

Table 1
Measures of interrater agreement for acute asthma intensity research score (AAIRS) among clinical team members caring for children with acute asthma exacerbations

Component	RT vs RN		RT vs Physician or NP		RN vs Physician or NP		Overall	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
SCM ^a	0.51	0.63	0.49	0.70	0.35	0.81	0.40	0.36
Intercostal ^a	0.76	0.63	0.53	0.53	0.27	0.42	0.43	0.23
Subcostal ^a	0.71	0.64	0.67	0.48	0.64	0.42	0.60	0.37
Air entry ^a	0.22	0.14	0.30	0.29	0.24	0.25	0.19	0.18
Wheezing	0.35	0.34	0.46	0.25	0.16	0.32	0.25	0.21
SpO ₂ ^a	0.62	0.69	0.60	0.36	0.40	0.49	0.40	0.41
Expiratory phase ^a	0.21	0.35	0.26	0.34	0.06	0.35	0.12	0.28
Total score ^b	0.74	0.64	0.77	0.66	0.61	0.53	0.65	0.49

Abbreviations: NP, nurse practitioner; RN, registered nurse; RT, respiratory therapist; SCM, sternocleidomastoid muscle; SpO₂, transcutaneous pulse oximetry.

^aκ statistic (categorical variable).

^bIntraclass correlation coefficient (continuous variable).

components of the score that have poor interrater reliability. Specifically, the evaluation of air entry, wheezing, and the expiratory phase have particularly poor interrater reliability before and after treatment. We believe this might relate to the lack of formal training in the AAIRS during the study period. Despite these observations, the AAIRS predicts PED disposition.⁸

The evaluation of asthma severity involves clinical assessment and spirometry when possible. However, there is evidence that concordance between spirometry and asthma symptoms can be low, with a significant proportion of children having greater severity of asthma on spirometry than would be predicted by clinical symptoms alone.⁹ Therefore, there is a need for clinical tools that help to better predict asthma severity and that are available at the bedside.

There are a number of pediatric asthma exacerbation scores available for clinical use, but few have been sufficiently validated.¹⁰ The AAIRS has been validated against forced expiratory volume in 1 second and has demonstrated similar discrimination and responsiveness to another score, the Pediatric Respiratory Assessment Measure.⁶ A next step is to implement an educational video that teaches correct severity assessment of pediatric asthma exacerbations using the AAIRS. After implementation of this teaching tool, we plan to reevaluate the interrater reliability of the AAIRS.

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Anaphylaxis as a delayed reaction of methimazole therapy



The thionamides methimazole and propylthiouracil are the most commonly used antithyroid medications for the treatment of Graves disease but are associated with a high frequency of adverse effects. The most common adverse reactions are hepatotoxicity, agranulocytosis, and cutaneous reactions.¹ Mild pruritus, urticaria, and rashes are the most common cutaneous reactions reported.² We report the case of an 18-year-old woman with Graves disease, who presented with repeated episodes of anaphylaxis after treatment

with methimazole for 5 years. Anaphylactic reactions subsided only after withdrawal of methimazole therapy.

An 18-year-old woman with a history of Graves disease was admitted with 3 days of sensation of throat closing; tongue, lip, and facial swelling; urticaria; shortness of breath; and recurrent bouts of emesis. Symptoms were unresponsive to prednisone, which was given at another hospital the day before. Medications included methimazole and atenolol with variable adherence to methimazole therapy. Her medical history included Graves disease treated with various doses of methimazole for 5 years, followed by an unsuccessful radioactive iodine ablation 3 months before presentation. Because of persistent clinical and biochemical hyperthyroidism, her

Disclosures: Dr Gavrilova has served as a consultant for Baxter. The other authors have nothing to disclose.

Table 1
Percutaneous methimazole testing^a

Methimazole concentration, mg/mL	Test
10	SPT
0.01	ID
0.1	ID
1	ID
10	ID

Abbreviations: ID, intradermal test; SPT, skin prick test.

^aEach test was performed 15 minutes apart.

methimazole dose was increased to 25 mg twice a day 1 month before admission.

On initial presentation, she was afebrile, tachypneic (respiratory rate, 28/min), and tachycardic (heart rate, 133–154/min), with systolic and diastolic blood pressures of 116 to 165 mm Hg and 53 to 85 mm Hg, respectively. Physical examination findings were significant for hoarseness, pharyngeal erythema, and swelling of the lips, tongue, and face. Anaphylaxis was suspected based on World Allergy Organization guidelines, and she was treated with intramuscular epinephrine, intravenous diphenhydramine, and methylprednisolone, with resolution of symptoms within 2 hours.³

Laboratory evaluation revealed a normal complete blood cell count with no peripheral eosinophilia, total IgE level of 33.9 IU/mL (reference range, 0–100 IU/mL), sedimentation rate of 9 mm/h (reference range, 0–20 mm/h), and negative rapid streptococcus and throat culture results. Her tryptase level was 3 ng/mL (reference range, 2–10 ng/mL), ruling out systemic mastocytosis. Hereditary angioedema was ruled out with the presence of urticaria, a normal C4 level of 40 mg/dL (reference range, 17–64 mg/dL), a C1q level of 6.2 mg/dL (reference range, 5–8.6 mg/dL), and an elevated level of C1 esterase inhibitor of 52 mg/dL (reference range, 21–39 mg/dL) with 100% normal function (reference range, >68%). She was biochemically hyperthyroid with an elevated free thyroxine level of 2.67 ng/dL (reference range, 0.8–1.7 ng/dL) and a low thyrotropin level of less than 0.005 (reference range, 0.400–4.60 μ U/mL).

The patient was admitted for further evaluation. She continued to have recurrent symptoms less than 24 hours apart and was responsive only to epinephrine. Our allergy evaluation revealed no food, insect, or infectious triggers based on history and laboratory values. Considering that her symptoms were only responsive to epinephrine, we suggested holding methimazole treatment because it was her only recent medication change. Methimazole was changed to propylthiouracil, 150 mg every 8 hours. Atenolol therapy was continued. She remained asymptomatic while taking propylthiouracil and was discharged home with an epinephrine autoinjector.

Drug allergy testing 4 weeks later revealed negative skin prick test and intradermal test results with methimazole at variable concentrations with a good histamine response (Table 1). However, approximately 8 hours later, the patient self-reported that she developed pruritus, erythema, and induration at the 10-mg/mL intradermal site.

The patient's initial presentation fulfills the criteria for anaphylaxis, and her recurrent episodes did not subside until she stopped taking methimazole. However, the time course is atypical for an IgE-mediated hypersensitivity reaction because her reactions were not immediate and occurred approximately 4 to 7 hours from the time she received her methimazole in the hospital. In addition, she had been taking methimazole for 5 years before presentation, with only a recent increase in dose a month before her presentation. Furthermore, her tryptase level was normal at

the time of her symptoms, her initial skin test results were negative, and she only developed induration and pruritus 8 hours after leaving our office.

There is limited literature regarding severe reactions, such as anaphylaxis, with methimazole. In a study of 100 pediatric patients with Graves disease, there was a 19% prevalence of adverse reactions, mostly pruritus, drug rash, and urticaria. Up to 90% of events occurred within 6 months of therapy, and only 3 children experienced events after 1½ years of treatment.²

There are 2 case reports describing serious reactions to methimazole. The first case presented as angioedema of the face, urticarial rash, and dyspnea that occurred days after initiation of methimazole therapy.⁴ The second case describes pruritus and urticarial rash 3 weeks after initiation of methimazole therapy with a dose of 15 mg twice daily.⁵ Treatment was discontinued and restarted 10 days later at a reduced dosage of 10 mg twice daily, with worsened urticaria and angioedema of the tongue and throat after reinstatement.⁵ Both cases, however, describe severe reactions that occurred within a month of initiating treatment. Our case is the first description of a serious adverse event caused by methimazole after 5 years of therapy, albeit intermittent secondary to nonadherence. Other medications that cause delayed anaphylaxis have also been reported with omalizumab, β -lactams, and intramuscular L-asparaginase.⁶

It is possible that our patient began to develop symptoms secondary to an increase in her methimazole to 25 mg twice a day. A previous study that examined the association between methimazole and propylthiouracil dosing and adverse events found that the frequency of adverse effects was lower with the 15-mg/d propylthiouracil dosing than with 30-mg/d propylthiouracil and 300-mg/d propylthiouracil dosing.⁷ Therefore, a direct relationship exists for methimazole with adverse events and an increase in dosing. Interestingly, hepatotoxicity developed later than cutaneous reactions for all 3 doses.⁷ It is possible that initial cutaneous reactions should alert the physician to further systemic adverse effects in the future. Furthermore, a normal tryptase level in the clinical setting consistent with anaphylaxis does not rule out anaphylaxis, especially one that is drug induced.

Our patient's skin tests were also atypical for an IgE-mediated hypersensitivity reaction. She developed delayed-onset pruritus, persistent erythema, and possible induration at the 10-mg/mL intradermal site, which correlated with her delayed symptom onset. Allergists should be aware that anaphylactic reactions to methimazole may be atypical in presentation with delayed onset and normal tryptase levels. Skin test results may not be immediately positive and should be followed up within 8 to 10 hours.

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Giant cell myocarditis in hypersensitivity reactions: is an early diagnose possible?



Hypersensitivity reactions include many types of clinical patterns. Among them, drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe delayed-type drug-induced reaction, with estimated incidence ranges of 1 in 1,000 to 1 in 10,000 drug exposures.¹ DRESS is characterized by rash, fever, hematologic abnormalities, internal organ involvement, reactivation of viral infections, and a prolonged resolution time.² In these cases, myocarditis can occur in various forms: hypersensitivity myocarditis, a generally self-limited form; acute necrotizing eosinophilic myocarditis, with a more rapid progression and a poorer prognosis³; and last but not least, giant cell myocarditis (GCM),⁴ which is a life-threatening form of myocarditis that affects young and middle aged persons and is typically related to tumors; autoimmune, infectious, and idiopathic diseases; and hypersensitivity reactions, including DRESS.⁵

We report a case of DRESS due to minocycline in a young woman who developed giant cell myocarditis with rapid demise. To our knowledge, there are 2 publications on hypersensitivity reactions with GCM related to minocycline; however, this is the first case with histologic confirmation before the patient's death. We want to emphasize the importance of considering this complication to act in a timely manner.

The patient was a 20-year-old woman who developed a maculopapular exanthema, lateral cervical lymphadenopathies (diameter of approximately 1.5 cm), erythematous pharynx and tonsils, and fever (temperature >39°C) 4 weeks after initiation of treatment with minocycline for acne. The patient discontinued minocycline treatment spontaneously 24 hours when the first symptoms occurred, and she presented immediately to the emergency room (ED).

Blood tests performed in the ED revealed leukocytosis (leukocyte count, 21,000/ μ L), eosinophilia (eosinophil count, 1,100/ μ L), and hepatic enzymes alterations (aspartate aminotransferase, 103 U/L; alanine aminotransferase, 155 U/L).

The results of serologic tests were negative for a recent infection with adenovirus, Epstein-Barr virus, cytomegalovirus, human herpesvirus 6, parvovirus B19, Coxsackievirus, hepatitis C virus, hepatitis B virus, *Rickettsia prowazekii*, *Toxoplasma gondii*, *Leishmania donovani*, *Chlamydia pneumoniae*, and human immunodeficiency virus. Polymerase chain reaction results for *Borrelia burgdorferi*, *Enterovirus*, varicella-zoster virus, herpes simplex virus, cytomegalovirus, Epstein-Barr virus, and H1N1 virus were negative too.

The immunologic study disclosed normal complement and immunoglobulin levels, negative rheumatoid factor, and absence of anti-DNA, anti-histone, anti-nuclear, anti-SSA, anti-SSB, anti-SSM, anticardiolipin, and antiphospholipid antibodies.

The patient achieved the RegiSCAR study criteria for DRESS; thus, methylprednisolone treatment (32 mg/d) was initiated and maintained for 3 weeks. The symptoms, hepatic enzymes, leukocytosis, eosinophilia, and cutaneous rash improved, but a week after corticosteroid treatment discontinuation she developed fever,

malaise, and abdominal and chest pain with dyspnea. Blood tests revealed leukocytosis (leukocyte count, 16,000/ μ L) with atypical leukocytes and mild eosinophilia (eosinophil count, 600/ μ L). Electrocardiography (ECG) revealed a right bundle branch block. Treatment with high doses of corticosteroids (methylprednisolone, 20 mg every 8 hours), prophylactic antibiotics (vancomycin, meropenem), fluconazole, and diuretic drugs was initiated, although no patients had positive blood culture results. The patient was moved to the intensive care unit. Thoracic computed tomography revealed pleural effusion, and echocardiography revealed a severe left ventricle dysfunction (ejection fraction, 10%) and pericardial effusion. Subsequent ECG revealed ST-segment elevation, with increased cardiac enzymes (CK-MB, 45 U/L; TnI, 4.0 μ g/L). Treatment with diuretics and fluid therapy was initiated. Despite treatment, liver function deteriorated (alanine aminotransferase, 478 U/L; aspartate aminotransferase, 583 U/L), and the patient developed multiorgan failure. An intra-aortic balloon pump was placed and an endomyocardial biopsy performed. The endomyocardial biopsy specimen revealed endocardial fibrosis, interstitial lymphocytes, eosinophils, necrotic myocytes, interstitial edema, and giant multinucleated cells (Fig 1).

Immunosuppressive treatment (mycophenolate, 1,000 mg every 12 hours, and antithymocyte globulin, 75 mg/d) was initiated, treatment with antibiotics and corticosteroids was continued as described above, and gancyclovir (250 mg every 12 hours) was administered as pretransplant prophylaxis against cytomegalovirus. Although repetitive blood cultures were sterile, the antibiotic treatment was maintained so a cardiac transplant could be performed.

An urgent cardiac transplant was performed, but the patient died of primary graft failure. Although other tetracyclines are known to have many adverse effects, minocycline and doxycycline

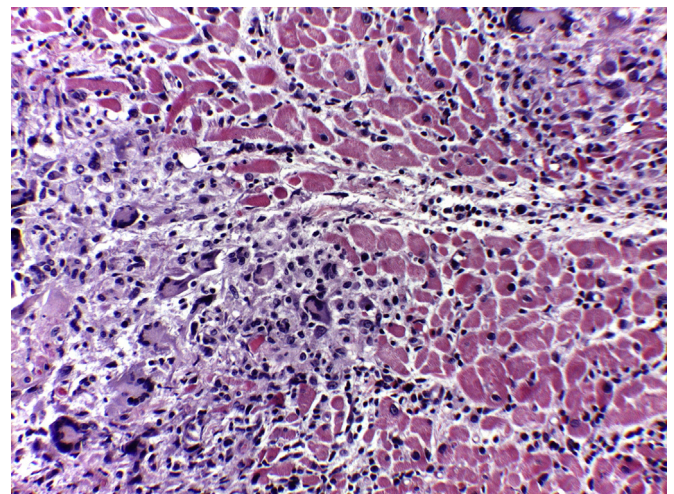


Figure 1. Lymphocytes, eosinophils, and histiocytes infiltrate the myocardium with a nodular pattern, with many giant multinucleated cells, myocardial necrosis, and edema.