Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9010-17
Intern Med 57: 253-258, 2018
http://internmed.jp

【 CASE REPORT 】

Daptomycin-induced Eosinophilic Pneumonia and a Review of the Published Literature

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Abstract:
A 53-year-old man was admitted to the hospital with a diagnosis of cellulitis and osteomyelitis. Twenty-four days after the initiation of daptomycin and sulbactam/ampicillin, he developed a fever and pulmonary infiltration. Bronchoalveolar lavage revealed a high number of eosinophils, while an intracutaneous test revealed positivity for daptomycin. The patient improved after discontinuing antimicrobial therapy. The plasma daptomycin minimum concentration (C_{min}) was elevated (27.4 μg/mL), but plasma protein binding of daptomycin was low (87.8%). Although the pathophysiology of eosinophilic pneumonia remains unclear, antigenic stimulation due to daptomycin accumulation in the alveoli may have caused continuous immune activation.

Key words: daptomycin, eosinophilic pneumonia, therapeutic drug monitoring

(Intern Med 57: 253-258, 2018)
(DOI: 10.2169/internalmedicine.9010-17)

Introduction

Daptomycin (DAP) is a novel cyclic lipopeptide with bactericidal activity that was approved for use in 2003 by the United States (US) Food and Drug Administration (FDA). This drug is effective against endocarditis and skin and skin-structure infections caused by Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (1-3). Using data from the US inpatient healthcare utilization system, a previous study reported a dramatic increase in DAP usage between January 2004 and December 2010, when the number of prescriptions increased from 12,688, to 14,231 per year (4).

The primary adverse effect of DAP reported by preclinical studies was skeletal myopathy; in phase III clinical trials, serum creatinine kinase (CK) elevation was reported in 2.8% of patients, while myopathic symptoms occurred in 0.2% of patients (5). In addition to this, the development of eosinophilic pneumonia (EP) is another side effect of treatment with DAP (6). Based on data from the FDA adverse event reporting system, Kim et al. (4) recently reported that, from 2004 to 2010, 63 patients developed DAP-associated EP. Though a prompt improvement after DAP withdrawal was generally observed, some patients with EP developed chronic pneumonitis and required long-term corticosteroid treatment. Some authors speculate that accumulation of the drug in alveolar spaces causes damage to the epithelium (7, 8); however, the mechanism underlying eosinophilic pneumonia induction has yet to be fully elucidated.

In this report, we document the case of a 53-year-old man with chronic kidney disease and obesity who developed acute EP that was likely induced by DAP.

Case Report

This study was approved by the Ethics Review Board of University of Toyama (approval number: clinical 24-118)

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Received: February 8, 2017; Accepted: May 25, 2017; Advance Publication by J-STAGE: November 1, 2017
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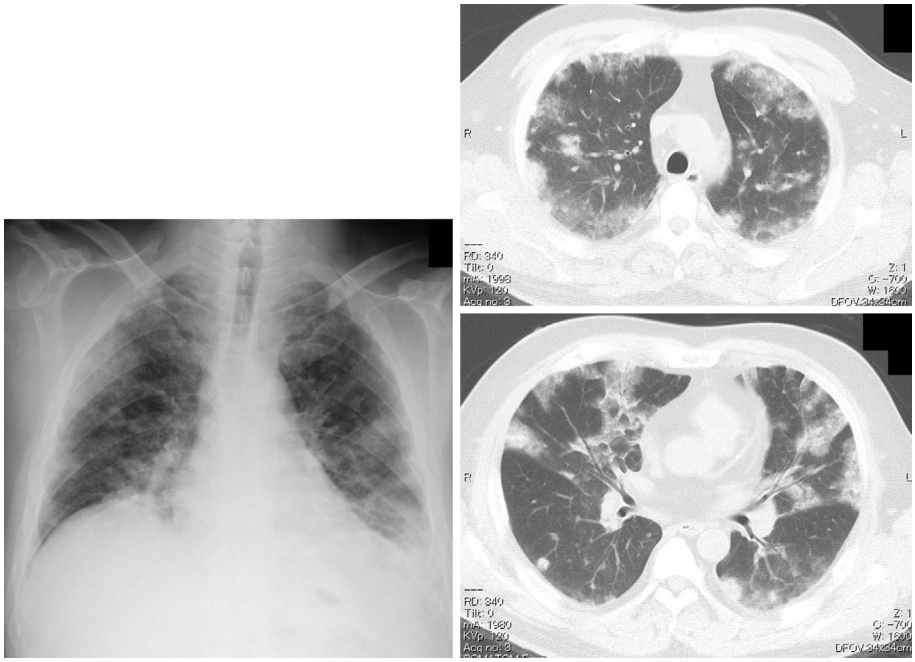

A B

Figure 1. Chest X-ray and computed tomography (CT) scans taken on day 28 after admission. (A) Chest X-ray revealed diffuse bilateral patchy consolidations and reticular shadow. (B) CT revealed diffuse bilateral patchy consolidations and multiple nodules that were thought to have a random distribution.

and performed in accordance with the Declaration of Helsinki; patients provided their informed consent regarding the publication of medical data. Patient privacy was fully protected, and personal information was handled in a manner that ensured patients could not be identified.

A 53-year-old Japanese man (height: 175.0 cm, total body weight: 97.0 kg, body mass index: 31.5) with type 2 diabetes and chronic kidney disease was admitted to our hospital with a fever and left lower extremity swelling. Laboratory studies revealed elevated markers of inflammation, including white blood cell count ($19.56\times10^3/mm^3$), serum C-reactive protein (CRP) (30.69 mg/dL), and procalcitonin (6.30 ng/mL). In addition, blood urea nitrogen (65 mg/dL) and creatinine (8.36 mg/dL) were also elevated. There was a 3.5 cm×3 cm ulcer with purulent drainage at the border on the front of the left foot.

Due to the patient's history of MRSA-related cellulitis, DAP (7 mg/kg, every 48 hours) and tazobactam/piperacillin (TAZ/PIPC; 4.5 g/day) were initiated after a diagnosis of cellulitis and osteomyelitis. He was followed up without dialysis despite the progression of renal failure. A purulent drainage sample from the ulcer revealed the presence of *Streptococcus agalactiae*, MRSA, *Staphylococcus schleiferi*, *Prevotella bivia*, and *Peptostreptococcus anaerobius*. In addition, *S. agalactiae* was identified in blood culture. Therefore, on day 7 after admission TAZ/PIPC was discontinued, and sulbactam/ampicillin (SBT/ABPC; 3 g/day) was initiated (administration of DAP was continued). The patient's fever subsided quickly, and the inflammatory markers gradually improved.

On day 24 after admission, the patient complained of cough with a fever (39.2°C). Laboratory findings revealed increased levels of inflammatory markers, including an elevated white blood cell count ($26.36\times10^3/mm^3$) with 3.0% eosinophils, serum CRP (31.9 mg/dL), and procalcitonin (1.92 ng/mL). Analyses of arterial blood gases determined after 5 L of O_2 was administered by mask revealed the following: partial pressure of arterial oxygen (PaO_2) was 73.8 Torr, partial pressure of carbon dioxide in arterial blood ($PaCO_2$) was 30.8 Torr, pH was 7.37, and HCO_3 was 17.4 mmol/L. Chest X-ray (Fig. 1A) and computed tomography (CT) (Fig. 1B) revealed diffuse bilateral patchy consolidations and multiple nodules in the peripheral regions. Test results for antinuclear antibody, myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA), proteinase 3 (PR3)-ANCA, serum cryptococcal antigen, and tuberculosis-specific interferon gamma release assays were all negative, and the levels of serum Krebs von den Lungen-6 (KL-6) were normal (201.5 U/mL). The evaluation of serum immunoglobulin E (IgE) was not performed. Furthermore, all blood cultures were negative, and transthoracic echocardiography did not identify any vegetations, indicating no infective endocarditis. Drug-induced pneumonia was suspected; therefore, the minimum concentration (C_{min}) of plasma DAP was measured by high-performance liquid chromatography (HPLC) using a Unison UK-C-8 column (3 μm, 150 mm×4.6 mm; Imtakt Corporation, Kyoto, Japan). DAP bulk powder for HPLC was purchased from Wako

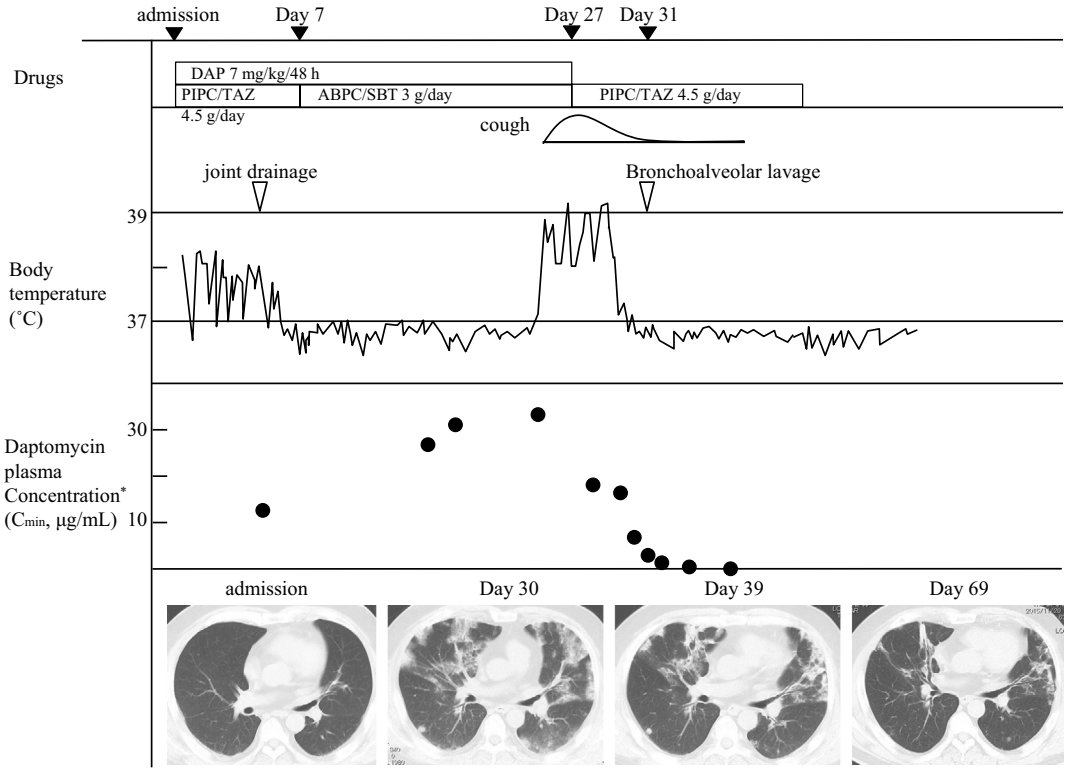

Figure 2. **Clinical course. *: the concentration of plasma DAP was measured before just before administration, DAP: daptomycin, TAZ/PIPC: tazobactam/piperacillin, SBT/ABPC: sulbactam/ampicillin, BAL: bronchoalveolar lavage**

Pure Chemical Industries (Tokyo, Japan). A mobile phase of phosphate buffer (pH 6.5) and acetonitrile [70/30 (v/v)] was used at a flow rate of 1.0 mL/min. The detection wavelength was 223 nm, and the lower limit of quantification was 0.25 μg/mL with an intra/inter-day coefficient of variation below 5%. The plasma DAP C_{min} was 33.4 μg/mL on day 23 after admission. DAP and SBT/ABPC were replaced by TAZ/PIPC on day 27 after admission. Bronchoalveolar lavage (BAL) was performed to assess the presence of infectious etiologies on day 31 after admission. The BAL cell counts identified 4.42×10^5 cells/μL comprising 9.3% macrophages, 7.1% neutrophils, 14.6% lymphocytes, and 69.0% eosinophils. A culture of BAL fluid (BALF) revealed intraoral indigenous (i.e. non-pathogenic) bacteria. Skin tests, including prick-puncture administration and patch tests, and drug lymphocyte stimulation tests (DLST), using DAP, SBT/ABPC, and TAZ/PIPC exhibited negative reactions. However, an intracutaneous test elicited a positive reaction with DAP (rapid type; 30 minutes: 11.5×11.3 mm/15.7×14.7 mm), but not SBT/ABPC or TAZ/PIPC.

After discontinuing DAP and SBT/ABPC, the patient's fever subsided quickly, and his oxygenation status resolved. Inflammatory markers, including the leukocyte count and serum CRP levels, gradually improved without systemic administration of corticosteroids. In addition, although the peripheral eosinophils increased on day 2 after antimicrobial discontinuation (1.98×10^3 cells/mm^3), they decreased gradually and returned to almost normal levels on day 14 after antimicrobial discontinuation. The clinical course of the patient is summarized in Fig. 2.

Discussion

EP has been associated with the use of numerous drugs, including diclofenac, loxoprofen, penicillin, minocycline, cephalosporin, and phenytoin, and should always be considered in the differential diagnosis of acute respiratory failure (9). The first case of DAP-associated EP was reported in 2007, and reports of this disease have recently increased, as DAP has been increasingly used in the treatment of endocarditis and skin and skin-structure infections (6). Kim et al. (4) described six criteria for inclusion in the diagnosis of DAP-associated EP: (1) concomitant exposure to DAP, (2) a fever, (3) dyspnea either with increased oxygen requirement, or requiring mechanical ventilation, (4) new infiltrates on chest X-ray or CT, (5) BAL with >25% eosinophils, and (6) clinical improvement following discontinuation of DAP. In the present case, all of the criteria for the diagnosis of DAP-associated EP were present, but a differential diagnosis was required to distinguish it from SBT/ABPC-associated EP.

Identification of the specific drug associated with the pneumonia is difficult, because rechallenge with the drug is neither warranted nor safe. In addition to this case, diagnostic procedures in 37 previously reported cases of EP implicating DAP are summarized in Table (4, 6-8, 10-25). A diagnosis was made based on the following: DAP rechallenge

Table. **Literature Review of Daptomycin-induced Eosinophilic Pneumonia.**

Case	Age	Sex	Dose of DAP	Duration	Fever	Respiratory symptoms or/and hypoxemia	BAL (% eosinophil)	Imaging findings	Initial treatment	Prognosis	References
1	60	M	Unknown	2 weeks	+	+	26%	Bilateral, peripheral and patchy areas of consolidations	Corticosteroid	Recover	6
2	84	M	4 mg/kg	6 weeks	-	-	Not performed	Bilateral, sharped nodules and consolidations with air bronchograms	Withdrawal	Recover	10
3	65	M	6 mg/kg	2 weeks	+	+	33%	Bilateral, peripheral diffuse air sparing and bilateral pleural effusion	Corticosteroid	Recover	11
4	54	M	Unknown	2 weeks	+	+	Not performed	Patchy consolidations and peripheral opacities	Corticosteroid	Recover	12
5	82	M	Unknown	3 weeks	+	+	14%	Bilateral, patchy areas of consolidations	Corticosteroid	Recover	13
6	87	M	Unknown	3 weeks	+	+	40%	Bilateral, patchy areas of consolidations	Corticosteroid	Recover	13
7	60	M	6 mg/kg	2 weeks	+	+	81%	Bilateral, GGO and peripheral consolidations	Corticosteroid	Recover	7
8	60	M	6 mg/kg	2 weeks	+	+	Not performed	Bilateral, peripheral nodular and ground glass changes	Withdrawal	Recover	7
9	83	M	6 mg/kg	4 weeks	-	+	Unknown	Bilateral, ground glass and reticular opacities	Corticosteroid	Recover	7
10	78	M	8 mg/kg	10 days	+	+	27.5%	Bilateral, sharped nodular consolidations with air bronchograms and bilateral pleural effusion	Withdrawal	Recover	8
11	69	Unknown	6 mg/kg	3 weeks	+	+	30%	Bilateral, patchy areas of consolidations	Corticosteroid	Recover	14
12	63	F	6 mg/kg	3 weeks	+	+	60-70%	Unknown	Corticosteroid	Recover	4
13	64	M	5.7 mg/kg	4 weeks	+	+	44%	Consolidations	Corticosteroid	Recover	4
14	79	M	6 mg/kg	6 weeks	+	+	9-13%	Extensive GGO	Corticosteroid	Recover	4
15	26	M	7.35 mg/kg	1.4 weeks	Unknown	Unknown	Unknown	Consolidations	Withdrawal	Recover	4
16	43	M	6 mg/kg	1-2 weeks	Unknown	+	Unknown	Bilateral, consolidations	Withdrawal	Recover	4
17	66	M	6 mg/kg	1 week	Unknown	+	Unknown	Unknown	Corticosteroid	Recover	4
18	71	M	4 mg/kg	7.7 weeks	-	+	Not performed	Bilateral, interstitial opacities	Withdrawal	Recover	4
19	77	F	5 mg/kg	1 week	Unknown	+	Not performed	Pneumonitis	Corticosteroid	Recover	4
20	67	M	6 mg/kg	4.3 weeks	Unknown	+	9%	Bilateral, consolidations	Corticosteroid	Recover	4
21	73	M	5 mg/kg	3.7 weeks	+	+	Unknown	Bilateral, ground glass appearance	Corticosteroid	Recover	4
22	81	F	6 mg/kg	1.6 weeks	Unknown	Unknown	2%*	Bilateral, mid lung consolidations	Corticosteroid	Recover	4
23	61	M	Unknown	2 weeks	+	+	15.6%	Bilateral, GGO and consolidations and bilateral pleural effusion	Corticosteroid	Recover	15
24	48	M	6 mg/kg	3 weeks	+	+	17%	Bilateral, patchy airspace opacities	Corticosteroid	Recover	16
25	28	M	6 mg/kg	4 weeks	Unknown	+	74%	Bilateral, consolidations	Corticosteroid	Recover	16
26	64	M	10 mg/kg	4 weeks	+	Unknown	47%	Bilateral, patchy GGO in the upper part of the lungs	Withdrawal	Recover	17
27	61	M	10 mg/kg	2 weeks	+	+	3%*	Bilateral, ground glass consolidation and bilateral effusion	Corticosteroid	Recover	17
28	61	F	Unknown	1 week	Unknown	+	30%	Bilateral, air space opacities and pleural effusion	Corticosteroid Inhaler	Recover	18
29	34	M	10 mg/kg	3 days	+	-	Not performed	Peripheral consolidation in the right upper lobe	Corticosteroid	Recover	19
30	62	M	Unknown	2 weeks	+	+	14%	Bilateral, GGO and consolidations and pleural effusion	Corticosteroid	Recover	20
31	76	M	Unknown	2 weeks	+	+	54%	Bilateral, peripheral GGO and consolidations	Corticosteroid	Recover	21
32	67	M	6 mg/kg	17 days	Unknown	+	10%	Bilateral, alveolar and interstitial opacities	Corticosteroid	Recover	22
33	77	M	6 mg/kg	6 weeks	-	+	18%	Bilateral, consolidations	Corticosteroid	Recover	23
34	74	M	6 mg/kg	3 days	+	+	Not performed	Increase in air space	Corticosteroid	Recover	23
35	60	M	5 mg/kg	24 days	-	+	Not performed	Bilateral tree-in-bud pattern and scattered GGO and right pleural effusion	Withdrawal Inhaler	Recover	24
36	67	F	500 mg/day	23 days	+	+	Not performed	Diffuse consolidation in the right lobe	Corticosteroid	Recover	25
37	53	M	7 mg/kg	24 days	+	+	69%	Bilateral, peripheral nodules and patchy consolidations	Withdrawal	Recover	present case

*: The patient had received corticosteroid therapy before bronchoalveolar lavage. DLST: drug-induced lymphocyte stimulation test, GGO: ground glass opacities

Intern Med 57: 253-258, 2018 DOI: 10.2169/internalmedicine.9010-17

(n=4), Kim's criteria without rechallenge (n=8), BAL with >25% eosinophils without Kim's criteria or rechallenge (n=3), and other clinical diagnoses (n=22). In Japan, DLST is widely used for the diagnosis of drug-induced pneumonia. DLST measures the *in vitro* proliferation of T cells in response to a drug and is useful for diagnosing the cause of a drug reaction (26). In contrast, the utility of DLST in identifying the offending drug in drug-induced pneumonia has not yet been established.

The hypothesized mechanism of DAP-associated EP is as follows: EP results from DAP retention in the pulmonary surfactant, which is then sequestered in the alveoli, leading to concentrations high enough to cause injury to the surrounding tissues (7). The pathophysiology seems to involve an antigen-mediated process that activates alveolar macrophages and T-helper 2 (Th2) cells. The Th2 cells then release interleukin-5, thereby promoting eosinophil production and migration to the lungs (8). However, the mechanism of DAP-associated EP remains unclear. In the present case, DLST was not useful, and the drug allergy was diagnosed using a rapid-type intracutaneous test. Skin testing is an important element in the diagnosis of IgE-mediated allergy, including allergic asthma. Yoshioka et al. (27) reported that positive findings were observed from skin-scratch tests using a tobacco leaf in a case of EP caused by exposure to tobacco during the harvesting and sorting of tobacco leaves. However, there have been no data regarding the utility of skin testing for DAP-associated EP. In addition, risk factors for DAP-associated EP remain unclear. Risk factors for amiodarone pulmonary toxicity were as follows: older age and higher maintenance dose of amiodarone, and pre-existing lung disease (e.g. chronic obstructive pulmonary dis-disease, sarcoidosis) (28). However, among the patients that are listed in Table, only 3 had pre-existing lung disease [chronic obstructive pulmonary disease (COPD), n=1; pulmonary embolus, n=1; alveolar edema, n=1]. Further studies and case reports are warranted to understand the mechanism and risk factors of DAP-associated EP.

Among the cases listed in Table, 22 received DAP doses ≤6 mg/kg, and 6 received >6 mg/kg. The median time interval (± standard deviation) between the instillation of DAP and the onset of EP was 22.0-23.0 days (±13.1-13.4) for ≤6 mg/kg DAP and 14.8 days (±9.4) for >6 mg/kg DAP. Dvorchik et al. (29) reported that the median plasma DAP C_{min} was 9.13 μg/mL for healthy volunteers who received DAP at 6 mg/kg every 24 hours, while the percentage of DAP plasma protein binding was consistent across dose levels. In the present case, the patient's median plasma DAP C_{min} was 27.4 μg/mL, and the percentage of plasma protein-bound DAP was 87.8%, even though the dose of DAP (7 mg/kg every 48 hours) was reduced due to chronic renal failure.

Dosage adjustment or therapeutic drug monitoring of DAP is not generally necessary; however, another study indicated that the pharmacodynamics of DAP vary markedly under different circumstances, such as in patients with morbid obesity, severe sepsis, or varying degrees of acute kidney injury (9). Among the 22 patients who received DAP doses ≤6 mg/kg listed in Table, 7 developed EP within 14 days post DAP administration. Of these seven patients, only three exhibited underlying diseases, with one being overweight, and none had a good renal function. In the present case, obesity and kidney failure may indeed have increased the plasma DAP concentration. Furthermore, the intratissue DAP concentration depends on the amount of free DAP in plasma (30).

The findings from the present case report indicate that an increased concentration of available DAP resulted in the excessive accumulation of DAP in the alveoli, continuously activating the immune system. However, the DAP concentrations in BALF were not measured in the present case, and to date there have been no studies about the intrapulmonary pharmacokinetics of DAP. Whether or not DAP plasma levels contribute to DAP concentrations in the BALF and whether or not the drug levels in the BALF contribute to the occurrence of EP itself remain unclear. Further studies are therefore warranted to understand this phenomenon. Bhavnani et al. (31) reported that a DAP C_{min} of 24.3 mg/L was associated with an increased probability of CK elevation. These findings suggest that therapeutic drug monitoring may be useful for ensuring safety, even in patients with infections who require long-term antibiotic administration.

In conclusion, we described a rare case of DAP-associated EP. Although the pathophysiology of drug-induced EP was not fully elucidated, one possible mechanism of action was the accumulation of DAP in the alveoli, causing continuous immune activation. Further studies and case reports are warranted to understand this phenomenon.

Author's disclosure of potential Conflicts of Interest (COI).
Yoshihiro Yamamoto: Honoraria, MSD.

References

1. Silverman JA, Perlmutter NG, Shapiro HM. Correlation of daptomycin bactericidal activity and membrane depolarization in Staphylococcus aureus. Antimicrob Agents Chemother **47**: 2538-2544, 2003.
2. Fowler VG Jr, Boucher HW, Corey R, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med **355**: 653-665, 2006.
3. Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI. Daptomycin 98-01 and 99-01 Investigators. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis **38**: 1673-1681, 2004.
4. Kim PW, Sorbello AF, Wassel RT, Pham TM, Tonning JM, Nambiar S. Eosinophilic pneumonia in patients treated with daptomycin: Review of the literature and US FDA adverse event reporting system reports. Drug Saf **35**: 447-457, 2012.
5. Package insert. Cubicin (daptomycin) Injection, Cubist Pharmaceuticals, Lexington, MA: November 2010.
6. Hayes D Jr, Anstead MI, Kuhn RJ. Eosinophilic pneumonia induced by daptomycin. J Infect **54**: 211-213, 2007.
7. Miller BA, Gray A, Leblanc TW, Sexton DJ, Martin AR, Slama TG. Acute eosinophilic pneumonia secondary to daptomycin: A report of three cases. Clin Infect Dis **50**: e63-e68, 2010.

8. Kalogeropoulos AS, Tsiodras S, Loverdos D, Fanourgiakis P, Skoutelis A. Eosinophilic pneumonia associated with daptomycin: A case report and a review of the literature. J Med Case Rep **5**: 13, 2011.

9. Allen JN. Drug-induced eosinophilic lung disease. Clin Chest Med **25**: 77-88, 2004.

10. Cobb E, Kimbrough RC, Nugent KM, Phy MP. Organizing pneumonia and pulmonary eosinophilic infiltration associated with daptomycin. Ann Pharmacother **41**: 696-701, 2007.

11. Kakish E, Wiesner AM, Winstead PS, Bensadoun ES. Acute respiratory failure due to daptomycin induced eosinophilic pneumonia. Respir Med **1**: 235-237, 2008.

12. Shinde A, Seifi A, DelRe S, Moustafa Hussein WH, Ohebsion J. Daptomycin-induced pulmonary infiltrates with eosinophilia. J Infect **58**: 173-174, 2009.

13. Lal Y, Assimacopoulos P. Two cases of daptomycin-induced eosinophilic pneumonia and chronic pneumonitis. Clin Infect Dis **50**: 737-740, 2010.

14. Rether C, Conen A, Grossenbacher M, Albrich WC. A rare cause of pulmonary infiltrates one should be aware of: a case of daptomycin-induced acute eosinophilic pneumonia. Infection **39**: 583-585, 2011.

15. Kagawa N, Tamagaki G, Sugiyama Y, Ijiri N, Kamoi H, Hirata K. A case of acute eosinophilic pneumonia probably induced by daptomycin. Nihon Kokyuki Gakkai Zasshi **2**: 284-288, 2013 (in Japanese, Abstract in English).

16. Phillips J, Cardile AP, Patterson TF, Lewis JS. Daptomycin-induced acute eosinophilic pneumonia: Analysis of the current data and illustrative case reports. Scand J Infect Dis **45**: 804-808, 2013.

17. Yusuf E, Perrottet N, Orasch C, Borens O, Trampuz A. Daptomycin-associated eosinophilic pneumonia in two patients with prosthetic joint infection. Surg Infect **15**: 834-837, 2014.

18. Patel JJ, Antony A, Herrera M, Lipchik RJ. Daptomycin-induced acute eosinophilic pneumonia. WMJ **113**: 199-201, 2014.

19. Hagiya H, Hasegawa K, Asano K, et al. Myopathy and eosinophilic pneumonia coincidentally induced by treatment with daptomycin. Intern Med **54**: 525-529, 2015.

20. Tujimoto K, Toki H, Ogawa Y, Yamato H, Miyake Y, Kodama K. A case of acute eosinophilic pneumonia probably induced by daptomycin. Nihon Kokyuki Gakkai Zasshi **4**: 468-472, 2015 (in Japanese, Abstract in English).

21. Wojtaszczyk A, Jankowich M. Dyspnea on daptomycin: eosinophilic pneumonia. R I Med J **98**: 41-43, 2015.

22. Roux S, Ferry T, Chidiac C, Valour F. Daptomycin-induced eosinophilic pneumonia. Int J Infect Dis **37**: 95-96, 2015.

23. Chiu SY, Faust AC, Dand HM. Daptomycin-induced eosinophilic pneumonia treated with intravenous corticosteroids. J Pharm Pract **28**: 275-279, 2015.

24. Akcaer M, Karakas A, Tok D, Coskun O. Eosinophilic pneumonia: Daptomycin-induced lung complication. Med Mal Infect **46**: 166-168, 2016.

25. Hatipoglu M, Memis A, Turhan V, Mutluglu M, Canoglu K. Possible daptomycin-induced acute eosinophilic pneumonia in a patient with diabetic foot infection. Int J Antimicrob Agents **47**: 414-415, 2016.

26. Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. Allergy **59**: 809-920, 2004.

27. Yoshioka D, Ishii H, Hatano Y, et al. A case of eosinophilic pneumonia in a tobacco harvester. Allergol Int **60**: 551-554, 2011.

28. Camus P, Martin WJ 2nd, Rosenow EC 3rd. Amiodarone pulmonary toxicity. Clin Chest Med **25**: 65-75, 2004.

29. Dvorchik BH, Brazier D, DeBruin MF, Arbeit RD. Daptomycin pharmacokinetics and safety following administration of escalating doses once daily to healthy subjects. Antimicrob Agents Chemother **47**: 1318-1323, 2003.

30. Traunmuller F, Schintler MV, Metzler J, et al. Soft tissue and bone penetration abilities of daptomycin in diabetic patients with bacterial foot infections. J Antimicrob Chemother **65**: 1252-1257, 2010.

31. Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. Clin Infect Dis **15**: 1568-1574, 2010.