Delayed Cutaneous Hypersensitivity Reactions to Antibiotics

Management with Desensitization

Caitlin M.G. McNulty, MD, Miguel A. Park, MD*

KEYWORDS

• Antibiotic allergy • Delayed cutaneous adverse reactions • Desensitization
• Management

KEY POINTS

- Mild to moderate delayed cutaneous adverse reactions to antibiotics can be successfully desensitized.
- Severe cutaneous adverse reaction to antibiotics is a contraindication to desensitization.
- Future research opportunities to the mechanism and protocol standardization for delayed cutaneous adverse reactions to antibiotics is needed.

INTRODUCTION

Drug reactions are a common event complicating patient care and can be immunologically mediated. Studies estimate that the incidence of drug reactions mediated by an immunologic mechanism is between 2.3 to 3.6 per 1000 patients, with almost all these reactions involving the skin and antibiotics being the most frequent precipitants of cutaneous reactions.[1–4] The incidence of delayed drug reactions is not well characterized because most epidemiologic studies of cutaneous drug reactions are retrospective and firm demonstration of causality is difficult. One study estimates that Gel-Coombs type IV reactions account for approximately 25% of hypersensitivity reactions and 5% of all adverse drug reactions; however, other studies estimate that 64% of drug reactions are delayed.[3,5] Management of patients with delayed cutaneous adverse reactions to antibiotics is mainly avoidance and use of alternative antibiotics. Alternatively, desensitization to an antibiotic that is suspected to have caused the delayed cutaneous adverse reactions has been described in the literature.

Disclosure Statement: None.
Division of Allergic Diseases, Mayo Clinic, 200 1st Street Southwest, Rochester, MN 55905, USA
* Corresponding author.
E-mail address: park.miguel@mayo.edu

Immunol Allergy Clin N Am 37 (2017) 751–760
http://dx.doi.org/10.1016/j.iac.2017.07.002
immunology.theclinics.com

This article explores the current literature of desensitization to delayed cutaneous adverse reactions to antibiotics.

PATHOPHYSIOLOGY

Given recent advancements in the understanding and management of drug allergy, a new classification system has been proposed by the recent PRACTALL guidelines to aid in the appropriate use of available testing and risk stratification.[6,7] This new classification system involves dividing drug reactions by phenotype and endotype, rather than using the traditional Gel-Coombs classification system, which is cumbersome in the face of recent understanding of the diverse mechanisms of drug allergy.[7] Here, phenotype refers to the timing of the drug reaction, with reactions occurring within 6 hours of administration as representative of immediate drug reactions, whereas reactions occurring in the days to weeks following administration are delayed.[7] Drug reactions are further classified by endotype, which describes the mechanism through which the reaction occurs. For example, immediate onset of urticaria following administration of penicillin would have been classified as a Gel-Coombs type 1 reaction, which now would be understood as an immediate, immunoglobulin (Ig)-E–mediated drug allergy, whereas the classic reaction to abacavir would be described as a delayed, human leukocyte antigen (HLA)-associated drug reaction (**Table 1**). This allows more precise labeling of drug allergy as understanding of drug-mediated reactions increases.

Delayed drug reactions have a variety of manifestations and the pathways by which they occur have not been fully elucidated. Drug reaction with eosinophilia and systemic symptoms (DRESS), as well as maculopapular exanthema with eosinophilia, are manifestations of an eosinophil-mediated endotype, whereas Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are secondary to a cytotoxic T-cell–mediated endotype. Agranulocytosis exanthematous pustulosis (AGEP) is characterized by the formation of sterile pustules by neutrophil recruitment. The effects of delayed drug reactions can affect the liver, kidneys, and lungs, in addition to hematopoiesis; however, skin reactions are the most common manifestation. This is thought to be due to the presence of high numbers of primed cells of both innate and adaptive immunity in the skin.[5] Due to the heterogeneous immune mechanisms that can precipitate a delayed adverse cutaneous drug eruption, there is diversity in the way drug reactions manifest in the skin. Maculopapular rashes are the most frequent, although life-threatening reactions are rare.[4] The mortality rate of these reactions is 1% to 5% in SJS and up to 25% to 35% in TEN.[8]

Outside of genetic tests for certain HLA haplotypes that are associated with severe adverse cutaneous reactions, there is no validated testing to determine if a patient is

Table 1
Phenotypes and endotypes of drug allergy to trimethoprim sulfamethoxazole

Reaction	Phenotype	Endotype
Anaphylaxis	Immediate	IgE-mediated
SJS	Delayed	Cytotoxic T cell
Maculopapular Rash	Delayed	Unknown
Serum Sickness	Delayed	Immune complex deposition
Aseptic Meningitis	Delayed	Possibly neutrophilic

Data from Refs.[25,26,30,32,33]