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Fulminant endocarditis and disseminated infection caused by carbapenem-resistant *Acinetobacter baumannii* in a renal-pancreas transplant recipient

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Abstract

Acinetobacter baumannii is an important cause of healthcare-associated infections, and is particularly problematic among patients who undergo organ transplantation. We describe a case of fulminant sepsis caused by carbapenem-resistant *A. baumannii* harboring the $bla_{\text{OXA-23}}$ carbapenemase gene and belonging to international clone II. This isolate led to the death of a patient 6 days after simultaneous kidney-pancreas transplantation. Autopsy findings revealed acute mitral valve endocarditis, myocarditis, splenic and renal emboli, peritonitis, and pneumonia. This

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case highlights the severe nature of certain *A. baumannii* infections and the vulnerability of transplanted patients to the increasingly intractable ‘high-risk’ clones of multidrug-resistant organisms.

Keywords

Acinetobacter baumannii; carbapenem resistance; simultaneous kidney-pancreas transplantation; endocarditis

Healthcare-associated infections are an important cause of inpatient morbidity and mortality (1). Infections with multidrug-resistant (MDR) gram-negative bacteria, especially carbapenem-resistant organisms, are of particular concern since their treatment is complicated by the paucity of active and reliable antibiotics and the limited availability of rapid and accurate diagnostics (2). In an era of organ shortages, transplant recipients, by nature of their underlying condition and anticipated clinical course, are at increased risk for infection with MDR organisms (3, 4). Given the impact of antimicrobial resistance in transplant recipients, defining fundamental strategies to prevent and manage infections will be critical for the advancement of transplantation. Here, we describe a fatal case of endocarditis and disseminated carbapenem-resistant *Acinetobacter baumannii* (CRAb) infection in a simultaneous pancreas-kidney transplant recipient. Our goal is to highlight the unappreciated virulence of *A. baumannii* and difficulties in recognizing and treating infections caused by CRAb after organ transplantation.

Case report

A 51-year-old man with type 1 diabetes mellitus underwent simultaneous pancreas and kidney transplantation after being maintained on peritoneal dialysis for 4 years, without peritonitis or other complications. He was managed with an insulin pump, and received thyroid replacement therapy. The prior surgical history was significant for a remote cholecystectomy and inguinal hernia repair, but he had not been admitted to the hospital recently. Before transplantation, the patient did not have fever or symptoms suggestive of recent or current infection.

The kidney and pancreas allografts were in good condition and the transplant procedure was uncomplicated; prophylaxis with cefazolin was administered. Immediate evidence was seen of acceptable renal allograft function, and the patient was transferred to the surgical intensive care unit (ICU), where he was extubated. Induction immunosuppression included anti-thymocyte globulin, mycophenolate mofetil, tacrolimus, and methylprednisolone. Pre-transplantation evaluation had revealed that the patient was cytomegalovirus-seronegative and he received valganciclovir, as well as trimethoprim-sulfamethoxazole and fluconazole prophylaxis. The immediate postoperative course was notable for leukocytosis and 2 episodes of hypoglycemia requiring supplemental dextrose. The patient was transferred to a regular inpatient medical unit on postoperative day (POD) 2.

On POD 4, hypothermia (34.9°C), tachycardia (115 beats per min), hypotension (90/60 mmHg), and leukopenia (1.7 white blood cells × 10^3/mm) were noted. During the next 24 h,

the patient continued to complain of weakness, remained hypothermic, tachycardic, and hypotensive, and was transferred to the surgical ICU with significant abdominal pain. Upon examination, the abdomen was distended. Blood and urine cultures were obtained; vancomycin and piperacillin/tazobactam were started empirically, and fluconazole continued.

An exploratory laparotomy was performed on the evening of POD 5 because of concern for an intra-abdominal source of sepsis. Two liters of serosanguinous peritoneal fluid were drained; both allografts were deemed viable, and there was no evidence of anastomotic leak, bowel perforation, or necrosis. Gram stain of a sample of peritoneal fluid revealed granulocytes and mixed bacteria with predominant gram-variable coccobacilli.

The patient returned to the surgical ICU in critical condition; acidosis progressed, despite continued broad-spectrum antibiotics (with meropenem instead of piperacillin/tazobactam) and support with vasopressors. A repeat exploratory laparotomy was performed <12 h later, on the morning of POD 6. The nonviable pancreatic allograft was removed. Further deterioration and cardiopulmonary arrest ensued, and the patient died later that day without further resuscitative efforts.

On the morning of POD 6, cultures obtained from peritoneal fluid yielded 4+ growth of gram-negative bacilli; that afternoon (1 h after the patient died) blood cultures became positive, with gram-negative bacilli present. Urine cultures remained sterile. Results of identification and susceptibility testing (MicroScan, Siemens Healthcare) of blood and peritoneal fluid isolates became available on POD 7, indicating *A. baumannii* resistant to piperacillin/tazobactam, all carbapenems, all cephalosporins, fluoroquinolones, and aminoglycosides, and with intermediate susceptibility to ampicillin/sulbactam. In contrast, the isolate was susceptible to colistin, polymyxin B, and tigecycline (Table 1; 5, 6).

Polymerase chain reaction (PCR) was used to query the presence of acquired carbapenemase genes ($bla_{\text{OXA-23-like}}$, $bla_{\text{OXA-24/40-like}}$, $bla_{\text{OXA-58-like}}$, bla_{KPC}, bla_{VIM}, bla_{IMP} and bla_{NDM}) in the *A. baumannii* blood isolate; only $bla_{\text{OXA-23-like}}$ was detected, and further sequencing of the amplicon identified it as $bla_{\text{OXA-23}}$ (7). Genetic typing with repetitive-sequence-based PCR demonstrated that the isolate was clonally related (>95% similarity) to the predominant strain in the hospital at the time, which was associated with an outbreak at the institution (8). Further genetic typing using multilocus sequence typing with the scheme devised at the Institut Pasteur confirmed that the isolate belonged to sequence type 2 (ST2) related to international clone II (http://www.pasteur.fr/recherche/genopole/PF8/mlst/Abaumannii.html).

An autopsy was performed. Significant findings included vegetations on a calcified native mitral valve, ascites, a splenic infarct, a hemorrhagic renal allograft, and congestion of lungs and liver. Histologic findings revealed gram-negative coccobacilli consistent with *Acinetobacter* species within the myocardium, in a thrombus associated with the mitral valve vegetation, in the diaphragm, native kidneys, left ureter and bladder, and thrombo-emboli laden with coccobacilli in the left upper lobe of the lung. The explanted pancreatic allograft showed ischemia, fat necrosis, with coccobacilli morphologically consistent with

Acinetobacter species (Figs. 1 and 2). Postmortem cultures from the spleen, lung, and heart all yielded *A. baumannii* with antimicrobial susceptibilities identical to those of the peritoneal fluid and blood isolates.

Discussion

Despite significant medical and surgical advances in organ transplantation and infection prevention, bacterial infections remain a significant source of post-transplant complications (9, 10). This report alerts us to the threat posed by CRAb to transplant recipients, compounded in this case by the unpredictable nature and incredibly rapid dissemination of the infection, the challenge of timely identification and antimicrobial susceptibility results, and the absence of effective treatment options.

A. baumannii is recognized for its ability to acquire and express multiple drug-resistance determinants (11). Carbapenem resistance surged in the past decade and now occurs in the majority of *A. baumannii* isolates, associated with overexpression of the chromosomal OXA-51 β-lactamase and acquisition of other OXA carbapenemases and metallo-β-lactamases through mobile genetic elements; high-level cephalosporinase expression and porin mutations also may lead to carbapenem resistance (12, 13). A striking feature of CRAb is that it harbors additional resistance determinants to other important classes of antibiotics, including mutations in the chromosomal quinolone-resistance determining region, genes encoding for aminoglycoside-modifying enzymes, 16S rRNA methyltransferases, and multidrug efflux pumps (7). In our case, the isolate contained $bla_{\text{OXA-23}}$ and belonged to international clone II, a successful ‘high-risk’ strain, sometimes associated with adverse clinical outcomes, and widely disseminated throughout the world (14–16).

The present knowledge regarding the epidemiology and clinical impact of *A. baumannii* is derived from institutional outbreaks and national and regional surveys (17–21). CRAb typically infects ill patients previously exposed to antibiotics and requiring critical care, including mechanical ventilation (9, 10). Thus, organ transplant recipients are especially vulnerable, acquiring CRAb from contact with the healthcare environment and personnel. In one report, 32% of organ recipients infected with CRAb were previously colonized (22). The impact of CRAb infections in the survival of transplant patients, however, is difficult to ascertain (12, 23–25). CRAb causes healthcare- and ventilator-associated pneumonia mainly after lung transplantation, and is associated with recurrent infection, allograft dysfunction, length of stay, and mortality (22, 24, 26–29).

Among recipients of abdominal organs, post-transplantation complications may predate or be unrelated to CRAb isolation (30–32). Renal transplant recipients with CRAb may suffer delayed graft function, nephrostomy placement, and renal replacement therapy (30). In general, the course of CRAb is insidious and protracted, with a median time from transplantation to infection of 20–349 days (4). Nevertheless, CRAb infections can present more immediately, as demonstrated by a case of necrotizing fasciitis that occurred 10 days after an uneventful kidney-pancreas transplant (33).

The rapid pace and fulminant nature of infection with CRAb in this case is noteworthy. Review of the autopsy findings revealed: (i) endocarditis of the mitral valve, (ii) myocarditis, (iii) splenic emboli, (iv) pneumonia, (v) peritonitis, and (vi) seeding of the native kidney and pancreatic allograft, but sparing of the renal allograft. How did overwhelming infection with *A. baumannii* come to occur in this case? Potential sources include healthcare-associated infection at or around the time of transplantation, prior colonization, or unrecognized pre-existent recipient infection exacerbated by immunosuppression, or donor-derived infection (34).

Acquisition of CRAb from the healthcare environment or personnel may be inferred by the similarity of the patient's isolate to the outbreak strain of CRAb circulating in the hospital at the time (8). The concurrent outbreak of CRAb was centered in the medical ICU, however, and no cases of CRAb had occurred in the surgical ICU until that time. Detailed genomic analysis of the outbreak isolates has revealed extensive variations in their gene content, suggesting plasmid transfers and 'microevolution' among a complex reservoir of strains (35). Furthermore, CRAb strains belonging to international clone II and harboring $bla_{\text{OXA-23}}$, such as the one responsible for this infection, also predominate among epidemiologically unrelated CRAb isolates from the same region and the rest of the United States (19, 21).

Evidence in our patient of previous colonization with CRAb is lacking, although pre-transplant screening for carriage of MDR organisms was not performed. Pre-operative colonization with MDR gram-negative organisms is infrequently associated with post-transplantation morbidity, with the exception of *Burkholderia cepacia* complex in lung transplantation (3, 4). It remains possible that intensive immunosuppression unmasked previously unrecognized *A. baumannii* acquired before his admission, resulting in the dramatic clinical presentation we witnessed. It is also possible that the infecting strain possessed characteristics, including changes in surface polysaccharide components, which altered the host response (35, 36).

The donor in this case was a young man involved in a motor vehicle accident; evidence of donor-derived infection was not found. We maintain that the presence of coccobacilli suggestive of *A. baumannii* in the pancreas allograft was likely the result of disseminated infection in the recipient. Even if established beforehand, bacterial infections in donors do not preclude organ procurement, because treatment of donors with broad-spectrum antibiotics and prophylaxis of recipients mitigate transmission risks (37). Donor-derived infections with MDR organisms (causing bloodstream infections and mycotic aneurysms) do occur, and present an average of 8 days post transplantation (38). Failures in timely communication of antimicrobial susceptibility results from donors' isolates have led to ineffective initial antibiotic treatment of transplant recipients (27, 39).

Delayed initiation of effective antimicrobials for the treatment of CRAb may be associated with increased morbidity and mortality (25, 32, 40). In this case, the microbial etiology of the sepsis syndrome was not available ante mortem. Gram stain of peritoneal fluid, the only result available before the patient died, revealed coccobacilli, in retrospect indicative of *A. baumannii* infection. Definite identification and antimicrobial susceptibility results,

however, only became available after the patient's demise. The patient was treated empirically with piperacillin/tazobactam followed by meropenem, reasonable choices based on the local epidemiology, but ultimately ineffective. In cases such as this, the implementation in clinical practice of rapid molecular diagnostics targeted to resistance gene identification offers the potential to inform early appropriate therapy by detecting antibiotic resistance determinants ($bla_{\text{OXA-23}}$, in this instance) (41, 42).

Even when antimicrobial susceptibilities are known, the treatment of CRAb infections is problematic because of the MDR nature of this pathogen and the shortcomings of available therapeutic options (e.g., polymyxins, tigecycline, and sulbactam). Therefore, attention has focused on combination therapy, where the data, derived mostly from *in vitro* evaluations, appear promising. Evidence from controlled clinical trials is limited, however, and the optimal combination of antimicrobials remains undefined (Table 2; 22, 29, 43–49). Only a few agents with activity against *A. baumannii* are in development (2, 50).

In revisiting this case, our current appraisal is that the patient was demonstrating evidence of sepsis in the early postoperative period, although his episodes of hypoglycemia could have been related to the recent pancreas transplant. Crucially, infection with CRAb was not recognized and empirical antibiotic treatment was ineffective. As noted, few cases of CRAb among surgical patients had occurred at the facility at the time in which the patient underwent transplantation. In addition, this patient did not present with healthcare-associated pneumonia, the most common syndrome of CRAb in organ transplant recipients. While there was increased concern for an intra-abdominal source, the possibility of endocarditis was unanticipated. The patient died before microbiological diagnostic results became available and could be incorporated into clinical decision-making. Although the use of rapid molecular diagnostics may accelerate the identification of the organism and its genotype, choosing an effective antibiotic therapy against CRAb is problematic, as reviewed.

With these caveats in mind, the fulminant nature of this patient's infection, and the degree of immunosuppression in the immediate post-transplant period, it is unclear whether the outcome would have been altered with more timely active antimicrobials or more aggressive surgical intervention. The unfortunate overlap of immune suppression and overwhelming infection likely preordained the poor outcome. The behavior of this isolate, causing valvular infection and widespread organ involvement, may also suggest unique virulence characteristics. Although the occurrence of endocarditis is a distinctly unusual complication of a gram-negative bacteremia, review of the clinical experience with *Acinetobacter* endocarditis involving native valves reveals this as a fulminant and aggressive infection, notable for its high organism load and the seeding of multiple organs (51).

In conclusion, this case illustrates the challenge that *A. baumannii* poses to organ transplantation, including the need for identification of virulence factors affecting outcome, development of novel antibiotics, and implementation of rapid diagnostic tests. Despite efforts in choosing appropriate transplant candidates and donors, the increasing prevalence of MDR organisms in our healthcare system may yet prove to be the "Achilles' heel" of organ transplantation. Therefore, a collaborative approach between intensivists, transplant

practitioners, infection preventionists, clinical microbiologists, and infectious diseases specialists remains imperative in the management of these patients. These efforts may lead to innovations in screening and early detection, insights into pharmacotherapy, and the development of passive and active immunological strategies against *A. baumannii* and other MDR organisms (52).

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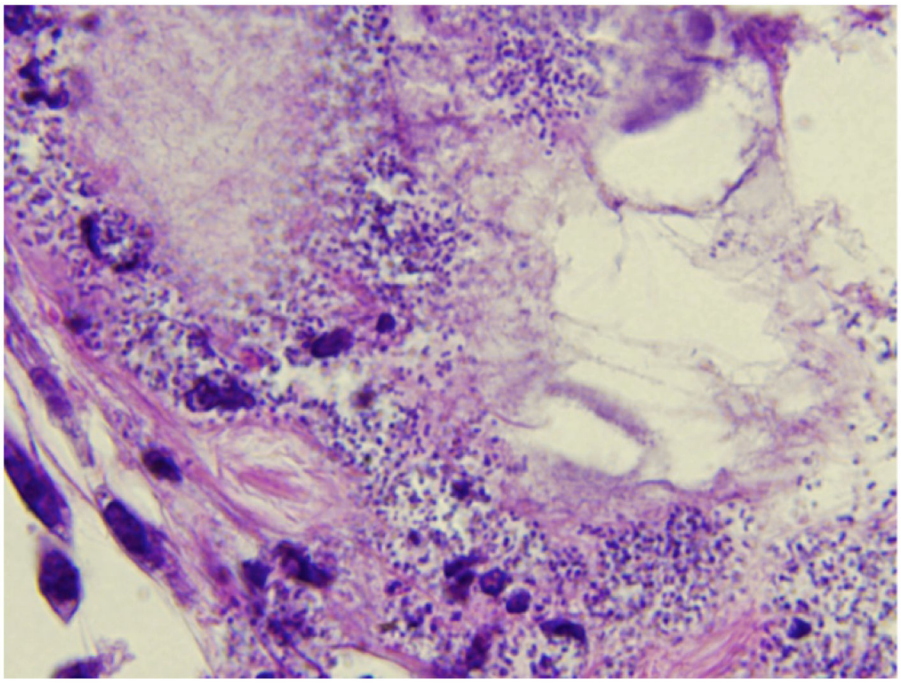

Fig. 1.

High-powered (100X) microscopic image of pancreatic graft with hematoxylin and eosin stain showing coccobacilli consistent with *Acinetobacter* species.

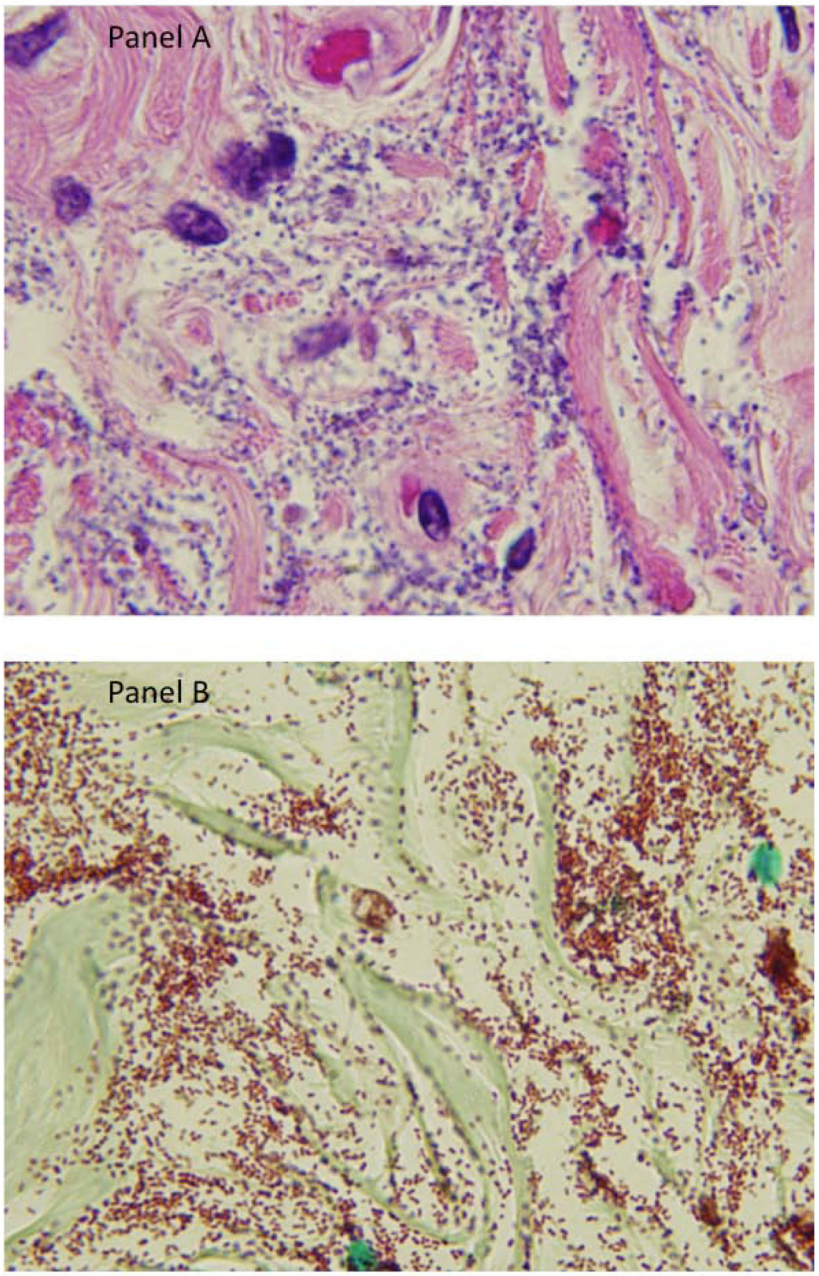

Fig. 2.

High-powered (100X) microscopic image of bladder with hematoxylin and eosin (panel A) and Gram stain (panel B) demonstrating abundant coccobacilli consistent with *Acinetobacter* species.

Table 1

Results of antimicrobial susceptibility testing for *Acinetobacter baumannii*, according to Clinical Laboratory Standards Institute and FDA guidelines (5, 6)

Antibiotic	MIC (μg/mL)	Interpretation
Amikacin	>32	R
Aztreonam	>16	R
Ampicillin/sulbactam	16/8	I
Ciprofloxacin	>2	R
Colistin	0.5	S
Doripenem	>2	R
Cefepime	>16	R
Gentamicin	>8	R
Imipenem	>8	R
Levofloxacin	>8	R
Meropenem	>8	R
Minocycline	8	I
Piperacillin/tazobactam	>64/128	R
Polymyxin B	0.5	S
Trimethoprim/sulfamethoxazole	>4/76	R
Tigecycline	1	S
Tobramycin	>8	R

FDA, US Food & Drug Administration; MIC, minimum inhibitory concentration; R, resistant; I, intermediate; S, susceptible.

Table 2

Therapeutic approaches to carbapenem-resistant *Acinetobacter baumannii* (CRAb)

Approach	Advantages	Limitations	References
Monotherapy			
Polymyxins	Highly active *in vitro* Mainstay against CRAb	Nephrotoxicity of colistin + calcineurin inhibitors Unclear pharmacokinetics and dosing regimen Emergence of resistance with monotherapy	(43, 44)
Tigecycline	Highly active *in vitro* Large volume of distribution Tissue penetration	Increased mortality Resistance during therapy Inadequate serum and urine concentrations	(22, 29, 45)
Sulbactam	Comparable to carbapenems for susceptible strains Optimized with high dose and prolonged infusion	Co-resistance of sulbactam in CRAb	(46)
Combination therapy			
Carbapenem + polymyxins	Favorable meta-analysis of *in vitro* data Successful in organ transplant recipients	Controlled trials needed	(22, 47)
Polymyxins + rifampin	Randomized controlled trial: increased bacterial clearance	No difference in 30-day mortality Rifampin interacts vs. azoles, calcineurin/mTOR inhibitors	(48)
Polymyxins + fosfomycin	Randomized controlled trial: favorable microbiological response	Not powered to detect differences in clinical outcomes IV fosfomycin not available in the US	(49)

mTOR, mammalian target of rapamycin; IV, intravenous; US, United States of America.