Outpatient Management and Follow-up Recommendations for Adverse Drug Reactions: Guidelines for Posthospitalization Care

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PRACTICE **POINTS**

- In the setting of an adverse drug reaction (ADR), discontinuing the concerning medication is the first and most important step.
- Acute generalized exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, and Stevens-Johnson syndrome/toxic epidermal necrolysis all require specific outpatient follow-up after discharge.

Acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) are types of adverse drug reactions (ADRs), each with their own set of characteristic symptoms and sequelae. Although guidelines for inpatient management of these conditions exist, guidelines for outpatient follow-up are lacking. Based on the existing literature, we propose guidelines for outpatient follow-up of AGEP, DRESS, and SJS/TEN.

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It has been estimated that 2 million serious adverse drug reactions (ADRs) occur annually in the United States, resulting in 100,000 deaths.[1] Although the acute morbidity and mortality of these ADRs are readily apparent, postdischarge sequalae are critical aspects of a patient's care. Herein, we present an approach to outpatient dermatologic follow-up of 3 ADRs: acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). For these ADRs, the first step is prompt diagnosis and discontinuation of any potentially causative medications.

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

Ninety percent of the time, AGEP is caused by medications, most commonly antibiotics, and less often it is caused by viruses.[2-4] It presents as a cutaneous eruption with nonfollicular sterile pustules, fever, and leukocytosis, usually within 5 days after starting a causative medication.[5] After stopping the medication, cutaneous findings generally improve within 1 week, and leukocytosis often resolves within 1 week.[3]

Notable Sequelae

Although AGEP typically is considered benign,[2] there have been reports of severe sequelae including death from a systemic inflammatory response and complications such as bacterial superinfection and sepsis.[6,7] Visceral involvement can be seen in up to 20% of AGEP patients, with systemic symptoms similar to those seen in DRESS syndrome. Mortality has been reported in up to 5% of cases, mainly in patients with comorbidities and notable mucosal involvement.[8] More severe disease can be seen in patients with known dermatologic disease, as AGEP can provoke an isomorphic phenomenon.[9] Laboratory alterations typically seen in AGEP include neutrophilia, eosinophilia, and elevated liver enzymes.[2]

Follow-up Recommendations

Patients should be informed of the expected timeline for resolution and should be counseled on the possibility of rare systemic symptoms. Laboratory abnormalities should be monitored every 2 to 4 weeks until normalized.

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DRESS SYNDROME

DRESS syndrome is characterized by a morbilliform eruption that can be accompanied by fever; eosinophilia; purpura; facial edema; lymphadenopathy; and liver, renal, or other organ dysfunction. DRESS syndrome most often presents within 8 weeks of exposure to a causative drug.[10,11] The most common causative agents are anticonvulsants, antimicrobials, and allopurinol.[12] Treatment includes topical corticosteroids and systemic corticosteroids for internal organ involvement.[10]

Short-term Sequelae

Several potential sequelae may occur within 6 months of resolution of DRESS syndrome, resulting from both the ADR itself and/or systemic corticosteroids that often are required for treatment.[13] Complications secondary to herpesviruses have been reported.[14] Cases of cytomegalovirus-induced gastric ulcers can lead to gastrointestinal tract bleeds.[15]

Infections including *Cryptococcus* species and herpes zoster also have been reported.[16] Patients, particularly those treated with systemic corticosteroids, should be monitored with close follow-up for infectious complications and treatment-related adverse effects.[13]

Long-term Sequelae

Endocrine—Thyroid gland abnormalities secondary to DRESS syndrome include Graves disease and Hashimoto disease as well as variations in biomarkers including elevated free thyroxine and low and elevated thyroid-stimulating hormone levels.[16,17] Type 1 diabetes mellitus also has been seen after DRESS syndrome, developing within the first 10 months after onset with unknown pathogenesis.[18]

Autoimmune—Other reported sequelae of DRESS syndrome include elevated antinuclear antibodies with possible development into systemic lupus erythematosus, autoimmune hemolytic anemia, vitiligo, and rheumatoid arthritis.[11,16] Symptoms may be exacerbated in patients with preexisting autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis, and patients with preexisting renal disease are at an increased risk for requiring lifelong hemodialysis after DRESS syndrome.[16]

Other—Studies have demonstrated that pneumonia, thrombosis, and alopecia can be complications of DRESS syndrome.[11,16] Psychiatric disturbances including fear of taking new medications, anxiety, and depression also have been reported.[19] Children with DRESS syndrome may develop vitiligo, alopecia, sclerodermatous lesions, photophobia, uveitis, and Vogt-Koyanagi-Harada disease.[17]

Follow-up Recommendations

It is important to inform patients of both the potential short-term and long-term sequelae of DRESS syndrome, including those associated with treatment. A thorough review of systems should be performed at each visit, along with laboratory evaluation including a complete blood cell count with differential and liver function testing every 1 to 2 weeks after discharge until normalized, with monthly monitoring of glucose, thyroid-stimulating hormone, and free thyroxine levels for 3 months after discharge.

STEVENS-JOHNSON SYNDROME/ TOXIC EPIDERMAL NECROLYSIS

Stevens-Johnson syndrome/toxic epidermal necrolysis are severe ADRs that present with dusky violaceous macules. Inciting medications include nonsteroidal anti-inflammatory drugs, allopurinol, antibiotics, and anticonvulsants, and symptoms begin 1 to 3 weeks after medication exposure.[12] Initially, the lesions often begin on the trunk and can progress to full-body erythema and exfoliation with a necrotic epidermis and mucosal involvement.[12,20]

Notable Sequelae

Cutaneous—Chronic eczema can present at any time and can vary in severity in SJS/TEN patients.[21] Xerosis and pruritus can be treated with emollients.[11] Dyschromia is common. Hypertrophic and keloidal scarring can result from surgical debridement and are best prevented with the use of nonadherent dressings.[22] Nail changes such as anonychia, dystrophy, longitudinal ridges, and pterygium also are seen, and topical steroids can be helpful. Other reported dermatologic sequelae include dyschromia and eruption of ectopic sebaceous glands.[21,22]

Ocular—Ocular sequelae include dry eyes, photophobia, symblepharon, corneal scarring, corneal neovascularization, corneal xerosis, trichiasis, reduced visual acuity, blindness, and subconjunctival fibrosis. The most common sequelae are bilateral conjunctivitis and corneal ulcerations.[22,23] Early and regular ophthalmologic follow-up is recommended, as SJS/TEN-induced blindness can result from delayed therapy, destroying corneal stem cells.[21] Amniotic membrane transplantation replaces the damaged corneal membrane, which may reduce corneal inflammation.[24]

Chronic dry eye syndrome can recur for years after SJS/TEN resolves and progresses over time.[22] Frequent use of nonpreserved artificial tears and salivary gland transplantation can be helpful.[24] Unfortunately, ocular disease may develop months after discharge; therefore, it is recommended that dermatologists ask all SJS/TEN patients about ocular symptoms in follow-up visits. If ocular involvement was present initially, patients should be followed by ophthalmology for at least 1 year after discharge.[23]

Genitourinary—Genitourinary sequelae in SJS/TEN include adhesions, particularly in the female urethra and vaginal opening; vaginal adenosis; vulvovaginal endometriosis; and persistent genital ulcerations most commonly reported in females.[22] Prompt inpatient gynecologic or urologic consultation is critical to reduce these potentially permanent outcomes. Topical corticosteroid therapy is recommended in the acute phase.[22]

Psychologic—Posttraumatic stress disorder may occur in patients with SJS/TEN. One study showed that 23% (7/30) of patients had posttraumatic stress disorder 6 months

after hospitalization for SJS/TEN. The investigators recommended routine psychiatric assessment in the acute disease period and for at least 1 year after discharge.[25]

Pulmonary, Gastrointestinal, and Renal—Interstitial pneumonia and obliterative bronchitis/bronchiolitis can be caused by SJS/TEN. Interstitial pneumonia tends to occur during the acute course, while obliterative airway disease manifests after resolution of SJS/TEN.[21,22] Abnormal pulmonary function testing can be seen in more than half of SJS/TEN patients 2 months after the ADR.[22] Gastrointestinal sequelae include esophageal strictures, intestinal ulceration, and cholestasis.[22] Renal sequelae include acute kidney injury and glomerulonephritis, which may be secondary to the volume loss seen in SJS/TEN but may be irreversible.[21]

Special Populations—A correlation with infertility in women has been documented in patients with SJS/TEN; thus, follow-up with obstetrics and gynecology is recommended in women of child-bearing potential. The most considerable risk in pregnant women with SJS/TEN is premature birth, and mucosal necrosis of SJS/TEN can impair vaginal delivery.[26] Antiretrovirals can be a cause of SJS/TEN in the human immunodeficiency virus–positive population.[27] In those cases, it is best to discontinue the medication and find an alternative.

Risk factors for children can be different and can include viral and febrile illnesses as well as mycoplasma infection.[28] Children also can be at an increased risk for poor ocular outcomes, such as permanent deficiency in visual acuity and blindness.[29]

Follow-up Recommendations

Patients should be counseled regarding sequelae and the multisystem nature of SJS/TEN. Inpatient referrals should be given as needed. It is important to watch for ocular symptoms for 1 year after SJS/TEN resolution. When ocular involvement is present, follow-up with ophthalmology is recommended within 1 month of discharge and then at the discretion of the ophthalmologist. Pulmonary function should be monitored for 1 year after SJS/TEN, starting 1 month after discharge and then at the discretion of the pulmonologist. Patients also should be screened for psychologic sequelae for at least 1 year after discharge.

FINAL THOUGHTS

Adverse drug reactions are notable causes of inpatient hospitalization and may lead to considerable sequelae. These ADRs range in severity from more common and benign maculopapular exanthems to severe multiorgan ADRs such as DRESS syndrome and SJS/TEN.

In AGEP, it is important to monitor patients with preexisting dermatologic diseases and to screen for visceral involvement. DRESS syndrome has the potential to cause immune dysregulation and variable long-term adverse sequelae, both from the disease itself and from corticosteroid therapy. Mucocutaneous sequelae of SJS/TEN can potentially affect a patient's cutaneous, ocular, genitourinary, mental, pulmonary, gastrointestinal, and renal health.

The baseline recommendations provided here warrant more frequent monitoring if the findings and symptoms are severe. In all of these cases, if a causative medication is identified, it should be added to the patient's allergy list and the patient should be counseled extensively to avoid this medication and other medications in the same class. If a single agent cannot be identified, referrals for patch testing may be of some utility, particularly in AGEP and DRESS syndrome.[30,31]

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CONTINUED ON PAGE 258

CONTINUED FROM PAGE 256

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