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REVIEW

Pseudomonas aeruginosa bacteremia among liver transplant recipients

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Abstract: *Pseudomonas aeruginosa* bacteremia remains as a life-threatening complication after liver transplantation (LT) and is intractable because of the high rate of drug resistance to commonly used antibiotics. To better understand the characteristics of this postoperative complication, PubMed and Embase searches as well as reference mining was done for relevant literature from the start of the databases through August 2018. Among LT recipients, the incidence of *P. aeruginosa* bacteremia ranged from 0.5% to 14.4% and mortality rates were up to 40%. Approximately 35% of all episodes of bloodstream infections (BSIs) were *P. aeruginosa* bacteremia, of which 47% were multidrug resistant and 63% were extensively drug resistant. Several factors are known to affect the mortality of LT recipients with *P. aeruginosa* bacteremia, including hypotension, mechanical ventilation, and increasing severity of illness. In LT recipients with *P. aeruginosa* bacteremia, alteration in DNA gyrase A genes and overexpression of proteins involved in efflux systems, namely the expression of KPC-2-type carbapenemase, NDM-1, and VIM-2-type MBL, contribute to the high resistance of *P. aeruginosa* to a wide variety of antibiotics. Because of complicated mechanisms of drug resistance, *P. aeruginosa* causes high morbidity and mortality in bacteremic LT patients. Consequently, early detection and treatment with adequate early targeted coverage for *P. aeruginosa* BSI are of paramount importance in the early posttransplantation period to obtain a better prognosis for LT patients.
Keywords: antimicrobial resistance, morbidity and mortality, risk factor, solid organ transplantation, liver transplantation

Introduction

Pseudomonas aeruginosa, one of the most lethal causative organisms of bacteremia, is classified as non-lactose-fermenting Gram-negative bacilli.[1] Beyond the striking virulence, it is intrinsically resistant to some commonly used antibiotics, and it is capable of acquiring resistance to multiple classes of antibiotics.[2–5] Consequently, it causes a wide array of life-threatening acute and chronic infections, particularly in immunocompromised patients.

P. aeruginosa bacteremia is a common condition that has a considerable impact on liver transplantation (LT), leading to significant morbidity and mortality. A large body of published studies showed that 0.5%–11.4% of LT recipients develop *P. aeruginosa* bacteremia, while the incidence of bacteremia caused by *Pseudomonas* spp. ranged from 0.9% to 11.8% in LT recipients.[6–29] Approximately 30% mortality was observed in LT recipients with multidrug resistance (MDR) *P. aeruginosa* according to three studies over the span of 20 years.[25,26,30]

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To date, a number of literature reviews have been published regarding the topic of *P. aeruginosa* bacteremia. However, much of them have been descriptive in the context of cystic fibrosis, respiratory disease, or AIDS. There has been no detailed investigation of *P. aeruginosa* bacteremia and its current impact in LT recipients. The present article will help to address this gap.

The remaining part of this review will discuss the epidemiology, mortality, microbiologic features, risk factors for bacteremia and mortality, mechanisms of drug resistance, prevention, and treatment for *P. aeruginosa* bacteremia in LT recipients.

Methods

To better understand the characteristics of bacteremia due to *P. aeruginosa* in LT recipients, PubMed and Embase databases were searched independently by two authors for relevant literature published from the start of these databases up to August 2018 by using the search terms "bloodstream infections (BSIs)", "bacteremia", "septicemia", "infection", "epidemiology", "microbiology", "non-fermenters", "nonfermenting", "*P. aeruginosa*", "therapy", "multidrug resistance", "extensively drug resistant (XDR)", "risk factor", "predictor", "morbidity", "mortality", "liver transplantation", and "solid organ transplantation (SOT)". We also screened relevant reviews and references available to identify potentially relevant studies. No restriction was applied during the literature search.

Morbidity of bacteremia caused by *P. aeruginosa* was defined using criteria proposed by Centers for Disease Control and Prevention (CDC): the isolation of *P. aeruginosa* in one culture with signs of infection or the isolation of *P. aeruginosa* from at least two consecutive cultures correlated with signs of infection. Mortality was defined as death occurring during the hospitalization of an LT recipient with *P. aeruginosa* bacteremia.[31]

In the present review, MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories (except for reference 35, which defined MDR as resistance to all of the agents in two or more antimicrobial categories), and XDR was defined as non-susceptibility to at least one agent in all but two or fewer antipseudomonal antimicrobial categories (ie, bacterial isolates remain susceptible to only one or two categories) according to the criteria introduced by Magiorakos et al.[32] Given that it is not only resistant to all β-lactam antimicrobials but also frequently to other classes of antimicrobials, such as aminoglycosides and fluoroquinolones, *P. aeruginosa* producing

carbapenem-hydrolyzing β-lactamase is considered to be an MDR isolate.[33,34]

Morbidity and mortality of *P. aeruginosa* bacteremia in LT recipients

P. aeruginosa or *Pseudomonas* spp. bacteremia has not been reported to be problematic in early studies in LT recipients, with only 0–9 episodes documented in four series.[21,28,35,36] However, *P. aeruginosa* bacteremia has become an emerging problem over the last three decades.

Among LT recipients, the morbidity caused by *P. aeruginosa* bacteremia was reported to be 0.5%–14.4%, while *Pseudomonas* spp. bacteremia was reported to be 0.9%, 1.0%, and 11.8%.[6–29]

As shown in Table 1, previous studies on LT recipients with BSIs reported that 2.5%–22.2% of their research subjects had *P. aeruginosa* bacteremia and 3.4%–6.9% carried *Pseudomonas* spp.[6–13,15–19,21–23,26–30,36–39] In studies on Gram-negative bacteremia after LT, *P. aeruginosa* was responsible for 8.5%–9.4% of all cases of Gram-negative bacteremia.[20,24] We found two other studies that investigated bacteremic LT recipients with focus on drug resistance; one of them reported that carbapenem- and quinolone-resistant *P. aeruginosa* bacteremia accounted for 5.2%–12.7% of all BSIs, while the second one reported that 9.3% of all episodes of BSIs was XDR *P. aeruginosa* bacteremia.[40,41]

P. aeruginosa is one of the most lethal causative organisms of bacteremia in LT populations. As shown in Table 2, the mortality rates varied in different studies, ranging from 0% to 40% in transplant recipients with *P. aeruginosa* bacteremia, and more than one-third of patients who developed XDR *P. aeruginosa* bacteremia after LT (38%) failed to survive.[6,14,25,26,30,41–43]

Antimicrobial resistance of *P. aeruginosa* causing bacteremia

Among all *P. aeruginosa* isolates causing bacteremia in LT recipients, MDR *P. aeruginosa* accounted for 47% and XDR for 63.2%.[41,43] Sganga et al conducted a retrospective cohort study in a single center and reported that 12.5% of non-lactose-fermenting Gram-negative bacilli (largely consisting of *P. aeruginosa*, 87.5%) were MDR and 62.5% were XDR.[9] Another single-center study conducted by Shi et al found 51.5% of *Pseudomonas* spp. to be MDR, defined by non-susceptibility to two or more antimicrobial categories; resistance rates of *Pseudomonas* spp. to ceftazidime, ciprofloxacin, and imipenem were 18%, 33%, and 32%, respectively.[38]

Table 1 The incidence rates of *Pseudomonas* spp. in all pathogens causing BSIs in LT recipients

Author (year /country)	Transplantation type	Type of NLF GNB	The incidence rates (the proportion of *Pseudomonas* spp. in all pathogens causing BSIs in LT recipients)
Fulginiti et al (1968/USA)	LT	*Pseudomonas* spp.	*Pseudomonas* spp.: 5.9% (2/34)
Schröter et al (1976/USA)	LT	*P. aeruginosa*	*P. aeruginosa*: 6.0% (9/151)
Colonna et al (1988/USA)	LT	*P. aeruginosa* + *Stenotrophomonas maltophilia*	*P. aeruginosa*: 18.2% (2/11)
George et al (1991/USA)	LT	*P. aeruginosa*	*P. aeruginosa*: 15.5% (9/58)
Wade et al (1995/ England)	LT	*S. maltophilia* + *Pseudomonas* spp.	*Pseudomonas* spp.: 4.5% (3/67)
Falagas et al (1996/USA)	LT	*Acinetobacter* + *P. aeruginosa*	*P. aeruginosa*: 8.4% (7/83)
Singh et al (2000/USA)	LT	*P. aeruginosa*	*P. aeruginosa*: 19.0% (8/42)
Munoz-Price et al (2004/USA)	LT	*Pseudomonas* spp.	*Pseudomonas* spp.: 3.4% (2/59)
Singh et al (2004/USA)	LT	*P. aeruginosa*	*P. aeruginosa*: 12.7% (10/79)
Kawecki et al (2007/USA)	LT	*P. aeruginosa* + *Pseudomonas putida* + *S. maltophilia*	*P. aeruginosa*: 3.7% (1/35)
Shi et al (2009/China)	LT	*Acinetobacter baumannii* + *S. maltophilia* + *Pseudomonas* spp.	*P. aeruginosa*: 6.8% (22/323)
Bert et al (2010/France)	LT	*A. baumannii* + *P. aeruginosa* + *S. maltophilia* + *Burkholderia cepacia*	*P. aeruginosa*: 8.8% (25/259)
Lee et al (2011/USA)	LT	NLF GNB	*P. aeruginosa*: 4.9% (6/123)
Karvellas et al (2011/UK)	LT	*A. baumannii* + *Pseudomonas* spp.	*Pseudomonas* spp.: 6.9% (2/29)
Sganga et al (2012/Italy)	LT	*A. baumannii* + *P. aeruginosa*	*P. aeruginosa*: 15.9% (7/44)
Kim et al (2013/Korea)	LT	*A. baumannii* + *P. aeruginosa* + *Pseudomonas fluorescens* + *P. putida* + *S. maltophilia*	*P. aeruginosa*: 8.9% (10/112)
Wan et al (2013/China)	LT (2002–2012)	*A. baumannii* + *S. maltophilia* + *Pseudomonas* spp.	*Pseudomonas* spp.: 5.2% (4/77)
Wan et al (2013/China)	LT (2002–2014)	*A. baumannii* + *S. maltophilia* + *Pseudomonas* spp. + *Achromobacer xylosoxidans*	*P. aeruginosa*: 8.5% (4/47) of all negative bacteremia
Wan et al (2015/China)	LT (2002–2013)	*A. baumannii* + *P. aeruginosa* + the other NLF GNB	*P. aeruginosa*: 3.7% (4/108)
Hashimoto et al (2008/Japan)	LDLT	*P. aeruginosa* + *Pseudomonas cepacia* + *S . maltophilia*	*P. aeruginosa*: 7.7% (2/26)
Kim et al (2009/Korea)	LDLT	*P. aeruginosa* + *A. baumannii* + *Chryseobacterium meningosepticum* + *Acinetobacter lwoffii*	*P. aeruginosa*: 2.5% (1/40)
Iida et al (2010/Japan)	LDLT	*A. baumannii* + *P. aeruginosa* + *S. maltophilia*	*P. aeruginosa*: 22.2% (26/117)
Wagener et al (1992/USA)	SOT	*P. aeruginosa*	*P. aeruginosa*: 21.7% (15/69)
McClean et al (1994/Canada)	SOT	*Pseudomonas* spp.	*Pseudomonas* spp.: 4.8% (1/21)
Moreno et al (2007/Spain)	SOT	*A. baumannii* + *S. maltophilia* + *P. aeruginosa*.	*P. aeruginosa*.: 6.5% (9/138)
Al-Hasan et al (2009/USA)	SOT	*P. aeruginosa*	*P. aeruginosa*: 9.4% (5/53) of all negative bacteremia
Yeşilkaya et al (2013/Turkey)	SOT	*A. baumannii* + *P. aeruginosa* + *S. maltophilia*	*P. aeruginosa*: 5.3% (12/228)
Bodro et al (2013/Spain)	SOT	*A. baumannii* + *P. aeruginosa* + the other NLF GNB	Carbapenem- and quinolone-resistant *P. aeruginosa*: 12.7% (9/97)
Bodro et al (2015/Spain)	SOT	XDR *P. aeruginosa*	XDR *P. aeruginosa*: 9.3% (10/107)

Abbreviations: BSIs, bloodstream infections; GNB, non-lactose fermenting Gram-negative bacilli; LDLT, living donor liver transplantation; LT, liver transplantation; NLF, non-lactose fermenting; SOT, solid organ transplantation; XDR, extensively drug-resistant.

In previous studies on drug resistance, 16% of *P. aeruginosa* were carbapenem-resistant and 25% were carbapenem- and quinolone-resistant in LT recipients with bacteremia.[18,30] The antibiotic resistance of *P. aeruginosa* causing bacteremia in LT recipients is shown in Table 3.

Interestingly, there were significant differences in the ratios of MDR *P. aeruginosa* in that 43% of transplant isolates and only 18% of non-transplant isolates were MDR in a study conducted in the USA.[40] A reasonable explanation could be

that transplant recipients usually have higher exposure to invasive devices.

The most common portals of *P. aeruginosa* identified was the abdominal/biliary tract or intravascular catheters in bacteremic LT recipients.[8,10,17,22,25,26] Intra-abdominal infections and the urinary tract were also reported as the most common source of *P. aeruginosa* bacteremia.[14,30] Kim et al in a retrospective study of 222 consecutive LT recipients found that the main focus of *Pseudomonas* spp. bacteremia was

Table 2 The mortality rates of *Pseudomonas aeruginosa* bacteremia in LT recipients

Author (year/ country)	Transplantation type	Microbiology of NLF GNB	Mortality due to *P. aeruginosa* bacteremia
Korvick et al (1991/USA)	LT	*P. aeruginosa* + the other NLF GNB	30% (7/23) for 14-day mortality rate after bacteremia.
Singh et al (2004/ USA)	LT	*P. aeruginosa*	30% (3/10) for 30-day mortality rate after bacteremia.
Bert et al (2010/ France)	LT	*Acinetobacter baumannii* + *P. aeruginosa* + *Stenotrophomonas maltophilia* + *Burkholderia cepacia*	28% (7/25) for 15-day mortality after bacteremia.
Kim et al (2009/ Korea)	LDLT	*P. aeruginosa* + *A. baumannii* + *Chryseobacterium meningosepticum* + *Acinetobacter lwoffii*	0% (0/1) within 6 months after transplantation.
Hashimoto et al (2009/Japan)	LDLT	*P. aeruginosa*	0% (0/4) within 3 months after transplantation.
Linares et al (2009/Spain)	SOT	*P. aeruginosa*	0% (0/13) for 30-day mortality after bacteremia.
Johnson et al (2009/USA)	SOT + HSCT	*P. aeruginosa*	40% (31/77) for 28-day mortality after bacteremia.
Bodro et al (2015/Spain)	SOT	XDR *P. aeruginosa*	38% (11/31) of XDR *P. aeruginosa* bacteremia for 30-day overall mortality.

Abbreviations: GNB, non-lactose fermenting Gram-negative bacilli; HSCT, hematopoietic stem cell transplant recipients; LDLT, living donor liver transplantation; LT, liver transplantation; NLF, non-lactose fermenting; SOT, solid organ transplantation; XDR, extensively drug-resistant.

Table 3 The proportion of MDR *Pseudomonas aeruginosa* to all *P. aeruginosa* isolates causing bacteremia in LT recipients

Author (published year/country)	The study period/ organisms	Drug-resistance rate
Johnson et al (2009/USA)	1996–2005/*P. aeruginosa*	MDR: 47% (36/77)
Shi et al (2009/China)	2003–2006/*Pseudomonas* spp.	Imipenem resistance: 32% (10/31); cefoperazone-sulbactam resistance: 24% (8/33); ceftazidime resistance: 18% (6/33); ciprofloxacin resistance: 33% (11/33); piperacillin-tazobactam resistance: 21% (7/33)
Bert et al (2010/France)	1997–2007/*Acinetobacter baumannii* + *P. aeruginosa* + *Stenotrophomonas maltophilia* + *Burkholderia cepacia*	imipenem or piperacillin-tazobactam resistance: 16%(4/25); ceftazidime resistance: 8% (2/25); cefepime or amikacin resistance: 24% (6/25); gentamicin resistance: 44% (11/25); ciprofloxacin resistance: 36% (9/25)
Sganga et al (2012/Italy)	2008–2011/*A. baumannii* + *P. aeruginosa*	MDR: 12.5% (1/8) of NLF GNB. XDR: 62.5% (5/8) of NLF GNB
Ouyang et al (2015/China)	2002–2013/*A. baumannii* + *P. aeruginosa* + the other NLF GNB	Carbapenem and quinolone resistance: 25% (1/4)
Bodro et al (2015/Spain)	2007–2013/*P. aeruginosa*	XDR: 63.2% (31/49)

Abbreviations: GNB, non-lactose-fermenting Gram-negative bacilli; LT, liver transplantation; MDR, multidrug resistance; NLF, non-lactose fermenting; XDR, extensive drug-resistant.

the biliary tract.[8] Table 4 shows the most common primary sources of *P. aeruginosa* or *Pseudomonas* spp. bacteremia in LT recipients.

The risk factors for the morbidity and mortality of *P. aeruginosa* bacteremia

Despite high rates of morbidity and mortality, predictors of *P. aeruginosa* bacteremia and its related mortality remain ill-defined in LT recipients. Recently, a prospective observational study from Spain claimed that in SOT recipients (mainly comprising renal and liver recipients), factors independently associated with XDR *P. aeruginosa* bacteremia were prior transplantation, nosocomial acquisition, and septic shock at onset.[41] Korvick et al demonstrated that in LT recipients with *P. aeruginosa* bacteremia, survival rates were significantly lower for patients with hypotension, mechanical ventilation, or increasing severity of illness.[25] In a large retrospective cohort study on *P. aeruginosa* BSI, Johnson et al focused on MDR in *P. aeruginosa* bacteremic transplant recipients, which included 52% of LT recipients. They found previous transplantation, hospital-acquired BSI, and prior intensive care unit admission to be independent risk factors for developing infection with MDR *P. aeruginosa* isolates. Their study also showed that onset of BSI during stay in the intensive care unit was the only independent predictor for 28-day in-hospital mortality.[43] To date, no other study of LT recipients has assessed the association of clinical or laboratory parameters and the risk for *P. aeruginosa* bacteremia and its related mortality.

Diagnosis of *P. aeruginosa* bacteremia

Generally, to identify *P. aeruginosa* bacteremia in liver recipients, blood samples were cultured using the BacT/ Alert automated instrument. The diagnosis of *P. aeruginosa* bacteremia was made by its isolation from one or more sets of blood culture bottles collected using standard sterile techniques, with the presence of clinical features consistent with signs of systemic infection, including fever, chills, or hypotension. Specific selective media and identification procedures such as using selective media with MacConkey agar and cetrimide were also recommended for the isolation of *P. aeruginosa*. The presence of MBLs was evaluated in imipenem- or meropenem-resistant *P. aeruginosa* by using both an EDTA screen test and the MBL E-test.[44] Analysis by pulsed-field gel electrophoresis was the "gold standard" for confirming relatedness among *P. aeruginosa*.[45] In addition to classic methods described above, new technologies have emerged.

Two FDA and CE marking (Conformité Européenne) approved commercial systems based on the concept of matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) are available in the market, including the Bruker Microflex Biotyper and the bioMérieux VITEK MS, which can rapidly identify clinical *P. aeruginosa*. However, ambiguities exist when using protein profiling to differentiate closely related bacterial species or strains because of similarity of proteins as well as the lack of representative spectra in the manufacturer's database.[46]

Lipid A signature platforms using MS has been established to detect the chemical structure of lipid A and mechanisms of antibiotic resistance of *P. aeruginosa*. Using MALDI-TOF MS, the chemical structure of lipid A, especially the fatty acid number, location, and distribution of lipid A moiety extracted from *P. aeruginosa* were elucidated.[47,48] With regard to antibiotic resistance of *P. aeruginosa*, Moskowitz et al confirmed that mutations in the pmrA/pmrB regulatory

Table 4 Primary sources of *Pseudomonas aeruginosa* bacteremia in LT recipients

Author (published year/ country)	Transplantation type	Organisms	The most common sources of bacteremia
Korvick et al (1991/USA)	LT	*P. aeruginosa*	Abdomen
Singh et al (2000/USA)	LT	*P. aeruginosa*	Abdomen/biliary tract
Singh et al (2004/USA)	LT	*P. aeruginosa*	Intravascular catheters
Bert et al (2010/France)	LT	*Acinetobacter baumannii* + *P. aeruginosa* + *Stenotrophomonas maltophilia* + *Burkholderia cepacia*	Urinary tract
Kim et al (2013/Korea)	LT	*A. baumannii* + *P. aeruginosa* + *Pseudomonas fluorescens* + *P. putida* + *S. maltophilia*	The biliary tract for *Pseudomonas* spp. bacteremia
Hashimoto et al (2008/Japan)	LDLT	*P. aeruginosa* + *Pseudomonas cepacia* + *S. maltophilia*	Intravascular catheters
Hashimoto et al (2009/Japan)	LDLT	*P. aeruginosa*	Intra-abdominal infections
Wagener et al (1992/USA)	SOT	*P. aeruginosa*	Abdomen/biliary tract

Abbreviations: LDLT, living donor liver transplantation; LT, liver transplantation; SOT, solid organ transplantation.

system resulted in the addition of epotaminoarabinose to lipid A, which led to polymyxin resistance.[49] Liu et al found that lipid A is modified by the addition of phosphoethanolamine in polymyxin-resistant *P. aeruginosa* strains.[50] However, as we stated above, MALDI-TOF analysis is not quantitative and very little structural information can be gained from the simple mass spectrum obtained; this limitation can be overcome by coupling it with tandem mass spectrometry.

Peptide nucleic acid fluorescence in situ hybridization assays is recently introduced as an alternative to other molecular methods to shorten the turnaround time of detection of *P. aeruginosa* from positive blood culture to 1.5–3 hours, but the information regarding antibiotic susceptibility profile is deficient.[51]

The mechanisms of drug resistance of *P. aeruginosa*

P. aeruginosa is intrinsically in vitro resistant to some commonly used antibiotics, such as trimethoprim/sulfamethoxazole and doxycycline. The high resistance of *P. aeruginosa* to a wide variety of antibiotics is due to its constitutive expression of β-lactamases as well as overexpression of AmpC and carbapenemases. Other likely causes of resistance include modification of penicillin-binding profiles, and the multidrug efflux pumps, such as MexAB-OprM, combined with the low permeability of its outer membrane and a high ability to generate acquired antibiotic resistance.[52–58]

The β-lactamase enzymes are divided into four functional groups A to D, where B or C β-lactamases are much more common enzymatic causes of resistance in *P. aeruginosa*. Oxacillinases are common in *P. aeruginosa*, and only oxacillinases 40 and 198 have been described in isolated reports to express carbapenemase activity.[59,60]

The clones carrying enzymatic resistance, particularly VIM-2, are of global concern. MBLs are the predominant group of carbapenemases, conferring resistance to all the β-lactams except aztreonam. IMP and VIM types are the most common MBLs found in *P. aeruginosa*.[61] Other types of MBLs include SPM-1, GIM-1, AIM-1, NDM-1, and FIM-1.[62–65] The study by Edelstein et al provided longitudinal data showing evidence of cross-transmission of a few successful clones such as ST111, ST175, or ST235, all of which belong to the majority of *P. aeruginosa* isolates, thereby contributing to the spread of resistance.[66]

Some studies showed that *P. aeruginosa* had higher level susceptibility to meropenem than to imipenem, a phenomenon representing reduced production of OprD porin, which is the preferential entry channel for imipenem.[67]

There are five superfamilies of efflux pumps that can reduce drug accumulation in the bacteria. Efflux pump upregulation can be a potential cause of MDR in a *P. aeruginosa* isolate. When the MexAB-OprM system is upregulated, it consequently reduces susceptibility to fluoroquinolone, penicillin, cephalosporin, and meropenem. Upregulation of MexCD-OprJ and MexEF-OprN confers *P. aeruginosa* resistance to fluoroquinolones and some β-lactams, whereas upregulation of MexXY-OprM may lead to reduction in susceptibility to aminoglycosides and fluoroquinolones.[4,68]

In addition to bla_{NDM}, the bla_{VIM} gene was also found in a carbapenem-resistant *P. aeruginosa* isolated from an institute of surgical gastroenterology and LT.[69] Liu et al reported that a total of 812 strains of *P. aeruginosa* were isolated from patients including LT recipients from January to September 2012 and 24 carbapenem-resistant *P. aeruginosa* strains were identified. The resistance mechanism of *P. aeruginosa* to carbapenems was mainly mediated by the VIM-2-type MBL in their hospital, followed by KPC-2. Among these 24 carbapenem-resistant *P. aeruginosa* strains, two strains were isolated from LT recipients; one harbored bla_{KPC-2} and carried the mobile genetic element gene insertion sequence common region 1, while the other harbored ISE_{cp1}.[70] Genotype analysis showed that in liver and other solid organ transplant recipients, the selected XDR *P. aeruginosa* strains belonged to a single clone ST-175.[41] Niga et al demonstrated that in a liver recipient, high fluoroquinolone resistance in *P. aeruginosa* resulted from cooperation between alteration in DNA gyrase A genes and overexpression of proteins involved in efflux systems.[71]

Treatment measures for *P. aeruginosa* bacteremia

With limited susceptibility to antimicrobial agents, frequent emergence of antibiotic-resistant mutants during therapy, and limited armamentarium of new antimicrobial agents in the pipeline, *P. aeruginosa* bacteremia has been an increasing problem in LT recipients in the modern era.[72]

P. aeruginosa accounts for the most common Gram-negative organism causing early posttransplant bacteremia in LT recipients. Early detection and treatment with adequate early targeted coverage for *P. aeruginosa* BSI are of paramount importance in the early posttransplantation period to obtain a better prognosis for LT patients.[24,73] Surveys such as that conducted by Korvick et al have shown that before transplant or biliary tract manipulation, prophylactic agents should have in vitro activity against *P. aeruginosa*.[25] SOT recipients with bacteremia due to XDR *P. aeruginosa* more

often received inadequate empirical antibiotic therapy and had high case-fatality rates compared to other etiologies.[41] Therefore, adequate empirical antibacterial coverage is essential. Detailed knowledge of the local epidemiology of *P. aeruginosa* bacteremia in LT recipients is also essential to help physicians prescribe adequate empirical antibiotics.

Management of infections caused by MDR *P. aeruginosa* is a major therapeutic challenge. Several previous studies of lung recipients have established that combination antibiotic therapies, including β-lactam, aminoglycoside, and/or fluoroquinolone, are preferred to monotherapy for infection due to MDR *P. aeruginosa*.[74–76] However, comparable resistance rates of *P. aeruginosa* to both aminoglycosides and fluoroquinolones were found and should be considered when devising an empiric combination regimen in SOT recipients.[24] Given the fact that nephrotoxicity risk due to aminoglycosides is a major concern among SOT recipients, combination therapy with β-lactam and fluoroquinolone antibiotics is a more reasonable option.[77] Although colistin in combination with rifampin showed promise, rifampin can hardly be used in SOT patients because of significant drug-drug interactions with immunosuppressive agents.[78] Meropenem with colistin showed synergy against *P. aeruginosa*; the combination of colistin and carbapenems is, therefore, a potential alternative.[79] However, further data are required to determine exactly how this combination works for MDR *P. aeruginosa*.

For XDR *P. aeruginosa*, few antibiotic options are currently available: examples are colistin or certain aminoglycosides, which are frequently associated with a higher risk of nephrotoxicity owing to decreased glomerular filtration rate, the need for renal replacement therapies, hypotension associated with medical and surgical procedures, or the use of concomitant nephrotoxic medications such as anticalcineurins.[27,73] Colistin alone or in combination with amikacin, β-lactam antibiotics in continuous or expanded perfusion, and high-dose carbapenem were recommended for treating XDR *P. aeruginosa* bacteremia.[41] According to a previous study, high doses of colistimethate sodium (6–9 MU daily) without a loading dose may also be effective.[41] Sun et al reported a case of a liver transplant recipient who developed intractable MDR *P. aeruginosa* bacteremia, which was finally controlled by a novel combination regimen of colistimethate, doripenem, and tobramycin.[80]

Usually, combination therapy is mandatory for treating MDR or XDR *P. aeruginosa* bacteremia, but little evidence of synergistic effects exists as the data available are based mostly on in vitro studies.[79–81] Several recent studies assessing nontransplant patients failed to find a benefit of combination therapy over monotherapy.[82–84] Of these studies, Bowers et al in an international multicenter retrospective cohort study failed to find through multivariate analysis that combination therapy was significantly different from monotherapy.[82]

Some promising new antimicrobial agents are now available for *P. aeruginosa* infection. For example, ceftolozane, a novel antipseudomonal cephalosporin, has demonstrated activity against carbapenem-resistant *P. aeruginosa* when used in combination with tazobactam.[85,86] In May 2016, ceftolozane/tazobactam was approved by the Pharmacy and Therapeutics Committee of Balearic Public Health System to treat infections caused by MDR *P. aeruginosa* in the absence of appropriate therapeutic alternatives according to the patient's characteristics.[87] Ceftazidime-avibactam (CZA) may also be a valuable option for serious infections due to resistant *P. aeruginosa,* as a 17-month retrospective descriptive study found that half of their patients with MDR or XDR *P. aeruginosa* infection who received CZA as initial or continuation therapy were clinical cured.[88] Furthermore, a new study published this year suggest a beneficial role of combination therapy with intravenous CZA and inhaled amikacin when treating pneumonia caused by *P. aeruginosa*, which indicate that inhaled antimicrobial therapy could be a good auxiliary method.[89] Pivmecillinam is a pro-drug of mecillinam which is a β-lactam with specific activity against non-lactose-fermenting Gram-negative bacilli including *P. aeruginosa*.[73]

P. aeruginosa bacteremic donor should not be used if not appropriately treated. In case of unknown donor with *P. aeruginosa* bacteremia, recipients should receive a longer (2–4 weeks) antibiotic course.[90]

Because the most frequent source was the abdomen/biliary duct or intravascular catheters in LT recipients with *P. aeruginosa* bacteremia, source control through central venous catheter removal, wound debridement, drainage of abscess, the biliary tree, and body fluid are crucial factors associated with better outcomes of LT recipients.[10,17,22,25,26]

Control and Prevention of *P. aeruginosa* bacteremia

As a significant nosocomial pathogen, *P. aeruginosa* colonization and infections occur as a result of multiple or prolonged hospital admission, excessive exposure to antibiotics, and breaches in infection control, with the capacity of the organism to adhere to various materials used frequently in clinical settings.[91,92] For *P. aeruginosa*, patient-to-patient transmission occurs mainly through the direct or indirect contact or droplet routes.[93] Nurse understaffing,

reduced isolation barriers, and absence of universal measures are pivotal in the spread of infection in the ICU or in wards. The measures to prevent *P. aeruginosa* bacteremia in LT recipients are the same as those for nonimmunosuppressed hospitalized patients. Generally, these measures include taking effective isolation measures, appropriate hand washing, restriction of the use of invasive devices, removing unnecessary catheter at the earliest possible time, and minimizing postoperative length of stay in intensive care unit. Strict adherence to the principles of intravascular catheter management recommended by CDC can sharply reduce the incidence of catheter-related bacteremia.[94,95] Surveillance using blood culture data can also facilitate choosing appropriate therapy and provide hospital antibiograms that can be used for empiric therapy of critically ill patients.[96]

Colonization with *P. aeruginosa* frequently precedes overt *P. aeruginosa* infection.[97] Rigorous infection control precautions aimed at preventing colonization with *P. aeruginosa* may be important steps against bacteremia caused by MDR or XDR *P. aeruginosa*. Specifically, recent guidelines recommend educational programs and environmental cleaning to limit the spread of MDR *P. aeruginosa*.[98]

No other factor might be more important in the development of antimicrobial resistance of *P. aeruginosa* than antimicrobial use in hospitals.[99] In light of recent events in antibiotic abuse, it is becoming extremely difficult to ignore the cornerstone role of antimicrobial stewardship programs, which have been shown to reduce inappropriate antimicrobial use and its consequences. The implementation of antibiotic management programs is an important strategy to reduce the dissemination of MDR or XDR *P. aeruginosa*.[100]

If serious *P. aeruginosa* infections occur, some measures can still be taken to prevent the occurrence of *P. aeruginosa* bacteremia, such as reduction of immunosuppression under close monitoring of graft function, and reduction or removal of steroids as soon as possible.

Hospital outbreaks of *P. aeruginosa* have been described in transplant units.[101–103] Contaminated water fittings, including drinking water, tap water, faucets, showers, water outlet, sinks, and waste water system, have been reported as the sources of many outbreaks of *P. aeruginosa* infection.[102–110] Soap, contaminated mouth swabs, or a contaminated graft can also act as a reservoir of *P. aeruginosa*.[101,107,108]

The outbreak of *P. aeruginosa* infection is generally considered to be the product of insufficient hand hygiene practices and contact precautions.[115] The measures of terminating the outbreak of *P. aeruginosa* infection consist of environmental investigation, intensification of hand hygiene

and isolation measures, replacing or installing contaminated reservoirs, water network hyperchlorination, excreta management, use of gloves, and the decontamination of medical utilities.[101,104,105,110–113]

For environmental investigation, the use of a molecular tool such as gene-based methods, for example pulsed-field gel electrophoresis or protein-based typing method involving surface-enhanced lasers desorption/ionization-time-of-flight MS, has been proposed to provide knowledge of the clonal origin of the outbreak and to find the accurate sources and transmission pathways, which are crucial for designing optimal infection control and prevention strategies and thus reduce the apparent scale of an outbreak.[101,114,115] Enhancing general infection control measures including hand hygiene and isolation measures led to a reduction in clinical cases in most studies but often did not completely terminate outbreaks.[116] Replacing reservoirs; point-of-use filtration; and decontaminating using bleach, hydrogen peroxide vapor, acetic acid, hot water, UV light, ozonation, and aldehyde-based disinfectants, were effective to end the outbreak.[103,117] Each method has advantages and disadvantages related to ease of implementation, cost, maintenance issues, and short- and long-term effectiveness. Point-of-use filtration and replacing reservoirs were thought to be a very effective method over the long term.[118,119] Acetic acid is highly effective against *P. aeruginosa* biofilms and may be used as a simple method to decontaminate sink drains and to prevent nosocomial transmission without evidence of indicated complete and persistent eradication of *P. aeruginosa* from drains.[104,105,120] Bundled approaches involving enhanced general infection control measures, disinfection, and replacing seem to be most successful.[105]

Future research

Despite the considerable mortality and morbidity, the quest for more intensive prophylactic measures and effective treatments for *P. aeruginosa* bacteremia is warranted for LT recipients. However, very little was found in the literature regarding the risk factors for the development of *P. aeruginosa* bacteremia and the predictors of poor outcome after LT transplantation, including mortality. Furthermore, most studies provided a general comment about preventive and therapeutic measures against *P. aeruginosa* bacteremia, which were not centered specifically for LT recipients. Additional research is therefore needed to better identify these predictors specifically for preventive and therapeutic strategies for LT population with *P. aeruginosa* bacteremia.

Because inadequate empirical therapy has been shown to be an independent risk factor for mortality in SOT recipients

with *P. aeruginosa* bacteremia, multicenter studies providing more robust and generalizable data regarding knowledge of local microbiology are urgently needed.

Given that colonization with *P. aeruginosa* is a precursor to overt *P. aeruginosa* infection, strict infection control precautions aimed at preventing colonization in high-risk LT recipients are required. However, data on the effectiveness of such strategies are lacking in LT population.[43] Future management should focus on the implementation of effective preventative strategies to limit the colonization with *P. aeruginosa*.

Studies examining treatment measures specific to LT recipients with bacteremia caused by *P. aeruginosa* are also deficient, with most studies being limited by small sample size. Although LT recipients with *P. aeruginosa* bacteremia may be benefit from combination therapy, it is also notable that not all combinations are created equal. In vitro combination synergy studies should be performed in future clinical practices to choose the most suitable agents for the combination regimen. Further studies regarding how we can better use our existing antibiotic armamentarium are required, and the exploration of new antibiotics needs to be fully supported.

Research studies have emerged that offer new strategies against *P. aeruginosa* infections, including new antibiotics, β-lactamase and efflux pump inhibitors, quorum quenching molecules, and nanoparticles with antibacterial activity. Methods to prevent *P. aeruginosa* infection through vaccines, therapeutic antibodies, and development of antimicrobial peptides are considered to support the human immunological system. Moreover, the development of alternative/supportive therapies such as phage therapy and photodynamic therapy, in which the mechanism of action is completely different from that of the current antibiotic therapy, is of great interest.[121] More funding and clinical trials are urgently needed to explore therapeutic options for MDR and XDR *P. aeruginosa*.

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