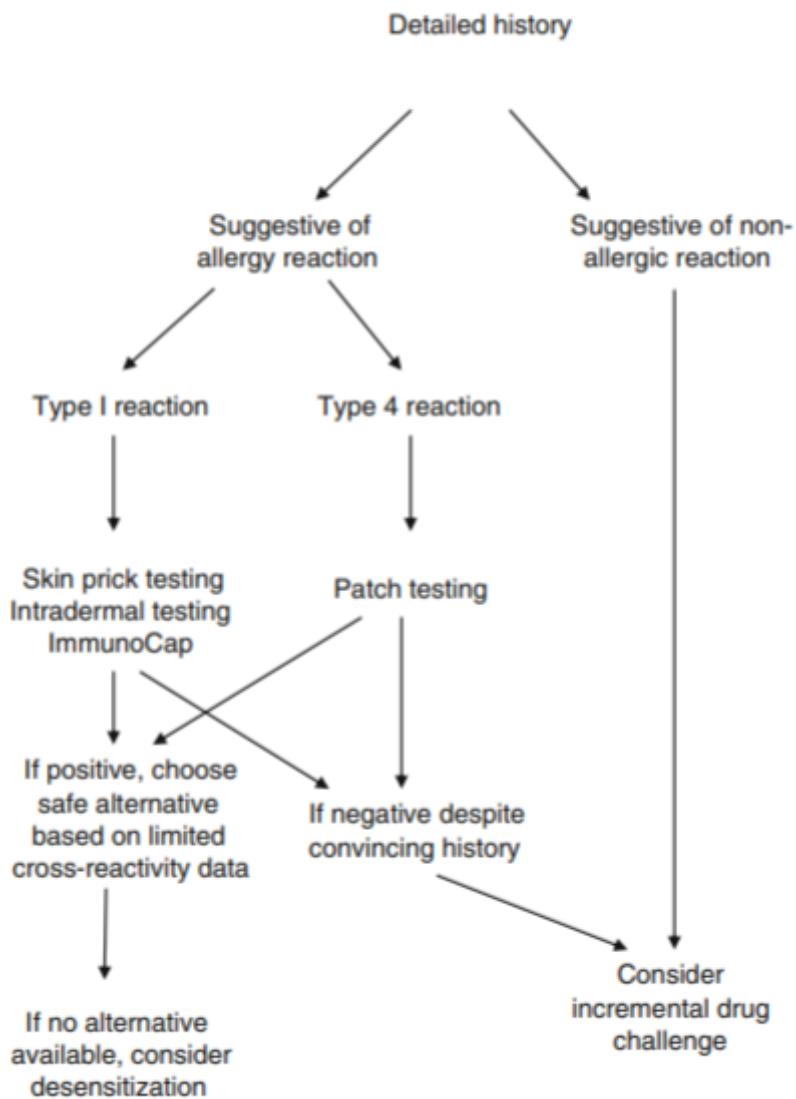


Figure 4

Algorithm for diagnostic approach to corticosteroid-induced hypersensitivity [2].

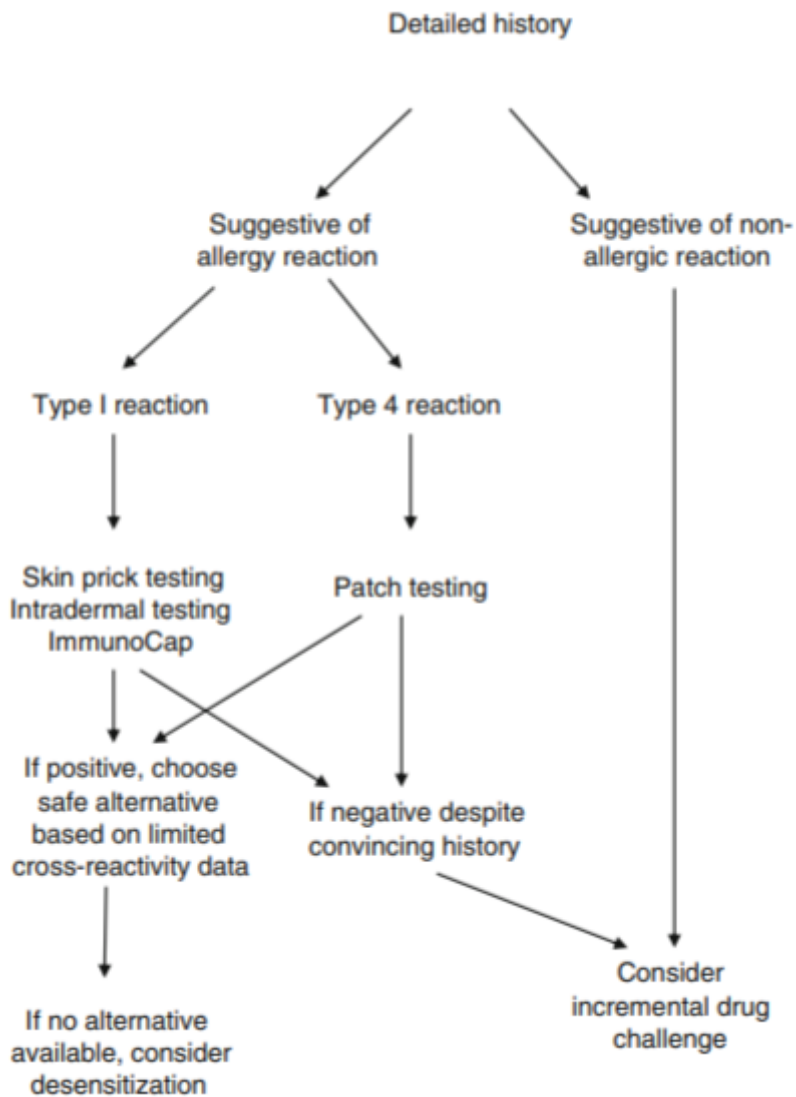


Figure 4

Algorithm for diagnostic approach to corticosteroid-induced hypersensitivity [2].