Successful Treatment With Daptomycin of MRSA Empyema Complicated by Right-Sided Loculated Pleural Effusion Refractory to Vancomycin

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ABSTRACT: Empyema is a serious complication of pneumonia and has been reported to have a mortality rate of 8.7%. For methicillin-resistant *Staphylococcus aureus* (MRSA) empyema, treatment includes drainage and specific antibiotics such as vancomycin and linezolid. Strikingly, there are increasing incidences of empyema refractory to vancomycin and linezolid. Despite being inactivated in the lung parenchyma by pulmonary surfactant, daptomycin can penetrate the pleural space and may be better at treating MRSA empyema than vancomycin and linezolid. Some case reports have shown that daptomycin has been used to successfully treat MRSA empyema refractory to linezolid and vancomycin-resistant enterococcus (VRE) empyema. Here, we present a 26-year-old male with a past medical history of intravenous (IV) drug use, newly diagnosed HIV, HCV, and multifocal pneumonia complicated by a left-sided MRSA empyema that partially resolved with vancomycin and drainage. However, he subsequently developed a right-sided loculated pleural effusion. After the patient was switched to daptomycin with continued drainage, the right and left pleural effusions improved significantly. Once medically stable, he was discharged to a rehabilitation facility for further recovery. Our case report demonstrates that daptomycin could be considered as an effective treatment for MRSA empyema, particularly when refractory to vancomycin.

KEYWORDS: Empyema, daptomycin, MRSA, HIV, vancomycin, pneumonia, pleural effusion

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Introduction

Empyema is the accumulation of pus within the pleural space and can be a serious complication of pneumonia, requiring extensive treatment with antibiotics and adequate drainage. Although the use of antibiotics has reduced the risk of empyema to 2% to 3% in patients with pneumonia, the incidence of empyema is now rising.[1] In the United States, the incidence of empyema is as high as 10% in hospitalized patients with pneumonia, with a reported mortality rate of 8.7%.[2,3] Additionally, *Staphylococcus aureus* has been shown to be the most common causative organism of pleural infections, including empyema, and has been associated with increasing rates of drug resistance.[4] Given the rise in cases of empyema, its significant mortality rate, and increasing drug resistance, treatment for empyema is of particular importance.

In a patient hospitalized with community-acquired pneumonia complicated by empyema, the Infectious Diseases Society of America guidelines recommend empiric treatment for MRSA while waiting for cultures.[5] Once MRSA is confirmed, recommended antibiotic regimen includes 7 to 21 days of IV vancomycin 600 mg twice per day, IV or oral linezolid 600 mg twice per day, or IV or oral clindamycin 600 mg 3 times per day.

Strikingly, scarce literature exists on the use of daptomycin to treat MRSA empyema. Since daptomycin is inactivated by pulmonary surfactant lining the alveolar surface of the lungs and therefore is unable to treat pneumonia, its use for empyema may preemptively be discarded.[6,7] However, it is important to remember that empyema forms within the pleural space, which is outside of the lung parenchyma. Although surfactant molecules are present on pleural mesothelium, their composition differs from that of pulmonary surfactant.[8,9] Therefore, pulmonary surfactant is not present within the pleural space. Moreover, no data could be found demonstrating that daptomycin is inactivated by pleural surfactant.

Furthermore, there have been 2 case reports suggesting that vancomycin may not be as effective as once originally thought; the reports demonstrated that daptomycin successfully treated MRSA empyema refractory to linezolid and vancomycin-resistant enterococci (VRE) empyema.[10,11] Although these reports are limited to a single patient, they suggest that daptomycin can treat MRSA empyema, particularly when unresponsive to standard antibiotics of choice including vancomycin and linezolid. As of yet, there has been no evidence-based comparison between daptomycin and vancomycin in the treatment of MRSA empyema. Here, we present a case of a 26-year-old male presenting with multifocal pneumonia complicated by left-sided MRSA empyema reduced to a small pleural effusion on vancomycin. However, he subsequently developed a right-sided loculated pleural effusion that, alongside the left pleural effusion, improved when switched to daptomycin.

Case Presentation

The patient was a 26-year-old male with a past medical history of IV drug use who was brought to the hospital by emergency medical services after being found obtunded at a train station. Emergency medical technicians administered naloxone to reverse the effects of opioid-induced altered mental status. On arrival at the emergency department, the patient's chief complaints were diffuse abdominal pain, dyspnea, and an associated cough with an unknown time of onset. He stated that, because of the distress caused by these symptoms, he injected IV heroin. The patient was febrile (102°F), tachycardic (105-120 beats per minute), and tachypneic (18-30 breaths per minute) with an oxygen saturation ranging from 92% to 98% on room air. His laboratory results demonstrated mild hyponatremia (sodium, 132 mEq/L) and elevated alanine aminotransferase (ALT, 82 IU/L) and aspartate aminotransferase (AST, 67 IU/L), while his lipase, lactate, creatinine, and glomerular filtration rate were within normal limits. White blood cell (WBC) count was also normal at 7600 cells/μL. A frontal chest x-ray demonstrated a moderate left-sided pleural effusion, further evaluated by a chest CT scan without contrast illustrating multifocal pneumonia and a large fluid collection spanning half of the left hemithorax concerning for empyema (Figures 1 and 2). Transthoracic echocardiogram demonstrated no valvular vegetations. The patient underwent diagnostic thoracentesis and left pleural chest tube placement. Thoracentesis fluid demonstrated a pH of 6.84, elevated lactate dehydrogenase (LDH, 13 740 IU/L), and normal protein (2.7 g/dL) consistent with empyema.

While awaiting pleural cultures, he was started on empiric IV vancomycin 1500 mg (25 mg/kg, dosing weight of 60 kg) every 8 hours and IV piperacillin/tazobactam 3.375 mg every 8 hours at 25 mL per hour. The target trough level for vancomycin was 15 to 20 μg/mL.

Pleural cultures returned positive for MRSA, which was susceptible to vancomycin, clindamycin, and linezolid. Blood cultures were negative. The patient was continued on vancomycin, and piperacillin/tazobactam was discontinued. Since trough levels at the initial vancomycin dose and frequency were subtherapeutic at 8-13 μg/mL, the dosage was adjusted to 1250 mg every 6 hours to achieve target trough levels. WBC count remained within normal range throughout treatment from 4900 cells/μL to 10 600 cells/μL.

Of note, during his hospital stay, the patient was newly diagnosed with HIV (viral load of 673 000 copies/mL, CD4 count of 339 cells/MCL, genotype of HIV-1 subtype B) and chronic HCV (viral load of 21 400 000 IU/mL). For HIV, he was started on bictegravir, emtricitabine, and tenofovir alafenamide. Additionally, the patient's hospital course was complicated by opioid withdrawal, for which he was given 30 mg of methadone daily with 10 mg as needed for withdrawal symptoms per the clinical opiate withdrawal score (COWS).

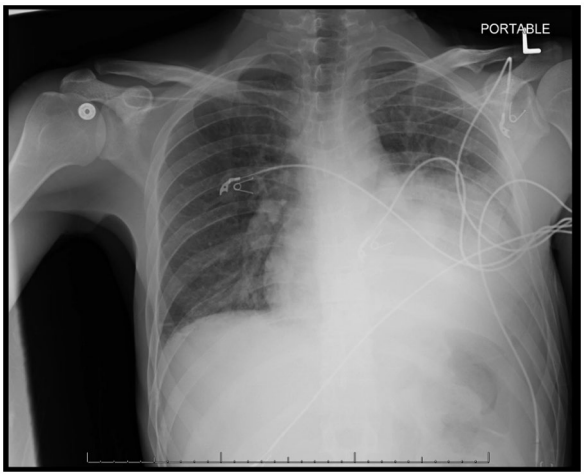

Figure 1. Initial chest X-ray on admission demonstrating a moderate left-sided pleural effusion.

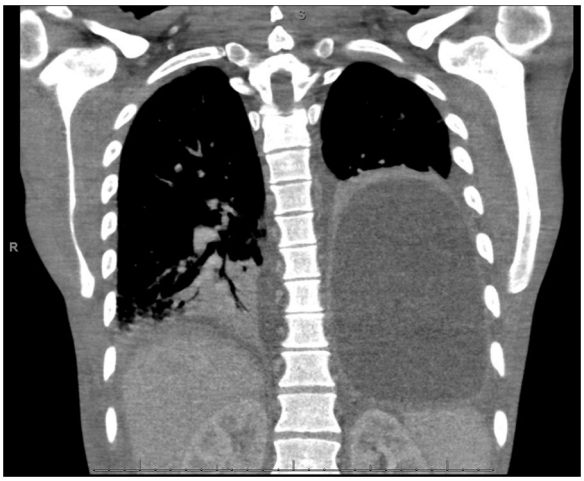

Figure 2. Initial chest CT on admission demonstrating multifocal pneumonia, healing fractures of the left fifth and sixth ribs, and a large fluid collection covering approximately half of the left hemithorax with concern for empyema.

Despite treatment with vancomycin at target trough levels, the patient experienced persistent, intermittent fevers throughout his stay. There was initially an interval decrease in the size of the left-sided empyema, resulting in chest tube removal after 1 week. However, repeat chest imaging including chest X-ray, CT, ultrasound, and continued clinical symptoms demonstrated that the patient had a persistent small, loculated pleural effusion in the left lung base alongside the development of a new moderate-sized right-sided loculated pleural effusion with associated right lower lobe atelectasis (Figure 3). Interventional radiology-guided thoracentesis of the right-sided pleural fluid revealed murky and bloody fluid with a pH of 7.55, protein of 5.22 g/dL, a cell count of 100 cells/μL with 69% neutrophils, and LDH of 850 IU/L. Subsequently, the patient underwent right chest tube placement and drainage of pleural fluid was facilitated by multiple doses of TPA/Dornase, given the significant loculations in

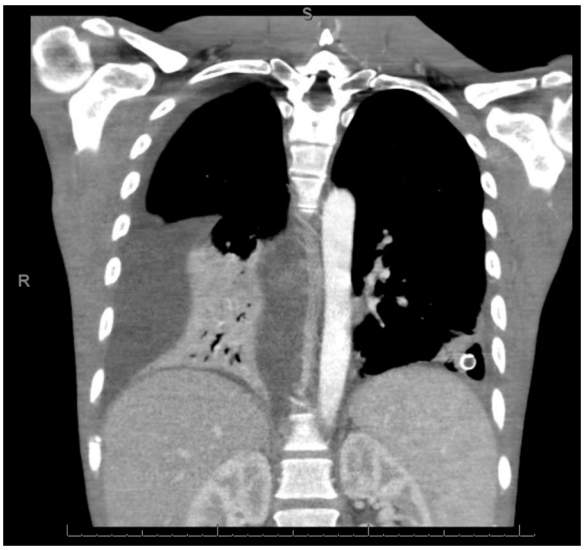

Figure 3. Chest CT within 1 week of treatment with IV vancomycin. Compared to prior CT (Figure 2), the loculated left pleural effusion has mostly resolved. There is a moderate enlarging right loculated pleural effusion with adjacent worsening of atelectasis of the right lower lobe.

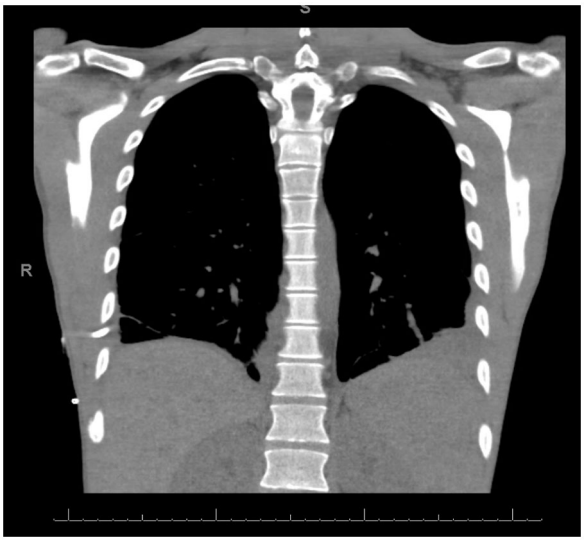

Figure 4. Chest CT after 6 days of daptomycin treatment. There is a small loculated pleural effusion at the right basal region, decreased from the prior study (Figure 3). The right chest tube is located distally within the mid-upper portion of the right lung pleura wherein there is minimal pleural fluid. There also remains a small stable left pleural effusion, as well as a continued decrease in parenchymal consolidation and atelectasis in the lower lobes.

the effusion. Interestingly, right pleural cultures were negative, although detectable bacterial growth may have been suppressed with ongoing vancomycin treatment.

Given his inadequate improvement on vancomycin, the patient was switched to IV daptomycin 300 mg (6 mg/kg per day, dosing weight of 50 kg) daily for a total treatment duration of 21 days. Having a similar spectrum of activity to linezolid and clindamycin to which the isolated MRSA was found to be susceptible, daptomycin was chosen for dosing convenience at once per day. The patient's intermittent fevers resolved after the initiation of daptomycin. WBC count throughout treatment with daptomycin was within normal range from 3500 cells/μL to 6000 cells/μL. Prior to initiation of daptomycin, creatine kinase (CK) was 18 IU/L, which is below the normal range (25-215 IU/L) given his low muscle mass and a BMI of 19 kg/m^2. CK levels were measured after days 1 and 4 of treatment at 19 IU/L and 16 IU/L, respectively.

Of note, 5 days after right chest tube placement, diminishing drainage amounts and repeat chest imaging demonstrated that the chest tube was not appropriately placed with respect to the remaining pleural fluid collection, requiring image-guided replacement. After chest tube replacement and with continued daptomycin treatment, the patient's clinical symptoms began to significantly improve. Chest CT without contrast after 6 days of daptomycin treatment demonstrated a decreased size of the right loculated pleural effusion with a remaining small left pleural effusion, allowing for right chest tube removal (Figure 4). A midline was placed for the continuation of IV daptomycin upon discharge and the patient was successfully discharged to a rehabilitation facility shortly thereafter once medically stable to complete the remaining antibiotic course. Per the discharge recommendations of the infectious disease team, C-reactive protein and CK levels were monitored weekly while on treatment, resulting within normal limits. Although the patient was contacted for his outpatient appointment, he was unreachable and lost to follow-up.

Discussion

Multiple sources have demonstrated that daptomycin is effective in treating MRSA for various infections.[12,13] However, daptomycin is scarcely used to treat respiratory infections because of its limited efficacy in the lung parenchyma. In this case report, we reiterate the importance of distinguishing between the lung parenchyma and pleural space to ensure an optimized treatment, especially in a potentially life-threatening situation such as our immunocompromised patient with multifocal pneumonia complicated by MRSA empyema.

Daptomycin is a desirable option for treating empyema due to its potentially stronger penetration into the pleural space compared to vancomycin; this may improve the recovery rate and reduce the risk of complications such as a loculated pleural effusion as seen in our patient.[10] However, this finding stemmed from a case report within the setting of VRE empyema, which limits its generalizability. Additionally, daptomycin can be more conveniently dosed at once daily, while vancomycin requires more frequent dosing at twice daily and serial measurements of trough levels.[5] Although daptomycin necessitates monitoring for myopathy via routine measurements of CK, its simple dose regimen eases administration and may improve patient compliance.[14] Despite these benefits of daptomycin,

more research is needed to quantify and compare the efficacy of antibiotics that can treat MRSA pleural infections, including daptomycin, vancomycin, and linezolid.

It is also important to consider the context in which daptomycin is used to treat MRSA empyema. Since it is inactivated in the lungs, daptomycin can only treat empyema in the setting of nonexistent or resolved pneumonia. Given that many cases of empyema arise in the setting of ongoing pneumonia, daptomycin may need to be used in adjunct with another antibiotic. Conversely, vancomycin could concurrently treat both pneumonia and empyema. However, a growing number of case reports have suggested that empyema can be refractory to vancomycin.[10,11] Our case report also found a concomitant pleural complication despite vancomycin treatment. Therefore, in the setting of ongoing MRSA pneumonia and empyema, one could consider using vancomycin to treat pneumonia and transition to daptomycin to treat empyema. This combination ensures adequate treatment of pneumonia and provides enhanced treatment for empyema. Further studies are needed to compare the use of combined vancomycin and daptomycin to vancomycin alone in the setting of pneumonia complicated by empyema.

While this case report reaffirms the findings of previous reports on daptomycin effectively treating empyema, it is limited to a single patient whose medical history, including IV drug use, HCV, and HIV, may not reflect the clinical course for all patients who have MRSA empyema. The right pleural effusion may have been due to the patient's immunocompromised state rather than to a drug limitation. Additionally, the right pleural effusion may have resolved as a result of correcting the chest tube placement. Nonetheless, our patient had no further complications and continued to improve after switching to daptomycin. This suggests that daptomycin can effectively treat MRSA empyema, particularly if unresponsive to vancomycin.

Conclusion

Although previous case reports have suggested that daptomycin can treat empyema, we believe that this is the first case report to demonstrate the successful treatment with daptomycin of MRSA empyema refractory to vancomycin. Our case report reiterates the importance of considering alternative medications in MRSA empyema that persists with sequelae of complications despite mainstay antibiotic treatment and drainage. Daptomycin's convenient dosing and potential to better penetrate the pleural space could not only optimize treatment efficacy and duration, but also hold the potential to reduce the risk of further complications and mortality. Therefore, daptomycin could be more strongly considered as a treatment option for MRSA empyema, especially when unresponsive to standard antibiotics of choice such as vancomycin.

Author Contributions

A.T: Conceptualization, study design, literature review, patient management, writing, review, and editing (original and final draft). D.S: Literature review, patient management, writing, review, and editing (original and final draft). J.H: Patient management, review, and editing (original draft). S.M: Patient management, acquisition of patient consent, review, and editing (original draft). A.B: Patient management, review, and editing (original draft). L.T: Supervision, patient management, review, and editing. All authors approved the final manuscript for publication.

Consent

Due to the patient's social circumstances and a lack of direct contact information, the authors were unable to obtain consent directly from the patient. However, the authors were able to contact the patient's mother, who gave a verbal and written informed consent for sharing imaging studies and information relevant to the case report.

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