Intracavitary and Systemic Daptomycin for Successful Treatment of a Postpneumonectomy Intrathoracic Infection

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ABSTRACT Treatment of an infected postpneumonectomy cavity is very difficult. We present a patient with an infection of a postpneumonectomy cavity by *Staphylococcus epidermidis* treated with local daptomycin for different dwell times, maintaining high antibiotic levels above the MIC. Clinical and microbiological cure were achieved successfully.

KEYWORDS daptomycin, intracavitary, postpneumonectomy cavity, *Staphylococcus*, treatment

The treatment of infection of a postpneumonectomy cavity is very difficult and should be based on a combined treatment that includes drainage of the infected cavity and an appropriate antibiotic regimen (1). However, antimicrobial options for both microorganisms with elevated MIC and vancomycin-resistant Gram-positive microorganisms are reduced. When pneumonia is excluded, the cyclic lipopeptide antibiotic daptomycin represents an excellent treatment option, not only because of its potent bactericidal activity, but also due to its rapid eradication in stationary phase and to the possibility of both local and systemic use (2, 3). There are no data available related to diffusion of antibiotics into a postpneumonectomy cavity, although it is reasonable to think it might be difficult due to fibrosis secondary to surgery.

We present the first case of local use of daptomycin introduced into a postpneumonectomy cavity for the treatment of an intrathoracic infection caused by *Staphylococcus epidermidis* with elevated MIC to vancomycin.

A male patient in his forties was admitted with general poor condition. In his past medical history there was a diagnosis of a left hilar primary pulmonary synovial sarcoma treated with a left pleuropneumonectomy, hilar and mediastinal lymphadenectomy, and resection of the ipsilateral diaphragm for malignant implants with the emplacement of a prosthetic diaphragm 1 year earlier. He then received chemotherapy and radiation therapy. Due to cardiac tamponade secondary to radiation-induced constrictive pericarditis, the patient required a pericardial window procedure, followed by a pericardiectomy by left thoracotomy 15 days before the described hospitalization.

On admission, the patient was afebrile, blood pressure was 92/62 mm Hg, and heart rate was 112 beats/min. Left pulmonary auscultation was silent. Serohepatic fluid leakage through surgical wound was observed. Baseline laboratory tests revealed hemoglobin 11 g/dl, leukocytes 10.5×10^9 /liter, C-reactive protein level 0.82 mg/dl (normal value [NV], 0 to 0.5), total proteins 7 g/dl, and an estimated glomerular filtration rate (eGFR) of 71 ml/min. Chest computed tomography showed the presence of an infected pleural air-fluid collec-

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FIG 1 Chest computed tomography with an infected intrathoracic air-fluid collection.

tion (Fig. 1). Under local anesthesia, two chest tubes were placed and connected to a drainage system. Pleural fluid presented the following features: pH 8, glucose level <2 mg/dl, total proteins 7 g/dl, and leukocytes 18×10^9 /liter.

The microbiological diagnosis was based on the growth of *Staphylococcus epidermidis* alone in all four consecutive cultures of the pleural fluid obtained with syringe, before and immediately after placing the chest tube. No anaerobes, fungi, or mycobacteria were isolated in any pleural fluid culture. Blood cultures were also negative. *S. epidermidis* isolates were resistant to oxacillin, levofloxacin, trimethoprim-sulfamethoxazole, clindamycin, clarithromycin, and gentamicin. *S. epidermidis* isolates presented a high vancomycin MIC (4 mg/liter) and were susceptible to daptomycin (MIC, 0.25 mg/liter), linezolid (MIC, 1 mg/liter), rifampin (MIC, 0.25 mg/liter), and doxycycline.

Intravenous (i.v.) daptomycin in monotherapy was given at a dose of 10 mg/kg/24 h (height of patient, 180 cm; weight 80 kg; absolute dose of 800 mg), despite which *S. epidermidis* persisted in pleural fluid isolates after 72 h of antibiotic treatment. The MIC for daptomycin remained at 0.25 mg/liter. The possible biofilm associated with the prosthetic diaphragm was initially considered as responder to daptomycin therapy, because the prosthetic diaphragm was placed only a year earlier. Rifampin was not used due to previous diagnosis of congestion of the liver and the current presence of hypertransaminasemia. At this moment, with prior formal patient consent, we started intrathoracic (i.t.) daptomycin once daily (20 mg/liter reconstituted in 0.9% saline fluid for a total volume of 1,800 ml) inside the left postpneumonectomy cavity for a 12-hour dwell time and for a total of 14 days in combination with i.v. daptomycin. Later, as the patient was hemodynamically stable and afebrile, i.v. daptomycin was discontinued and only i.t. daptomycin lock solution was left for a 48-hour dwell time. Finally, he was discharged under monotherapy with i.t. daptomycin for a 7-day (168 h) dwell time on an outpatient basis. He completed a total of 30 days of i.t. daptomycin treatment (Fig. 2). In addition to clinical cure of the infection, microbiological eradication was obtained. Pleural fluid cultures were taken under i.t. daptomycin therapy (at third, seventh, 14th, 16th, and 23rd days) and at the end of treatment. Microbiological cultures were made with withdrawn lock solution and with pleural fluid taken immediately before each new i.t. daptomycin administration. After a follow-up period of 199 days, cultures of the pleural fluid remained negative.

Based on previous published data of safety and efficacy with intraperitoneal daptomycin (4), we used a concentration of 20 mg/liter, which means 80 times the MIC of the *S. epidermidis* culture isolated. Daptomycin was reconstituted in 0.9% saline solution so as to avoid instability of the antibiotic in other fluids, such as dextrose-water solutions at 5% concentration or greater (5, 6). Recently, Prax et al. described increased activity of daptomycin using glucose, with a maximal effect at 1g/liter glucose; how-

FIG 2 Plasma and intrathoracic concentrations of daptomycin, microbiological data, and CPK levels, after systemic and local administration of a dose of 20 mg/liter daptomycin, remaining for 12 h, 2 days, and 7 days lock therapy.

ever, this effect appears to decrease with higher concentrations (5g/liter) and over time (7). A total volume of 1,800 ml was prepared because it was the largest volume that fit in the intrathoracic cavity and was well tolerated by the patient. Concentrations of i.t. daptomycin were measured using high-performance liquid chromatography with UV detection. Samples of 2 ml of pleural fluid were obtained 12, 48, and 168 h after intrathoracic instillation of daptomycin.

After 12 h of lock therapy, i.t. daptomycin concentration was 19.1 mg/liter. This represented 95% of the administered concentration (76 times the MIC against *S. epidermidis*). At this moment, the patient was concurrently being treated with i.v. daptomycin, so the doubt of systemic daptomycin diffusion into the postpneumonec-tomy space was raised. We obtained an i.v. daptomycin peak (maximum concentration of drug in serum [C_{max}]) and trough (minimum concentration of drug in serum [C_{min}]) of 151 mg/liter and 36.21 mg/liter, respectively. The systemic concentrations observed were compatible with anticipated levels based on population pharmacokinetics (PK). With a renal clearance of 0.545 liter/h, the estimated area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) was 1,470 mg · h/liter. Intrathoracic daptomycin was administered at the same time as i.v. daptomycin, which could be a confounding factor. Still, pharmacological analysis recommended continuing with this regimen for efficacy. When antimicrobial lock was left for a 48-hour dwell time without i.v. daptomycin the concentration of antibiotic recovered was 17.3 mg/liter (86.5% of the administered concentration and 69 times MIC against *S. epidermidis*). These data might indicate poor diffusion of systemic daptomycin into the postpneumonec-tomy cavity, although dap-tomycin concentration in pleural fluid before starting i.t. daptomycin should have been measured.

The concentration of i.t. daptomycin decreased over time and after 7 days of lock therapy daptomycin concentration recovered represented 58% of that administered (11.6 mg/liter). However, it was 46.4 times the MIC against *S. epidermidis*. Huen et al. achieved intraperitoneal bacterial eradication with daptomycin (20 mg/liter) at a concentration 5 times the MIC against the isolate (4).

The question of optimal time for replacing the daptomycin lock solution remains unanswered. However, our own unpublished data have confirmed both stability and antimicrobial activity of daptomycin in long-term catheter-related bloodstream infections after 7 days of lock therapy (8). Additionally, length of treatment is not well established either. In our case, we prolonged local antimicrobial treatment due to the presence of a prosthetic diaphragm device.

The primary outcome of this case was achievement of clinical and microbiological cure. No daptomycin-resistant organisms were isolated during the study period. Tolerance to treatment was good. Pleuritic pain progressively decreased during hospitalization. Despite the fact that trough serum concentrations of daptomycin of ≥ 24.3 mg/liter are correlated with a 50% probability of creatinine phosphokinase (CPK) elevation (9), our patient, with a daptomycin $C_{\min}$ of 36.21 mg/liter, had normal basal CPK levels and even normal levels during the treatment (Fig. 2). No other adverse effects related to administration of daptomycin were seen.

In conclusion, i.t. daptomycin represents a novel, safe and effective option for local treatment of infections by Gram-positive microorganisms with high MIC or resistance to vancomycin in a postpneumonectomy cavity. Based on i.t. daptomycin concentration and antimicrobial activity, this treatment allows even weekly outpatient replacements. This therapy ensures not only microbiological and clinical efficiency, but also safety and good tolerability.

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