

# Daptomycin-induced Acute Eosinophilic Pneumonia

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## ABSTRACT

**Introduction:** Daptomycin is a cyclic lipopeptide antibiotic with activity against gram-positive organisms. With increasing use, acute eosinophilic pneumonia is a rare, but potentially fatal adverse drug reaction that requires prompt recognition. The authors present a definite case of daptomycin-induced acute eosinophilic pneumonia.

**Case Summary:** A 61-year-old woman with poorly controlled type 2 diabetes who presented with bilateral foot pain was found to have bilateral calcaneal osteomyelitis. She was started on an antibiotic regimen that included daptomycin. Within 1 week, she developed fever, a dry cough, and shortness of breath and was treated for hospital-acquired pneumonia (HAP). Daptomycin was discontinued. Upon completion of therapy for HAP, the patient was subsequently restarted on daptomycin for continued therapy of bilateral calcaneal osteomyelitis. Within 48 hours of restarting daptomycin, the patient developed hypoxemic respiratory failure, bilateral pulmonary infiltrates, and peripheral eosinophilia. Bronchoscopic lavage revealed 30% eosinophils. Daptomycin-induced acute eosinophilic pneumonia was diagnosed. Daptomycin was discontinued, and the patient had complete resolution of symptoms, peripheral eosinophilia, and radiographic findings.

**Discussion:** Daptomycin initially was approved for skin and soft tissue infections, but its utility has expanded to bacteremia and endocarditis. Daptomycin-induced acute eosinophilic pneumonia is rare. A recent Federal Drug Administration review identified a total of 58 cases of daptomycin-induced acute eosinophilic pneumonia. Of these, 38 were possible, 13 were probable, and 7 were definite. We believe this is the 8th definite case of daptomycin-induced acute eosinophilic pneumonia to be reported in the literature.

## INTRODUCTION

Drug-induced pulmonary eosinophilia is rare. The spectrum of disease ranges from a pulmonary infiltrate with eosinophilia, pleural disease, to acute eosinophilic pneumonia (AEP). AEP is a rare cause of acute respiratory failure, usually presenting with rapid onset of nonproductive cough and dyspnea with nonspecific radiographic

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findings.<sup>1</sup> The most common etiology is idiopathic.<sup>1</sup> There are reports of inhalational exposures and drug-induced AEP.<sup>1</sup> Recently, the Food and Drug Administration (FDA) reported 58 cases of daptomycin-induced AEP, 7 of which were definite.<sup>2</sup> Here, we present the 8th definite case of daptomycin-induced acute eosinophilic pneumonia.

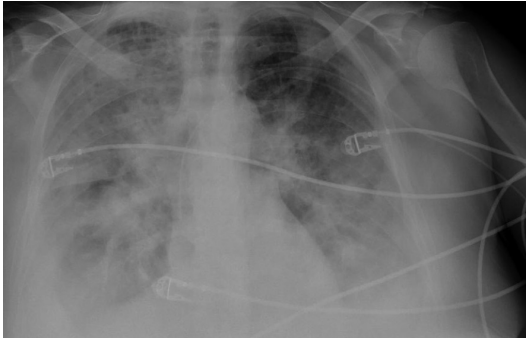
## CASE PRESENTATION

A 61-year-old woman with poorly controlled type 2 diabetes, complicated by nephropathy and neuropathy, presented to the emergency department with bilateral foot pain for 1 week. She reported draining heel ulcers with central eschars that were increasing in size. There were no fevers or chills. Vitals signs were normal. The physical exam was pertinent for bilateral lower extremity swelling, erythema, and warmth. The right heel had a 5 cm x 6 cm ulcer with insensate eschar at the base and purulent drainage from the borders. The left heel

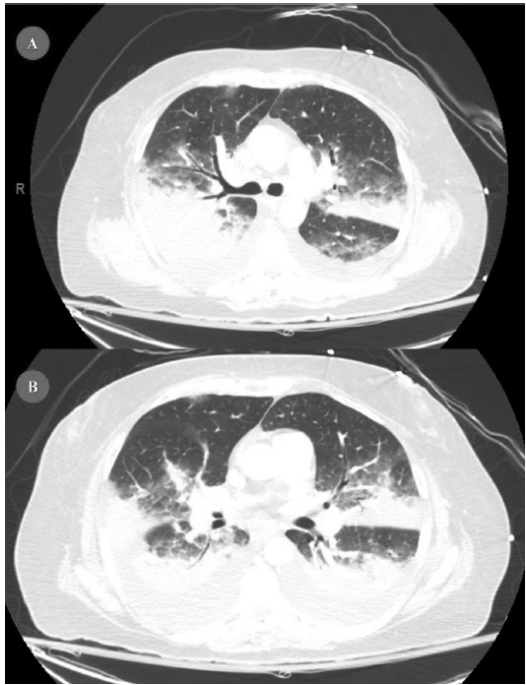
had a 2 cm x 3 cm ulcer with similar characteristics. Magnetic Resonance Imaging (MRI) revealed bilateral calcaneal osteomyelitis with left tibial and fibular fractures. Due to multiple drug allergies, the patient was started on daptomycin, aztreonam, and metronidazole to complete 6 weeks of therapy.

On day 7 of therapy, the patient developed shortness of breath and a dry cough. Vitals signs were normal except for oxygen saturation of 90% on 3 L/min. Exam revealed inspiratory crackles throughout both lungs with decreased breath sounds. Chest radiograph (CXR) showed new bilateral pulmonary infiltrates (Figure 1). White blood cell count was 16,100 per  $\mu\text{L}$  (reference range 4000–11,000 per  $\mu\text{L}$ ) with 15% eosinophils (reference range 0 to 6%). She was thought to have hospital-acquired pneumonia (HAP). Due to unsuitability of daptomycin for pneumonia, it was changed to linezolid. Aztreonam and metronidazole were continued. Symptoms and peripheral eosinophilia resolved, and all cultures were negative.

**Figure 1.** Portable Anterior-posterior (AP) Chest Radiograph Demonstrating Diffuse Bilateral Alveolar Infiltrates with Bilateral Pleural Effusions.

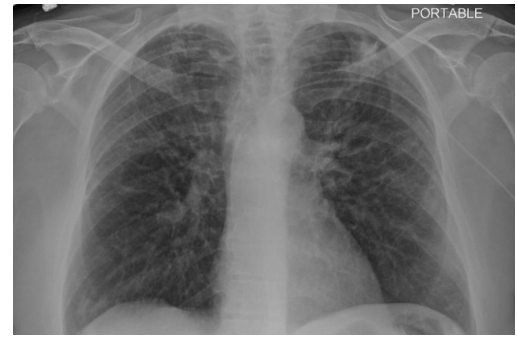


**Figure 2.** Chest Tomography Demonstrates Dense Bilateral Airspace Opacities in Both (A) Upper and (B) Lower Lung Fields.



Upon completion of 8 days of therapy for HAP, daptomycin was resumed for the osteomyelitis. Within 2 days of restarting daptomycin, the patient was admitted to the intensive care unit for hypoxemic respiratory failure requiring intubation. White blood cell count was 21,200 per  $\mu\text{L}$  with 11.3% eosinophils. Chest computed tomography (CT) showed bilateral pleural effusions and diffuse bilateral patchy infiltrates (Figure 2). Bronchoalveolar lavage (BAL) demonstrated 30% eosinophils. The Naranjo algorithm is a questionnaire used to determine whether an adverse drug reaction (ADR) is actually due to the drug and not other factors.<sup>3</sup> A diagnosis of daptomycin-induced acute eosinophilic pneumonia

**Figure 3.** Portable Anterior-posterior (AP) Chest Radiograph Demonstrates Resolution of Dense Bilateral Opacities.



was made based on a Naranjo score of 9, indicating a definite ADR. Daptomycin was discontinued and corticosteroids were started to hasten recovery. Within 72 hours, the patient was extubated with complete clinical resolution of symptoms. Infectious workup was negative. There was resolution of peripheral eosinophilia and CXR demonstrated marked improvement (Figure 3).

## DISCUSSION

Pulmonary eosinophilia is a heterogeneous group of disorders that share the common finding of an increased number of eosinophils in the lung parenchyma.<sup>4</sup> These entities include helminth infections, Churg-Strauss syndrome, allergic bronchopulmonary Aspergillosis (ABPA), acute and chronic eosinophilic pneumonias, and reactions to medications and toxins.<sup>1</sup> Drug-induced pulmonary eosinophilia can present as an asymptomatic infiltrate, a pleural effusion, and/or AEP.<sup>5</sup> AEP commonly presents with an acute onset of fever, dry cough, and shortness of breath that can progress to hypoxemic respiratory failure.<sup>6</sup> Corresponding radiographic findings may include new infiltrates, but changes are nonspecific.<sup>6</sup> AEP is idiopathic in the majority of cases.<sup>6</sup> Medications reported to induce AEP include non-steroidal anti-inflammatory drugs (NSAID), antidepressants, antipsychotics, and antimicrobials such as nitrofurantoin, minocycline, and daptomycin.<sup>5</sup> Diagnosis of AEP is based on greater than 25% eosinophils in lung tissue or BAL fluid in the setting of pulmonary infiltrates, thus obtaining a BAL remains an important intervention.<sup>6</sup>

Solomon and Schwartz<sup>5</sup> described 5 criteria that could be used to confidently diagnose drug-induced AEP: (1) presence of AEP, as defined by the aforementioned criteria, (2) presence of a causative drug with appropriate temporal relationship, (3) no other cause of AEP such as a fungal or parasitic infection, (4) clinical improvement after cessation of the drug, and (5) recurrence of AEP with rechallenge to the drug. When the etiology is uncertain, lung biopsy should be performed. Histopathology demonstrates acute and organizing diffuse alveolar damage with eosinophil and other inflammatory cell infiltration within lung parenchyma.<sup>6</sup>

**Table.** Definite Cases of Daptomycin-induced Acute Eosinophilic Pneumonia (AEP) that Underwent Drug Rechallenge

Age and Gender	Indication	Reaction	BAL eosinophil (%)	Outcome
61-year-old woman <sup>a</sup>	Bilateral calcaneal osteomyelitis	Dyspnea, dry cough, and respiratory failure, with recurrence within 2 days of rechallenge requiring mechanical ventilatory support.	30	Daptomycin held, corticosteroids started, and patient extubated within 3 days with full recovery.
60-year-old man <sup>4</sup>	MSSA <sup>b</sup> endocarditis	Fever, dyspnea, and respiratory failure requiring mechanical ventilation, with recurrence within 4 hours of rechallenge.	26	Daptomycin held, corticosteroids started, and patient extubated within 3 days with full recovery.
60-year-old man <sup>8</sup>	Left foot osteomyelitis	Fever and dyspnea with increased oxygen requirements, with recurrence within 2 days of rechallenge.	81	Daptomycin held, no mention of corticosteroids, reported "prompt" recovery.

<sup>a</sup> Our case

<sup>b</sup> Methicillin-sensitive *Staphylococcus aureus*  
Abbreviation = BAL, Bronchoalveolar lavage

Daptomycin is a cyclic lipopeptide antibiotic with activity against gram positive organisms. In the lung, daptomycin irreversibly binds to surfactant, rendering the daptomycin inactive with sequestration of the drug.<sup>7</sup> Thus, daptomycin is unsuitable for treatment of pneumonia.<sup>7</sup> Daptomycin-induced AEP is rare. A recent review by the FDA revealed 7 definite, 13 probable, and 38 possible cases of daptomycin-induced AEP.<sup>2</sup> In this review, definite cases were characterized by concurrent exposure to daptomycin, fever, dyspnea with increased oxygen requirement, new pulmonary infiltrates, bronchoalveolar lavage with >25% eosinophils, and clinical improvement after withdrawal of daptomycin.<sup>2</sup> Among the 7 definite cases, the onset of symptoms ranged from 10 to 28 days after initiation of daptomycin therapy. Of the 7 definite cases, 2 reported recurrence of AEP on rechallenge with daptomycin.<sup>2</sup> Table 1 compares these rechallenge cases with our patient. Recurrence of symptoms was seen anywhere from 4 hours to 2 days from rechallenge. These patients again demonstrated clinical recovery after repeat withdrawal of daptomycin. In addition to drug cessation, 5 of the 7 definite cases also were given systemic steroids.

The mechanism of daptomycin-induced AEP remains unclear. A proposed hypothesis is that the drug's sequestration in the lung as an inactive drug could lead to it acting as an antigen, being taken up by alveolar macrophages, and culminating in an inflammatory response.<sup>4</sup> As with other eosinophilic disorders, the eosinophil is under the control of the lymphocyte.<sup>6</sup> Thus, alveolar macrophages recruit T helper-2 cells (Th-2), which in turn release interleukin-5 (IL-5).<sup>2</sup> The accompanying eosinophil granules released into the interstitium and into alveoli can inflict considerable damage to the lung.<sup>6</sup>

Daptomycin initially was approved for treatment of complicated skin and soft tissue infections, but its use continues to expand for bacteremia and endocarditis.<sup>2</sup> Clinicians must be aware of its potential to cause AEP, especially since the entity has a rapid onset with poor morbidity. A drug-induced etiology of AEP should be suspected if the patient has a temporal exposure to

the offending drug with corresponding signs and symptoms with findings of greater than 25% eosinophils on BAL. Importantly, infectious etiologies should be ruled out, and if the diagnosis is uncertain, lung biopsy may be necessary. The management of daptomycin-induced AEP necessitates discontinuation of the drug. A brief course of corticosteroids can hasten recovery. Given the morbidity of the reaction, rechallenge is not recommended. Our case underscores the importance of not rechallenging a patient with daptomycin-induced AEP. Our case adds to the literature the 8th definite case of daptomycin-induced AEP. In the other 2 definite cases where a rechallenge was done, a Naranjo causality score was not mentioned.<sup>4,8</sup> Based on our patient's Naranjo causality score of 9 and fulfillment of all Solomon and Schwartz<sup>5</sup> criteria, ours is the 3rd definite case of daptomycin-induced AEP with rechallenge.

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