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Prevalence and risk factor for MDR-GNB infection in liver transplantation

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1. ABSTRACT

Liver transplantation (LT) has emerged as a viable therapy for various end-stage liver diseases. Multi-drug resistant Gram-negative bacilli (MDR-GNB) have emerged as predominant pathogens. The prevalence of MDR-GNB infection has been increasing in LT recipients, especially in early post-LT stages. MDR-GNB infection has become a main cause of death following LT. Since key elements of MDR-GNB infection after LT mainly include the pre-LT severity of underlying disease, technical problems, acute rejection, and so on, appropriate measures, such as improvement of LT technology and management, restriction of antibiotic use and immunosuppressive therapy advancement, should be commenced to prevent and control the occurrence of MDR-GNB infection. A better understanding of the prevalence of and risk factors for MDR-GNB infection complications is needed to improve quality of life and survival rate after LT.

2. INTRODUCTION

For more than three decades, liver transplantation (LT) has emerged as a promising therapy for various end-stage liver diseases. In 1982, the first Nordic LT surgery was carried out in Finland. In 2002, approximately 5300 LTs were performed in the United States, where more than 17,000 people are currently on waiting lists (1). In Europe, more than 5500 LTs are performed annually (2). Presently, LT is widely considered for chronic liver disease patients, who would likely develop life-threatening complications and have a prognosis of less than one-year of life, or can not sustain a normal life (3). Although the United Network for Organ Sharing (UNOS) has reported that the one-year survival rate exceeded 80% in most transplant centers (1), bacterial infections account for most complications, and the highest morbidity and mortality in LT (2). More than 50% of liver transplant recipients develop an infection during the first year following transplantation (4-6).

Multi-drug resistant (MDR) bacteria are resilient to three or more classes of antimicrobial agents. Over the past decade, Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *enterococci*, have attracted attention in the battle against MDR microorganisms (7). Paralleling the developments in Gram-positive bacteria, infections caused by multi-drug resistant Gram-negative bacilli (MDR-GNB) have become a growing problem (8). Three categories of MDR-GNB, namely, extended-spectrum cephalosporin-resistant *Escherichia coli* and *Klebsiella* spp., MDR *Pseudomonas aeruginosa*, and carbapenem-resistant *Acinetobacter* spp. have been specifically addressed by the Infectious Diseases Society of America (9). At present, MDR-GNB has emerged as predominant pathogens and the leading cause of death in LT patients (10, 11). Thus, the main purpose of this study was to review the prevalence and risk factors for MDR-GNB infection in LT recipients.

3. PREVALENCE OF MDR-GNB IN LT

The emergence and rapid spread of MDR-GNB has become a great concern around the world (12-14), and MDR-GNB infections have attracted the attention of LT researchers. In 2007, Kawecki *et al.* investigated bacterial isolates from bile samples obtained from 83 liver recipients during the first 30 days following LT. In the first week after orthotopic liver transplantation (OLT), five (14%) of 59 patients developed MDR-GNB infections, in which two patients were infected with *Escherichia coli*, one with *Citrobacter freundii* and two with *Acinetobacter baumannii*. Susceptibility of Gram-negative bacteria (n=39) showed the presence of four extended spectrum beta-lactamase (ESBL)-positive strains of the *Enterobacteriaceae* family as well as MDR Gram-negative non-fermenting rods, including five *Acinetobacter baumannii* strains and two *Stenotrophomonas maltophilia* strains (15).

In 2009, Shi *et al.* retrospectively analyzed data of 475 LT recipients and identified 152 (32.0.%) patients with Gram-negative bacillus bacteremia occurring during the first 6 months following LT. A total of 190 bacteremic episodes were caused by *Stenotrophomonas maltophilia, Enterobacteriaceae, Ochrobactrum anthropi, Pseudomonas*, and *Acinetobacter baumannii*, which were the most frequent Gram-negative isolates in this study, and MDR bacilli constituted 56.3.%. There were 70 patients with MDR-GNB (16). In 2010, Shi *et al.* found that pneumonia caused by MDR-GNB after LT included 58.9.% of 124 Gram-negative bacilli isolates, and Gram-negative bacilli accounted for 69.6.% of all pneumonia pathogens (17). Thus, MDR-GNB has become common in post-LT bacteremias, especially pulmonary infections. The increasing number of MDR-GNB isolates poses a significant challenge for clinical LT treatment and prognoses.

In 2010, Bert *et al.* investigated bloodstream infections (BSIs) in 704 LT recipients. One year after LT, 205 patients sustained BSIs and 259 episodes were documented, among which *Enterobacteriaceae members* (41%) and *Pseudomonas aeruginosa* (8.8.%) were the most frequent pathogens. Further, antibiotic-resistant *Enterobacteriaceae* were found in 116 patients, and antibiotic-resistant *Pseudomonas aeruginosa* was detected in 25 patients (18). Besides pulmonary infections, antibiotic-resistant GNB were also responsible for BSIs, especially over long periods following LT. Immunosuppressive therapy may play an important role in MDR-GNB infections in LT recipients over extended periods.

Previously, we carried out a retrospective cohort study that included 217 liver transplant patients who received cadaveric livers. Sixty-seven MDR-GNB isolates were identified from 66 infected liver transplant patients. The most common extended-spectrum β-lactamase-producing bacilli were *Stenotrophomonas maltophilia*, *Klebsiella pneumoniae*, *Enterobacter cloacae* and *Escherichia coli*. The incidence of *Stenotrophomonas maltophilia* infection was 100% (8/8), *Klebsiella pneumoniae* 61.5.% (8/13), *Enterobacter cloacae* 75% (3/4) and *Escherichia coli* 81.3.% (13/16). Furthermore, metallo-β-lactamase-expressing isolates were identified as S. *maltophilia* (100%, 8/8), *Pseudomonas aeruginosa* (83.3.%, 5/6), and *Acinetobacter baumannii* (95%, 19/20) (19).

Studies on MDR-GNB infection in LT recipients suggested that the prevalence of MDR-GNB infection has been increasing and becoming common in LT patients, especially in early stages following surgery. Monitoring MDR-GNB infection should be prioritized in LT patients as it is strongly associated with prognoses.

4. CLINICAL IMPACT OF MDR-GNB IN LT

The most serious clinical impact of MDR-GNB infection is the significantly increased mortality following LT. In the studies by Shi *et al*, MDR-GNB bacteremia-related mortality was significantly higher than that due to antibiotic-susceptible bacillus in the first 6 months after LT (16), while MDR Gram-negative bacterial pneumonia-related mortality was significantly higher than that because of antibiotic-susceptible bacilli (17). Our previous study also found that mortality in the MDR group was 37.8.%, among which 27% of deaths were caused by MDR-GNB, while the mortality in the non-MDR group was 24.1.% (19). This indicated that MDR-GNB accounted for a high percentage of MDR-related deaths.

In addition, patients with MDR Gram-negative bacterial pneumonia had significantly longer duration of ICU stays and more endotracheal intubations following LTs, compared with patients with antibiotic-susceptible bacilli pneumonia (17).

5. RISK FACTORS OF MDR-GNB INFECTION IN LT

LT is associated with a set of technical factors and medical conditions that predispose recipients to MDR-GNB infection. Factors predisposing to infection can be

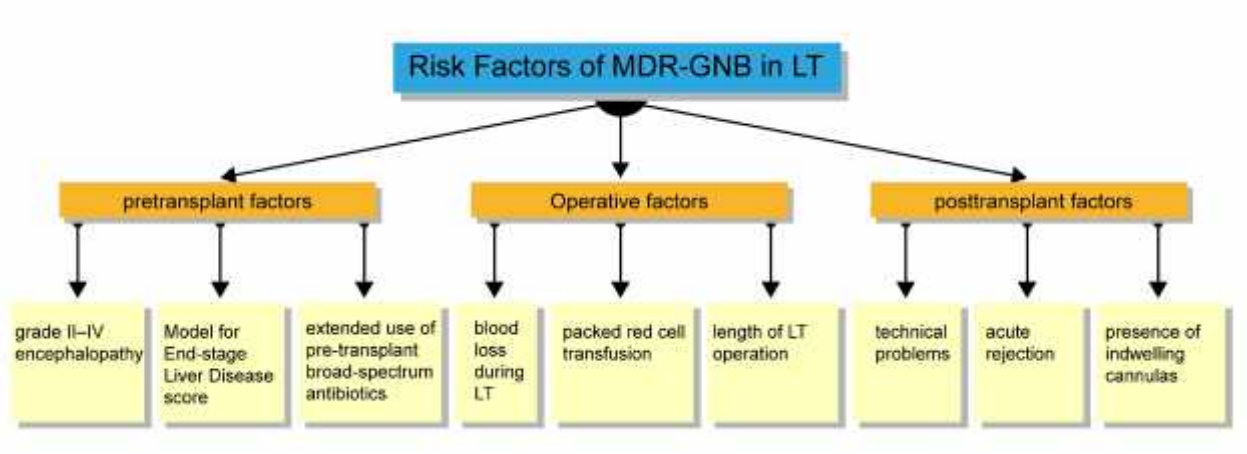

Figure 1. Risk Factors for MDR-GNB infection in LT. Factors predisposing to MDR-GNB infection after LT can be divided into those that existed prior to transplant surgery and those secondary to intraoperative and post-transplant activities. First, pre-transplant factors included grade II–IV encephalopathy, Model for End-stage Liver Disease score and extended use of pre-transplant broad-spectrum antibiotics. Operative factors were blood loss during LT, packed red cell transfusion and the length of LT operation. Furthermore, technical problems, acute rejection and the presence of indwelling cannulas were major post-transplant factors predisposing to infection complications.

divided into those that existed prior to transplantation and those secondary to intraoperative and post-transplant activities (Figure 1). Shi *et al.* (2010) analyzed pre-transplant factors and found that pneumonia caused by MDR-GNB was independently associated with grade II–IV encephalopathy and Model for End-stage Liver Disease score (17). Our previous study (2012) found that extended use of pre-transplant broad-spectrum antibiotics can increase the incidence of MDR-GNB infection (19). Other pre-transplant factors such as age and donor-related issues may also influence the prevalence of MDR-GNB infection, since these factors have been demonstrated in infection complications of LT (20). Age was not determined to be a risk factor for MDR-GNB infection following LT; however, this finding may have been due to a small sample size. To our knowledge, donor-related issues have not been fully investigated in MDR-GNB infection of LT recipients. Thus, further investigations need to be conducted with large sample sizes to discern donor-related MDR-GNB infection complications in LTs.

Operative factors may predispose recipients to MDR-GNB infection complications. Shi *et al.* (2010) showed that blood loss during LT, packed red cell transfusions and the length of operation were risk factors for MDR-GNB infection in LT recipients (17). These factors were likely a surrogate marker for the technical difficulty of the surgery. Intraoperative events, such as contamination of the operative field and the inability to close the abdomen after transplantation appear to increase the risk for postoperative infections.

Furthermore, technical problems, acute rejection and the presence of indwelling cannulas are major post-transplant factors predisposing to infection complications. Our previous study (19) and Shi *et al.* (16,17) found that endotracheal intubation duration, post-LT abdominal infection, post-LT reoperative episodes, or one or more episodes of acute rejection can increase the incidence of MDR-GNB infection following LT.

In summary, MDR-GNB infection was mainly dependent on pre-LT severity of underlying disease as reflected by encephalopathy grade, use of mechanical ventilation, such as prolonged duration of intubation and tracheostomy, and post-LT upper abdominal reoperations, technical problems and acute rejection.

6. PREVENTION AND CONTROL OF MDR-GNB IN LT

MDR-GNB infections can be transmitted from patient to patient, and the increasing prevalence of resistant organisms limits therapeutic options available for treatment of bacterial infections following LT. Appropriate measures should be taken to prevent and control the occurrence of MDR-GNB infection by addressing key elements such as pre-LT severity of underlying diseases, technical problems, acute rejection, and so on.

6.1. Improvement in LT technology and management

Since pre-transplant conditions such as age, donor relationship, lymphocyte mismatch, surgical history, and particularly underlying liver disease are usually uncontrollable, it is particularly important to improve technology. Post-LT reoperative episodes and post-LT abdominal infection are independent risk factors for MDR-GNB infection as previously reported (16, 17). Technological improvement, including reduced duration of endotracheal intubation and tracheostomy, post-transplant management and early catheter removal can reduce infection risk following LT surgery (17),

6.2. Restriction of Antibiotic Use

Since MDR bacteria are characterized by antibiotic resistance, it is inevitable to focus on antibiotic use. Previous studies have reported that decreased use of broad-spectrum cephalosporins was temporally associated with decreased antibiotic resistance among Gram-negative bacilli (22-25). MDR-GNB infection is a common early problem after LT, as we mentioned above. Our previous study showed that extended use of pre-transplant broad-spectrum antibiotics was an independent risk factor for MDR-GNB infection (19). Thus, restriction of antibiotic use could reduce the risk of MDR-GNB infection in LT recipients. In addition, restriction of antibiotic use can reduce medical cost. Himmelberg *et al.* (26) demonstrated that institution of restriction policies was associated with reduced antibiotic expenditures, but elimination of a restriction policy resulted in a 103% cost increase in the previously restricted antibiotics. However, the influence of antibiotic restriction on clinical outcomes, especially on the control of MDR-GNB infection after LT, needs to be further addressed.

6.3. Concerning immunosuppressive therapy

Although no report has yet fully described a direct relationship between immunosuppression and MDR-GNB infection after LT, immunosuppressive therapy is inevitable in LT. Acute organ rejection is an independent risk factor for MDR-GNB infection after LT, as we mentioned above, and immunosuppressive therapy is crucial to control rejection. As immunosuppressive therapy is an important risk factor of post-LT infection (27, 28), research should focus on controlling MDR-GNB infection through novel immunosuppressive agents (29). Data on drug/immune monitoring specific to LT are fairly limited (30); thus, immunosuppression remains a critical post-transplant risk-factor for infection in transplant recipients. Additional or higher doses of immunosuppressants increase the risk of invasive and potentially fatal infections. Therefore, efforts to improve immunosuppressive regimens could be evolved to achieve more specific rejection control, without immunity impairment, to decrease morbidity and mortality from infections in patients receiving immunosuppressive therapy.

Improvement of LT technology and management, restriction of antibiotic use, immunosuppressive therapy advancement, improvement in general and short-term post-transplant care in the ICU, and shorter hospital stays may be helpful in reducing MDR-GNB infections.

7. CONCLUSION

Post-LT MDR-GNB infection has become common and significantly influences the mortality of LT recipients. Underlying disease, technical problems and acute rejection were independent risk factors for MDR-GNB infection in LT recipients. Future prevention and control of MDR-GNB infection could be achieved through technological improvements, restriction of antibiotic use and immunosuppressive therapy advancement. A better understanding of the prevalence of and risk factors for MDR-GNB infection complications is anticipated to improve quality of life and survival rate following LT.

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Abbreviations: LT: Liver transplantation; MDR-GNB: Multi-drug resistant Gram-negative bacilli; UNOS: the United Network for Organ Sharing; OLT: orthotopic liver transplantation; ESBL: extended spectrum beta-lactamase; BSIs: bloodstream infections

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