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High-Dose Continuous Infusion Beta-lactam Antibiotics for the Treatment of Resistant *Pseudomonas aeruginosa* Infections in Immunocompromised Patients

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Abstract

OBJECTIVE—To report a case series of high-dose continuous infusion beta-lactam antibiotics for the treatment of resistant *Pseudomonas aeruginosa* infections.

CASE SUMMARY—Continuous infusion ceftazidime or aztreonam was administered to achieve target drug levels at or above the MIC when possible in three patients with *P. aeruginosa* infections. The maximal calculated target drug level was 100 mg/L. In the first patient with primary immunodeficiency, neutropenia, and aggressive cutaneous T cell lymphoma/leukemia, continuous infusion ceftazidime (6.5 to 9.6 g/day) was used to successfully treat multidrug-resistant *P. aeruginosa* bacteremia. In the second patient with leukocyte adhesion deficiency type 1, continuous infusion aztreonam (8.4 g/day) was used to successfully treat multidrug-resistant *P. aeruginosa* wound infections. In the third patient with severe aplastic anemia, continuous infusion ceftazidime (7 to 16.8 g/day) was used to treat *P. aeruginosa* pneumonia and bacteremia. In each patient, the bacteremia cleared, infected wounds healed, and pneumonia improved in response to continuous infusion ceftazidime or aztreonam.

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DISCUSSION—Treatment strategies for multidrug-resistant *P. aeruginosa* infections are limited. A novel treatment strategy when no other options are available is the administration of existing beta-lactam antibiotics by continuous infusion in order to maximize their pharmacodynamic activity. High-dose continuous infusion ceftazidime or aztreonam was used for the successful treatment of resistant systemic *P. aeruginosa* infections in three chronically immunocompromised patients.

CONCLUSION—Continuous infusion beta-lactam antibiotics are a potentially useful treatment strategy for resistant *P. aeruginosa* infections in immunocompromised patients.

Keywords

beta-lactam; continuous infusion; immunocompromised; *Pseudomonas aeruginosa*; resistance

Introduction

Pseudomonas aeruginosa is a bacterial pathogen commonly recovered from patients with bacteremia, pneumonia, and urinary tract infections in intensive care units.[1,2] Blood stream infections and pneumonia caused by *P. aeruginosa* are associated with high mortality, especially in immunocompromised patients.[3-5] Unfortunately, antimicrobial resistance in *P. aeruginosa* is increasing and is an expanding global problem.

Treatment strategies for multidrug-resistant *P. aeruginosa* infections are limited and include the application of newer agents, the use of older antibiotics with greater toxicity, and the novel administration of existing drugs. Unfortunately, there has been a continuous decline in the discovery, clinical development, and approval of new antibacterial agents with activity against Gram-negative bacteria.[6,7] The utility of older agents, such as colistin and polymyxin B, may be limited in immunocompromised patients receiving concomitant nephrotoxic agents. In addition, colistin resistant *P. aeruginosa* has been recently reported.[8] An alternative treatment strategy when no other options are available is the novel administration of existing beta-lactam antibiotics by using continuous infusion in order to maximize their pharmacodynamic activity against resistant Gram-negative bacilli.

The pharmacodynamics of beta-lactam antibiotics are characterized by time dependent killing where antibacterial activity is dependent on the amount of time that the drug concentration is above the MIC of the bacteria.[9-11] Continuous infusion administration can achieve time above MIC for the entire dosing interval, which may be critical for the treatment of multidrug-resistant *P. aeruginosa*. Intermittent dosing may allow drug levels to fall below the MIC of the resistant organism which would permit bacterial survival and regrowth.

As more infections caused by resistant *P. aeruginosa* are encountered, continuous infusion antimicrobial strategies may achieve successful outcomes and diminish the probability of breakthrough infections. However, to our knowledge there are few reported cases and no case series in the available literature that document continuous infusion beta-lactam antibiotic therapy against these infections. The objective of this case series is to describe our use of continuous infusion beta-lactam antibiotics for the treatment of resistant *P. aeruginosa* infections in immunocompromised inpatients at the NIH Clinical Center. This case series describes a unique strategy, using high-dose continuous infusion ceftazidime or aztreonam to target high drug concentrations at or above the MIC for the treatment of resistant *P. aeruginosa* infections.

Case Reports

Continuous infusion ceftazidime in two immunocompromised patients and aztreonam in a third such patient were used for the treatment of *P. aeruginosa* bacteremia, pneumonia, and serious wound infections (Tables 1 and 2). Formulas used to calculate the dosage regimens are shown in Appendix 1.[12-15] The case histories of these patients are summarized below.

Case 1

An 18-year-old female with a history of a poorly characterized primary immunodeficiency, disseminated molluscum contagiosum, and disseminated herpes simplex virus infection developed aggressive cutaneous T-cell lymphoma/leukemia. After finishing the second cycle of EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) chemotherapy (9/12 – 9/16), the patient became febrile and was found to have positive blood cultures for *P. aeruginosa* (9/17). An IV catheter tip was also positive for *P. aeruginosa* and *Staphylococcus aureus*. On physical exam, the patient had multiple ulcerative cutaneous lesions associated with her lymphoma and viral infections. Cultures of these cutaneous lesions grew *P. aeruginosa*.

Ciprofloxacin, trimethoprim-sulfamethoxazole, and tobramycin 200 mg (5 mg/kg) IV every 24h were added to the patient's antibiotic regimen on 9/18 which also included vancomycin and imipenem. The antibacterial susceptibility profile showed that the *P. aeruginosa* isolates were susceptible to tobramycin (MIC ≤ 4 mg/L) and intermediate or resistant to all other antibiotics (Table 2). *P. aeruginosa* isolates were resistant to the patient's imipenem and ciprofloxacin.

In order to more effectively treat this life-threatening bacteremia, ciprofloxacin, imipenem, and trimethoprim-sulfamethoxazole were discontinued, tobramycin continued, and continuous infusion ceftazidime was initiated on 9/19 (loading dose of 2 g and a maintenance infusion rate of 271 mg/h) to target a mean steady state concentration (C_{ss}) of 64 mg/L. Neutropenia following chemotherapy lasted for five days and resolved with filgrastim therapy. As the *P. aeruginosa* MIC of ceftazidime was found to be 64 mg/L, the maintenance infusion rate of ceftazidime was increased to 400 mg/h (9.6 g/day) on 9/22 to target a C_{ss} of 80 to 100 mg/L.

Within six days of initiation of continuous infusion ceftazidime, repeated blood cultures became negative (Table 1). During neutropenia from 9/19 to 9/22, blood cultures remained negative. Blood cultures became positive again while neutropenic on 9/23 and remained so during recovery from neutropenia on 9/24. Blood cultures again became negative with continuous infusion ceftazidime and recovery from neutropenia. Unfortunately, the patient's lymphoma failed to respond to the chemotherapy and she was given comfort care and expired on 10/1. Postmortem cultures of the lung and liver were negative for *P. aeruginosa*.

Case 2

A 17-year-old male with leukocyte adhesion deficiency type 1, non-healing cutaneous ulcers on the thighs and scrotum, failed skin grafts, and multidrug-resistant *P. aeruginosa* wound infections developed bilateral pneumonia on 11/23. While receiving broad spectrum antibiotics, *P. aeruginosa* and *Mycobacterium intracellulare* (1 colony) were recovered from a bronchoalveolar lavage on 11/24. *P. aeruginosa* also was recovered from thigh wound cultures on 11/23 and 11/25. The antibacterial susceptibility profile showed that the *P. aeruginosa* isolates were susceptible to polymyxin B and intermediate or resistant to all other antibiotics (Table 2). Based upon a previously successful response of the non-healing ulcers to continuous infusion aztreonam, this infusion was reinitiated at 260 mg/h on 11/26. Traditional dosing of tobramycin was changed to tobramycin 270 mg (5 mg/kg) IV every

24h, and ciprofloxacin (11/19 to 12/1) and vancomycin were also continued. In addition, nebulized colistin (11/26 to 12/13), intravenous polymyxin B (11/26 to 12/1), and azithromycin were initiated for resistant or atypical pneumonia. Donor granulocyte infusions were started on 11/27 and continued until 7/16. After only one day of continuous infusion, aztreonam was held and then resumed on 12/1 at 350 mg/h (8.4 g/day) and continued for more than eight months thereafter. The only concomitant medication active against *P. aeruginosa* during this time was nebulized colistin for 13 days. The wounds responded to continuous infusion aztreonam with multiple negative cultures over eight months.

After the wounds were substantially reduced in size and *P. aeruginosa* eradicated from the wounds, the patient was referred for plastic surgery, where he received multiple cultured epidermal autograft (Epicel®) skin grafts. Continuous infusion aztreonam, intermittently dosed tobramycin (to which the organism was resistant), and vancomycin were continued until 8/17. Continuous infusion aztreonam was well tolerated throughout the eight month course of treatment. The patient was discharged from the hospital on 8/23 with healed skin grafts.

Case 3

A 44-year-old male with severe aplastic anemia associated with profound neutropenia developed recurrent *P. aeruginosa* infections, which were treated with several cycles of high-dose continuous infusion ceftazidime over two months while he was awaiting an unrelated cord blood transplant. Intermittently dosed ceftazidime was initially administered for fever and sinusitis from which *P. aeruginosa* was recovered from sinus biopsy cultures on 1/20. The fever and sinusitis responded to ceftazidime; however, *P. aeruginosa* pneumonia was subsequently documented by bronchoalveolar lavage on 2/3. Meropenem was administered from 2/1 to 2/13, but was followed by fever, hypotension, and *P. aeruginosa* bacteremia on 2/15. Other *P. aeruginosa* related events at this time included thyroiditis and myositis. The organism at this time was susceptible to ceftazidime (MIC ≤ 8 mg/L) but resistant to aztreonam, imipenem, and meropenem. In light of these recurrent infectious events, the rapid emergence of resistance to carbapenems, and increasing MICs of the organism, intermittently dosed ceftazidime was changed to continuous infusion ceftazidime 700 mg/h (16.8 g/day) with a target level of 64 to 100 mg/L on 2/19 in order to control the infection and prevent further emergence of resistance. Ciprofloxacin 400 mg IV every 12h was administered concomitantly with continuous infusion ceftazidime. After blood cultures cleared on continuous infusion ceftazidime, the dosing regimen was changed to 2 g IV every 8h on 2/25. Both ceftazidime and ciprofloxacin were then discontinued on 3/1, but resumed on 3/10.

On 3/10, the patient again developed fever and *P. aeruginosa* bacteremia. The isolate was susceptible to ceftazidime (MIC ≤ 8 mg/L) and ciprofloxacin (MIC ≤ 1 mg/L), intermediate to levofloxacin, and resistant to aztreonam and meropenem. Given the patient's previous response to continuous infusion administration, ceftazidime was restarted at 700 mg/h (16.8 g/day) from 3/11 to 3/14. New pulmonary infiltrates and pleuritic chest pain, which were thought to be caused by recurrent *P. aeruginosa*, prompted a change to ceftazidime 2 g IV every 8h from 3/14 to 3/18 and then to continuous infusion ceftazidime 417 mg/h (10 g/day) on 3/18. The ceftazidime infusion rate was decreased to 375 mg/h (9 g/day) on 3/21 for a decline in the patient's renal function (Table 1). On 3/25, the patient developed facial fasciculation and the ceftazidime infusion rate was further decreased to 292 mg/h (7 g/day). The twitching resolved after dose reduction. The patient's bacteremia cleared and pneumonia improved while receiving continuous infusion ceftazidime, which was discontinued on 4/29.

During administration of antithymocyte globulin conditioning for an unrelated cord blood transplant, the patient developed fever, tachycardia, chest pain, and required intubation for

diffuse pulmonary edema and pleural effusions. Following transplant conditioning, two unrelated donor cord blood units were infused on 5/5. Before neutrophil recovery could occur, ceftazidime resistant *P. aeruginosa* bacteremia, pneumonia, ventriculitis, and choroid plexitis developed that became refractory to antimicrobial therapy. These events coincided with recovery of *P. aeruginosa* with ceftazidime MIC > 16 mg/L from tracheal aspirate on 5/2 and blood on 5/8 (Table 1). In response to this deterioration, imipenem, colistin and aminoglycoside were administered. The patient expired on 6/1 and postmortem cultures of the brain and lung grew *P. aeruginosa*.

Discussion

In vitro and *in vivo* studies, limited clinical data, and basic principles of continuous infusion beta-lactam antibiotic therapy against *P. aeruginosa* were recently reviewed elsewhere and are summarized throughout this discussion.[14] A paucity of clinical studies has been published on continuous infusion beta-lactam antibiotics for the treatment of serious infections caused by *P. aeruginosa*. These studies are largely limited to respiratory infections in cystic fibrosis and cutaneous lesions in neutropenic hosts.[16-21] Clinical studies using continuous infusion beta-lactam antibiotics for the treatment of serious multidrug-resistant *P. aeruginosa* infections are even more limited.[22,23]

This report describes in detail high-dose continuous infusion beta-lactam antibiotics for the treatment of resistant systemic *P. aeruginosa* infections in three chronically immunocompromised patients. The rationale for high-dose continuous infusion beta-lactam antibiotics in such compromised patients is to provide sustained bactericidal concentrations above the MIC and to prevent emergence of resistance until the infection is resolved or the immune impairment (e.g., profound neutropenia) is reversed. The rationale for use of ceftazidime in cases 1 and 3 is based upon several factors: its well established use as monotherapy in neutropenic patients; its safety profile; and/or its favorable MICs. The rationale for use of aztreonam in case 2 is based upon a previously successful response in management of the non-healing ulcers and an initial MIC of 16 mg/L.

In the first case, continuous infusion ceftazidime (target drug level ≥ 1.5 times MIC) was used to successfully treat multidrug-resistant *P. aeruginosa* bacteremia in a patient with primary immunodeficiency, neutropenia, and aggressive cutaneous T cell lymphoma/leukemia. In the second case, continuous infusion aztreonam was used to successfully treat multidrug-resistant *P. aeruginosa* wound infections and pneumonia in a patient with leukocyte adhesion deficiency type 1. In the third case, continuous infusion ceftazidime (target drug level ≥ 4 times MIC) was used to treat *P. aeruginosa* pneumonia and bacteremia in a patient with severe aplastic anemia. In each case, the bacteremia cleared, infected wounds healed, and pneumonia improved in response to continuous infusion ceftazidime or aztreonam.

We believe that the concomitant use of tobramycin in case #1 and #2 and ciprofloxacin in case #3 were ancillary in the treatment of *P. aeruginosa* infections in these profoundly compromised patients. Neither tobramycin nor ciprofloxacin are recommended as monotherapy in persistently neutropenic patients.[24]

Among the *in vitro* and *in vivo* studies of continuous infusion beta-lactam antibiotics for the treatment of *P. aeruginosa*, several reports suggest that maximum bactericidal activity occurs when drug levels are 4 to 5 times MIC.[25-28]*In vitro* and *in vivo* studies also suggest that beta-lactam antibiotic drug levels 2 times MIC may be bactericidal against some strains of *P. aeruginosa*.[29,30] While drug levels 4 to 5 times MIC are optimal, this may not be safely achievable in all patients. Given the elevated MIC of 64 mg/L for ceftazidime in the

first patient, a target maximum C_{ss} of 100 mg/L (1.5 times MIC) was approximated. Although higher concentrations (4 times MIC) of cefazidime would have been preferable, these concentrations could not be administered due to potential neurotoxicity. A similar situation occurred in the second patient. The MIC of aztreonam was 96 mg/L and for other beta-lactam antibiotics the MICs were off-scale. An infusion rate of aztreonam was administered to approximate this MIC in order to avoid neurotoxicity. In comparison, the third patient demonstrated that targeting a C_{ss} of ≥ 4 times MIC was feasible when the MIC was 8 mg/L. Thus, factors of both efficacy and toxicity should be considered when calculating a dosage for continuous infusion beta-lactam antibiotics.

Neurotoxicity is one of the most serious potential side effects of beta-lactam antibiotics and may include confusion, disorientation, somnolence, twitching, myoclonus, and seizures.[31] Risk factors for neurotoxicity include high dosages, history of seizures, other CNS disorders, renal failure, and concomitant drugs that lower the seizure threshold.[31,32] Patient #3 developed facial fasciculations consistent with beta-lactam antibiotic neurotoxicity that resolved with dose reduction. Vigilant monitoring for the signs and symptoms of neurotoxicity and careful adjustment of dosage for renal failure are critical when using continuous infusion beta-lactam antibiotics, particularly when targeting drug levels ≥ 4 times MIC, for the treatment of multidrug-resistant *P. aeruginosa* infections.

This case series describes a continuous infusion beta-lactam antibiotic dosing strategy for the treatment of resistant *P. aeruginosa* infections in immunocompromised patients when antibiotic options are limited. Loading doses and maintenance infusion rates should be calculated as described in Appendix 1. A more detailed description of these calculations has been recently published.[14] Total daily doses of continuous infusion beta-lactam antibiotics are traditionally less than or equal to their intermittent infusion regimens. However, our approach in targeting high drug concentrations is unique in that it results in higher total daily doses of ceftazidime or aztreonam compared to intermittent administration. Nonetheless, in order to prevent neurotoxicity the maximum recommended drug concentration of ceftazidime or aztreonam is 100 mg/L; this concentration is based on our clinical experience and review of the literature.[14]

The limitations of this case series are the small number of patients, the absence of drug concentrations, and use of combination therapy for the treatment of *P. aeruginosa* infections. Assays for determination of concentrations of ceftazidime and aztreonam were not available within our institution. However, the case series described herein is unique in that it demonstrates that high-dose continuous infusion beta-lactam antibiotic therapy is feasible in immunocompromised patients, that it may be useful in managing multidrug-resistant *P. aeruginosa* infections, and that it may improve outcome.

In conclusion, this report demonstrates that high-dose continuous infusion beta-lactam antibiotics are a potentially useful treatment strategy for resistant *P. aeruginosa* infections in critically ill immunocompromised patients. While this approach is not a panacea for multidrug-resistant *P. aeruginosa* infections, it may provide an additional treatment option when antibiotic choices are limited. This report also may provide a conceptual framework for prospective clinical studies to determine the safety and efficacy of high-dose continuous infusion beta-lactam antibiotics in immunocompromised hosts.

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Appendix 1: Formulas

Loading doses and maintenance infusion rates of aztreonam and ceftazidime were calculated using Equations 1 and 2.[12-14] Continuous infusion aztreonam or ceftazidime were administered to achieve target drug levels at or above the MIC when possible. The dosage regimens were calculated with the following parameters: maximal target drug level of 100 mg/L; half-life of two hours; volume of distribution of 0.3 L/kg. Renal dosing of ceftazidime was calculated using equation 5. Creatinine clearance (CrCl) was calculated using the Cockroft-Gault equation.[15]

$$\text{Loading dose (mg)} = C_{peak}\,(\text{mg/L}) \times V_d\,(\text{L/kg}) \times \text{weight (kg)}$$
C_{peak}=target peak concentration, V_d=volume of distribution 1.

$$\text{Maintenance infusion rate (mg/h)} = C_{ss}\,(\text{mg/L}) \times Cl_{total}\,(\text{L/h})$$
C_{ss}=target mean steady state concentration, Cl_{total}=total body clearance 2.

$$Cl_{total}\,(\text{L/h}) = K_e\left(h^{-1}\right) \times V_d\,(\text{L/kg}) \times \text{weight (kg)}$$
K_e=elimination rate constant, V_d=volume of distribution 3.

$$K_e\left(h^{-1}\right) = 0.693/t_{1/2}\,(\text{h})$$
K_e=elimination rate constant, $t_{1/2}$=half−life 4.

Maintenance infusion rate for Crcl<100 mL/min

$$\text{Maintenance infusion rate (mg/h)} = (\text{maintenance infusion rate from equation2}) \times (\text{CrCl}/100)$$ 5.

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Table 1

Summary of patient cases with continuous infusion beta-lactam antibiotics for the treatment of *P. aeruginosa* infections

Case #	Age / Gender	Primary Diagnosis	Type of Infection	Beta-lactam Antibiotic	Weight (kg)	Scr^a (mg/dL) -------- CrCl (mL/min)	Dosage	Target C_{ss} (mg/L)	Outcome
1	18 yo Female	Primary immunodeficiency Cutaneous T cell lymphoma/leukemia	Blood stream	ceftazidime	40	0.4 144 mL/min	9/19 LD: 2 g IV 9/19 – 9/22 MD: 271 mg/h 9/22 – 9/29 MD: 400 mg/h	80 to 100	Blood culture negative on repeat cultures Deceased
2	17 yo Male	Leukocyte adhesion deficiency type 1	Wound Pneumonia	aztreonam	49	11/26 0.7 11/30 0.7 52.6 mL/min[b] 12/1 0.6	11/26 – 11/27 LD: not given MD: 260 mg/h 12/1 – 8/17 LD: not given MD: 350 mg/h	> 16	Wounds healed Pneumonia resolved
3	44 yo Male	Severe aplastic anemia	Pneumonia Blood stream	ceftazidime	71.4	2/19 0.8 110 mL/min 3/18 1 88 mL/min 3/21 1.3 68 mL/min 3/25 1 88 mL/min	2/19 – 2/24 3/11 – 3/14[c] LD: not given MD: 700 mg/h 3/18 – 3/21 LD: not given MD: 417 mg/h 3/21 – 3/25 MD: 375 mg/h 3/25 – 4/29 MD: 292 mg/h	64 to 100	Bacteremia cleared and pneumonia improved with initial treatment Patient subsequently developed bacteremia, pneumonia, and meningitis Deceased

a = serum creatinine at start of continuous infusion beta-lactam antibiotic therapy

b = measured CrCl from a 24 hour urine collection adjusted for body surface area

c = new pulmonary infiltrates thought to be caused by recurrent *P. aeruginosa* were associated with pleuritic chest pain and prompted a change to ceftazidime 2 g IV every 8h from 3/14 to 3/18

CrCl = estimated creatinine clearance

LD = loading dose

MD = maintenance dose

Table 2

Antibiotic susceptibility of *P. aeruginosa* isolates

Case #	Date	Source	MIC (mg/L)[a]													
			Amik	Aztr	Cefe	Ceft	Cip	Gent	Imi	Levo	Mero	Pip	Pip /taz	Tic /clav	Tobr	Coli	Poly
1	9/17	Blood	32	> 16	> 16	> 16	> 2	> 8	> 8		> 8	> 64			≤ 4		
	9/17	Catheter tip	≤ 16	> 16	48	64	> 2	8	> 8		> 32	> 64			≤ 4		
	9/19 9/22	Blood (no growth)															
	9/23 9/24	Blood	≤ 16	> 16	48	64	> 2	8	> 8		> 8	> 64			2		
	9/25 9/26 9/29	Blood (no growth)															
	10/1	Post mortem cultures of lung and liver tissue (no growth)															
2	11/23	Wound (right graft site)	32	16		> 16	> 2	> 8	> 8		> 8	> 64			8		
	11/24	BAL	≤ 16	96		> 256	2	> 8	> 32		> 8	> 64			≤4	4	S[c]
	11/25	Wound[b] (left thigh)	32	> 16		> 16	2	> 8	> 8		> 8	> 64			≤4	6	
			32	> 16		> 16	> 2	> 8	8		> 8	> 64			8	2	
	11/25	Wound (right groin)	> 32	48		128	> 2	> 8	> 32		> 8	> 64			> 8	6	S[c]
		Wounds (all no growth)															
	12/06 1/3	Right thigh Right and left thighs															
	1/11	Right thigh, left groin skin graft															
	1/17	Left groin, right thigh															

Case #	Date	Source	MIC (mg/L)[a]													
			Amik	Aztr	Cefe	Ceft	Cip	Gent	Imi	Levo	Mero	Pip	Pip /taz	Tic /clav	Tobr	Coli	Poly
	2/26 – 8/07[d]																
3	1/20	Sinus	≤ 16	≤ 8	≤ 8	≤ 8	≤ 1	≤ 4	≤ 4	≤ 2	≤ 4		≤ 16	≤ 16	≤ 4		
	2/3	BAL	≤ 16	16	≤ 8	≤ 8	≤ 1	≤ 4	≤ 4	≤ 2	≤ 4		≤ 16	64	≤ 4		
	2/15	Blood	≤ 16	> 16	≤ 8	≤ 8	≤ 1	≤ 4	> 8	≤ 2	> 8		≤ 16	> 64	≤ 4		
	2/16 2/20 3/6	Blood (no growth)															
	3/10	Blood	≤ 16	> 16	≤ 8	≤ 8	≤ 1	≤ 4	≤ 4	4	> 8		≤ 16	64	≤ 4		
	3/12 4/28 4/29	Blood (no growth)															
	4/29	Tracheal aspirate (no growth)															
	5/2	Tracheal aspirate[b]	≤ 16	> 256	> 16	> 256	≤ 1	≤ 4	> 8	≤ 2	> 8		> 64	> 64	≤ 4		
			≤ 16	> 256	> 16	> 256	> 2	≤ 4	I[e]	> 4	> 8		> 64	> 64	≤ 4		
	5/8	Blood	≤ 16	> 16	> 16	> 16	> 2	≤ 4	8	> 4	> 8		64	> 64	≤ 4	1	

[a]= amik = amikacin, aztr = aztreonam, cefe = cefepime, ceft = ceftazidime, cip = ciprofloxacin, gent = gentamicin, imi = imipenem, levo = levofloxacin, mero = meropenem, pip = piperacillin, pip/taz = piperacillin/tazobactam, tic/clav = ticarcillin / clavulanate, tobr = tobramycin, coli = colistin, poly = polymyxin B

[b]= Multiple strains isolated

[c]= susceptibility testing done by Kirby-Bauer disk diffusion

[d]= multiple wound cultures remained negative

[e]= susceptibility testing done by E-Test