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ORIGINAL ARTICLE

Retrospective Study

Ventilator associated pneumonia following liver transplantation: Etiology, risk factors and outcome

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Abstract

AIM: To determine the incidence, etiology, risk factors and outcome of ventilator-associated pneumonia (VAP) in patients undergoing orthotopic liver transplantation (OLT).

METHODS: This retrospective study considered 242 patients undergoing deceased donor OLT. VAP was diagnosed according to clinical and microbiological criteria.

RESULTS: VAP occurred in 18 (7.4%) patients, with an incidence of 10 per 1000 d of mechanical ventilation (MV). Isolated bacterial etiologic agents were mainly *Enterobacteriaceae* (79%). Univariate logistic analysis showed that model for end-stage liver disease (MELD) score, pre-operative hospitalization, treatment with terlipressin, Child-Turcotte-Pugh score, days of MV and red cell transfusion were risk factors for VAP. Multivariate

analysis, considering significant risk factors in univariate analysis, demonstrated that pneumonia was strongly associated with terlipressin usage, pre-operative hospitalization, days of MV and red cell transfusion. Mortality rate was 22% in the VAP group *vs* 4% in the group without VAP.

CONCLUSION: Our data suggest that VAP is an important cause of nosocomial infection during post-operative period in OLT patients. MELD score was a significant risk factor in univariate analysis. Multiple transfusions, treatment with terlipressin, preoperative hospitalization rather than called to the hospital while at home and days of MV constitute important risk factors for VAP development.

Key words: Liver transplantation; Ventilator associated pneumonia; Perioperative period; Infection

Core tip: Ventilator associated pneumonia (VAP) is a serious perioperative complication in liver transplant recipients, and its etiology and risk factors are still poorly understood. Therefore, we conducted this retrospective study in a big sample of patients to evaluate the incidence, risk factors, etiological agents and outcome of VAP considering 242 consecutive liver transplant recipients. VAP occurred with an incidence of 10 per 1000 d of mechanical ventilation (MV). Multivariate analysis demonstrated that VAP was strongly associated with terlipressin usage, pre-operative hospitalization, days of MV and red cell transfusion. Mortality rate was 22% in the VAP group *vs* 4% in the group without VAP.

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is the main hospital acquired infection in intensive care unit (ICU) and correlates with increased duration of mechanical ventilation (MV), length of ICU and hospital stay, and healthcare costs[1]. The reported rates vary significantly depending on the population, the specific ICU, the preventive strategies and the definition[2].

Liver recipients have high risk for prolonged post-operative MV due to multiple causes: Slow resolution of hepatic encephalopathy, muscle atrophy caused by pre-transplant poor nutrition and postoperative diaphragmatic dysfunction related to upper abdominal surgery.

The risk of pneumonia may be increased because of the presence of alveolar oedema and pleural effusion, as a consequence of low serum protein concentration, large amount of blood product transfusions, immuno-suppression and pre-existing risk factors like cardiac or renal failure.

The reperfusion damage has an important role in delaying extubation, which seems to be caused by the increased tumor necrosis factor (TNF) release from Kupffer cells. TNF leads to a histological damage in liver and lung tissue and could be a cause of alveolar oedema, haemorrhage and leukocyte invasion of the parenchyma.

Our study aimed to determine the incidence, etiology, risk factors and outcome of VAP in patients receiving orthotopic liver transplantation (OLT) from a deceased donor.

MATERIALS AND METHODS

Study design

After institutional review board approval, this retrospective study involved the patients who were admitted to our liver transplantation center from December 2006 to December 2010 and survived for at least 48 h. All patients had a diagnosis of end stage liver disease (ESLD) and underwent deceased donor OLT at the Transplantation Center of St. Orsola-Malpighi Policlinic in Bologna.

ESLD referred to the 4th stage or cirrhosis and was defined as the development of either a first major clinical complication of cirrhosis (variceal bleeding, ascites, jaundice, encephalopathy or spontaneous bacterial peritonitis) or hepatocellular carcinoma (HCC)[3]. Clinical evaluation of those patients used the model for end-stage liver disease (MELD) score reporting the value of the day of the transplantation.

The exclusion criteria were acute liver failure, simultaneous kidney/liver or liver/heart transplantation.

We analyzed the incidence, etiology, risk factors and impact of VAP on clinical outcome. All patients were evaluated, at the moment of the admission, to confirm the absence of pneumonia. Patients were followed until hospital discharge or death.

Definitions

The suspicion of VAP was based on clinical criteria (new or progressive radiological pulmonary infiltrates plus two or more of the following: Temperature > 38.3 ℃ or < 36 ℃, leukocyte count > 10 × 10^9/L or < 4 × 10^9/L and purulent respiratory secretions)[4] appearing 48-72 h post intubation and initiation of MV.

A microbiologic strategy was then followed for diagnosis: Microbiologic lower respiratory tract samples were obtained with bronchoalveolar lavage (BAL) or endotracheal aspirate.

VAP diagnosis was defined in case of positive results

Table 1 Etiologic agents of ventilator-associated pneumonia

Microorganism	Total (n = 18)
Klebsiella pneumonia	5/18 (28%)
Escherichia coli	5/18 (28%)
Klebsiella oxytoca	2/18 (11%)
Enterobacter spp.	1/18 (6%)
Citrobacter spp.	1/18 (6%)
Pseudomonas aeruginosa	8/18 (44%)
Staphylococcus aureus	4/18 (22%)
Corynebacterium striatum	4/18 (22%)
Xantomonas spp.	2/18 (11%)
Acinetobacter spp.	2/18 (11%)

The *Enterobacteriaceae* are written in bold. Note that in some patients more than one microorganism was found.

of quantitative culture of specimens from BAL or tracheoaspirate with protected brush (considering a threshold of 1×10^5 cfu/mL in a BAL fluid specimen, and 1×10^6 cfu/mL in an endotracheal aspirate specimen[5].

Postoperative management

Immunosuppressive induction was achieved by administrating 1 g of methylprednisolone at the time of reperfusion; the immunosuppressive regimen consisted of a combination of calcineurin-inhibitor and prednisone.

Postoperative interventions according to the European guidelines since 2002[6] for VAP prevention consisted of semi-recumbent patient positioning, sedation resolution and use of a weaning protocol, strict hand hygiene, non-invasive ventilation, oral care with chlorhexidine, no ventilatory circuit tube changes unless specifically indicated, appropriately educated and trained staff, cuff pressure control every 24 h, enteral feeding, use of heat moisture exchangers and unit-specific microbiological surveillance.

Data collection

Pre-operative, intra-operative and post-operative data were recorded.

Preoperative data included age, weight, height, body mass index (kg/m^2), body surface (m^2), etiology of cirrhosis, presence of HCC at pre-operative investigation, MELD score at the transplantation day, Child-Turcotte-Pugh (CTP) score, serum bilirubin (mg/dL), serum creatinine (mg/dL), international normalized ratio, glycated haemoglobin (%), serum urea (mg/dL), serum glucose (mg/dL), serum albumin (g/dL), transjugular intrahepatic portosystemic shunt presence, ongoing therapy with diuretics, and terlipressin (instead of its indications as the clinical and laboratoristic parameters are included in other scores) at the time of transplantation, patient preoperative hospital stay rather than called to the hospital while at home.

Intra-operative data included length of surgery, anhepatic phase duration, number of packed red blood cells (RBC), fresh frozen plasma and platelets transfusions (units), duration of cold ischemia (h), vasopressors usage in pre and post-reperfusion phase, donor age and gender. Quality of liver allograft was classified on the basis of Donor risk index (DRI)[7] as low risk (DRI < 1.8) or high risk graft (DRI > 1.8)[8].

Postoperative data considered: VAP incidence and etiology, duration of MV, time between intubation and VAP clinical manifestation, length of ICU stay and hospital mortality.

Statistical analysis

Statistical analyses were performed with SPSS 16.00. Continuous data are expressed as medians (25-75 interquartile range) while discrete data are represented by numerosity and relative frequencies. Patients were divided into two subgroups on the basis of presence or absence of VAP. Incidence of VAP is reported as episodes per 1000 d of MV. Differences between groups were assessed using χ^2 test or Fisher exact test for categorical variables and student's t-test or Mann-Whitney test for continuous variables. Variables which were significantly different between the two groups were individually analyzed with a univariate logistic regression model, considering VAP insurgence the dependent variable. Predictor variables found in univariate analysis were included into a multivariate logistic regression model using the Enter method, considering VAP insurgence the dependent variable. Results are expressed as hazard ratios, and P values with 95%CIs.

RESULTS

During the study period from 2006 to 2010, 284 patients underwent OLT at the Transplant Center of St. Orsola-Malpighi Hospital. Forty-two patients were not included in the analysis because they had: Combined liver/kidney or liver/heart transplantation (29 cases), transplantation for acute liver failure (6 cases) and other causes without concomitant cirrhosis (7 cases). The final analysis considered 242 patients with ESLD related to histologically proven liver cirrhosis.

Microbiologically confirmed VAP occurred in 18 (7.4%) patients, with an incidence of 10 episodes per 1000 d of MV, and none of these patients presented any criteria of pneumonia, from the in-hospital admission to the time of transplantation. The 18 patients received a diagnosis of VAP after positive BAL culture, and all of them were extubated within 48 h since pneumonia detection.

Isolated microbes belonged mainly to the group of *Enterobacteriaceae* (79%, 14 patients), including *Klebsiella pneumoniae*, *Escherichia coli*, *Klebsiella oxytoca*, *Enterobacter* spp. and *Citrobacter* spp. The remaining bacterial etiologic agents were represented by *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Staphylococcus aureus* (*S. aureus*) (Table 1).

We observed that 25% of VAP episodes involved more than one microorganism.

Demographic data of the study population and

Table 2 Preoperative, intraoperative and postoperative variables

Variable	Patients in study (*n* = 242)	VAP-yes (*n* = 18)	VAP-no (*n* = 224)	*P*-value
Age (yr)	56 (19-69)	55 (37-66)	56 (19-69)	0.624
Weight (kg)	72 (39-106)	73 (47-93)	72 (39-106)	0.515
Height (cm)	170 (148-193)	169 (155-182)	170 (148-193)	0.495
BMI (kg/m^2)	25 (16-38)	24 (19-34)	25 (16-38)	0.452
BSA (m^2)	1.9 (1.3-2.3)	1.9 (1.4-2.1)	1.9 (1.3-2.3)	0.505
HCV$^+$	128 (53%)	8 (44%)	120 (54%)	0.455
HBV$^+$	49 (20%)	3 (17%)	46 (21%)	0.486
Alcohol abuse	37 (15%)	3 (17%)	34 (15%)	0.540
HCC	118 (49%)	4 (22%)	114 (51%)	0.019
MELD score	21 (6-48)	23 (14-48)	20 (6-45)	0.032
CTP score	11 (5-15)	11 (9-14)	11 (5-15)	0.060
Bilirubin (mg/dL)	5.9 (0.4-71.1)	8.0 (2.1-71.1)	5.6 (0.4-68.6)	0.054
Creatinine (mg/dL)	1.0 (0.0-5.2)	1.1 (0.5-5.2)	1.0 (0.0-4.9)	0.708
INR	1.6 (0.8-7.6)	1.9 (1.3-3.8)	1.6 (0.8-7.6)	0.020
HbA1c (%)	10.8 (4.5-17)	9.9 (8.1-14.9)	10.9 (4.5-17)	0.085
Urea (mg/dL)	0.3 (0.1-3.1)	0.3 (0.1-2.6)	0.3 (0.1-3.1)	0.554
Serum glucose (mg/dL)	105 (60-358)	102 (63-284)	105 (60-358)	0.369
Albumin (g/dL)	3.5 (2.0-5.3)	3.3 (2.6-4.5)	3.5 (2.0-5.3)	0.189
TIPS presence	15 (6%)	1 (6%)	14 (6%)	0.691
Furosemide therapy	144 (60%)	11 (61%)	133 (59%)	0.885
Canrenoate therapy	112 (46%)	5 (28%)	107 (48%)	0.102
Terlipressin therapy	20 (8.3%)	7 (39%)	13 (5.8%)	< 0.001
Preoperative hospital stay	82 (34%)	11 (61%)	71 (32%)	0.018
Intraoperative and postoperative variables				
Length of surgery (min)	560 (512-650)	570 (490-630)	580 (460-660)	0.067
Anhepatic phase duration (min)	120 (88-138)	118 (85-138)	140 (116-145)	0.067
RBC transfusions (units)	8 (0-65)	16 (6-48)	7 (0-65)	< 0.05
FFP transfusions (units)	9 (0-75)	10 (0-31)	9 (0-35)	0.122
Platelet transfusions (units)	2 (0-4)	2 (1-3)	2 (1-3)	0.587
CIT (h)	7 (6-9)	7 (7-9)	8 (7-9)	0.354
Pre-reperfusion VP infusion	68 (28%)	8 (22%)	60 (26%)	0.530
Post-reperfusion VP bolus	110 (45%)	8 (44%)	102 (45%)	0.520
Post-reperfusion VP infusion	118 (48%)	10 (55%)	108 (48%)	0.510
Duration of ICU stay (d)	5 (3-10)	16 (20-59)	5 (3-8)	< 0.05
Hospital mortality	14 (6%)	4 (22%)	10 (4%)	< 0.05
Median duration of MV (d)	0.42 (0.208-0.417)	1.125 (0.375-11.75)	0.38 (0.208-0.864)	< 0.05
Time between intubation and VAP insurgence (h)	-	72 (48-336)	-	-

Statistical analyses were performed using parametric tests and nonparametric tests (Wilcoxon's rank sum) when normality or variance assumptions were not met. Proportions were compared by Fisher's test. Statistical significance was defined as $P < 0.05$. HCV: Hepatitis C virus; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; BMI: Body mass index; BSA: Body surface; MELD: Model for end-stage liver disease; CTP: Child-Turcotte-Pugh; INR: International normalized ratio; HbA1c: Glycated hemoglobin; TIPS: Trans-jugular intrahepatic porto-sistemicity shunt; RBC: Packed red blood cells; FFP: Fresh frozen plasma; CIT: Cold ischemia time; VP: Vasopressor; ICU: Intensive care unit; MV: Mechanical ventilation; VAP: Ventilator-associated pneumonia.

Table 3 Donor variables *n* (%)

Variable	Patients in study (*n* = 242)	VAP-yes (*n* = 18)	VAP-no (*n* = 224)	*P*-value
Donor age (yr)	56 (14-89)	58 (20-86)	56 (19-80)	0.624
Donor gender (male)	182 (75)	14 (77)	168 (69)	0.624
Donor risk index > 1.8	52 (21)	4 (22)	48 (21)	0.345

VAP: Ventilator-associated pneumonia.

general preoperative, intraoperative and postoperative characteristics are reported in Table 2 and the donor variables in Table 3.

Significant differences in MELD score were observed between the two groups; VAP patients had a mean MELD score of 23 *vs* 20 of control patients. Treatment with terlipressin was associated with a higher risk of pneumonia (39% of VAP episodes receiving terlipressin *vs* 5.8% in the control group).

Intraoperative data (Table 2) showed statistically significant differences between the two groups in red cell transfusion (red cell transfusion refers to the large amount of red cell transfusion): A median of 16 units per patient in the VAP group *vs* 7 in controls. Postoperative data (Table 2) showed that ICU stay of VAP patients was significantly longer (16 d *vs* 5 d) and was associated with a higher hospital mortality (22% of VAP patients died *vs* 4% of controls). VAP was

Table 4 Variables associated with ventilator-associated pneumonia in multivariate analysis

Variable	OR	95%CI	*P*-value
MELD score	0.98	0.8-10	0.670
CTP score	0.79	0.5-1.1	0.27
RBC transfusions (units)	1.1	1.04-1.1	< 0.001
MV (d)	1.10	1.03-1.15	< 0.001
Terlipressin therapy	31.49	4.7-49.2	< 0.001
Preoperative hospital stay (d)	1.8	1-1.9	< 0.05

Statistical significance was defined as $P < 0.05$. MELD: Model for end-stage liver disease; CTP: Child-Turcotte-Pugh; RBC: Packed red blood cells; MV: Mechanical ventilation.

documented after a median of 72 h post intubation. Median intubation duration among all studied patients was 0.42 d, patients without VAP required a median of 0.38 (0.208-0.864) d of MV, while VAP patients required a median MV duration of 1.13 (0.375-11.75) d. This interval ran from the first intubation to the extubation or need for reintubation. The time from the second intubation to the extubation/exitus was not considered in the study.

Univariate logistic regression analysis found that MELD score, treatment with terlipressin, CTP score, days of MV, preoperative hospitalization and red cell transfusion were significantly associated with VAP (data not shown).

The multivariate logistic regression model constructed considering the variables which resulted significantly associated with VAP in univariate analysis resulted in a significantly increased risk of VAP for terlipressin use, red cell transfusion, duration of MV and preoperative hospitalization (Table 4).

DISCUSSION

It has been reported that the rate of VAP is usually 1 to 3% per day of intubation and MV and the rates of pneumonia are increased 6- to 21-fold for intubated patients and show a further rise with the duration of MV. It has been estimated that the overall rates are most commonly 10 to 15 cases per 1000 ventilator days for ICU patients, depending on the population studied. The National Nosocomial Infections Surveillance System reports a median occurrence of VAP of 4.6 -5.1 for 1000 ventilator days either in medical or surgical ICUs. Also, rates are generally higher in surgical ICU patients than in medical ICU patients[9,10].

Data about the incidence of VAP in OLT patients are poor and highly variable, the incidence rates range from 5% to 48% and the rates of the VAP-related mortality from 36% to 53%[11]. A recent monocentric Italian study was not able to detect increased frequency of VAP in a small population of OLT patients compared to a control group of non-OLT patients admitted to the same surgical ICU[12]. Another study[13] on the infections after OLT reported the occurrence of VAP in 17.5% of their samples.

Our results show a higher incidence of VAP than previous results from similar patients. We have to underline that our patients presented a higher MELD score (mean values 20-23) than those considered in other studies (mean values 14-15), which could reflect worse general preoperative conditions predisposing to infections, although the mortality rate was comparable (22%).

As stated before, MELD score has already been associated with postoperative complications, and this association is concordant with the correlation between MELD score and the seriousness of the post-operative complications[9].

The early identification of clinical predictors of severe prognosis, *i.e.*, the MELD score, could help to identify patients at major risk and to take appropriate measures, earlier intensive treatment and several strategies including the use of non-invasive ventilation when possible to reduce the rate of VAP[14,15].

The quality of the liver graft, which has an important role in determining prognosis of transplanted organs, does not seem to play a role in early infectious complications like VAP. In fact, high risk grafts were equally distributed in the two groups, and this result has been corroborated in the literature[11].

The microorganisms associated with VAP vary widely depending on the characteristics of the patients, the different ICUs and the length of in-hospital stay. Common pathogens include *Enterobacteriaceae*, *P. aeruginosa* and *S. aureus*[16]. In our series, the microorganisms associated with VAP, after liver transplantation, are not different from those in non-OLT patients in ICU[17]. The *Enterobacteriaceae* predominated over *P. aeruginosa* and *S. aureus.*

Our study confirmed previous finding that multiple blood transfusions were associated with VAP insurgence. This is because longer duration of significant bleeding during OLT may lead to more alveolo-capillary membrane damage and prolonged postoperative intubation.

Our study shows that patients receiving terlipressin for hepatorenal syndrome had an odds ratio of 31.49 times higher for VAP, in the multivariate analysis. Further studies may investigate if hepatorenal syndrome (HRS) or its treatment with terlipressin is the effective risk factor for VAP. That is a limitation of the current study. Terlipressin therapy for HRS requires hospital admission and this could influence the outcome, but it has a notorious detrimental effect on splancnic microcirculation. We suppose that the vasoconstricting action could damage intestinal barrier and foster bacterial migration through haematic and lymphatic circulation to pulmonary parenchyma, and this mechanism could also explain the high incidence of *Enterobacteriaceae* among etiologic agents in our case series. Westphal *et al*[17] showed in an animal study that terlipressin treatment induced important alterations in pulmonary circulation, decreased cardiac index, and

diminished systemic oxygen delivery and consumption.

Despite the mentioned results, this study presents some limitations. We reported a low number of pneumonia cases due to its globally low incidence and the limited sample size, since our data came from a single center.

In conclusion, this study was designed to investigate the incidence, the risk factors and the outcome of VAP after OLT. Incidence has been estimated to be 10 per 1000 d of MV. Our study confirms some of the risk factors for VAP found in other studies: RBC transfusion, duration of MV and preoperative hospitalization rather than direct admission from home. MELD score is higher in the VAP group and it represents a significant risk factor in univariate analysis, reflects worse general conditions and prospects higher postoperative complications. The adoption of MELD score could rationalize VAP prevention practice in patients at major risk, earlier intensive treatment to increase the ventilator-free days and several stategies including the use of non-invasive ventilation. Among the risk factors, we found the therapy with terlipressin, used for the treatment of hepatorenal syndrome. This drug exhibited, in animal models, some effects on pulmonary circulation and has a detrimental effect on splancnic blood flow that could contribute to bacterial migration. Also hepatorenal syndrome could have contributed to this effect. Further studies are needed to clarify this correlation.

COMMENTS

Background

Patients undergoing orthotopic liver transplant (OLT) represent a special subpopulation at risk for nosocomial infections, in particular ventilator-associated pneumonia (VAP) is the main hospital acquired infection in intensive care unit and it is a serious perioperative complication in liver transplant recipients.

Research frontiers

VAP's etiology and risk factors are still poorly understood.

Innovations and breakthroughs

The authors conducted this retrospective study in a big (considering the peculiar population) sample of patients, 242 consecutive liver transplant recipients. Of course, none of the patients who developed VAP presented signs or symptoms of infection before liver transplantation. Model for end-stage liver disease score was a significant risk factor in univariate analysis, and probably it reflects worse general conditions. In multivariate analysis the authors found a statistically significant association with terlipressin therapy. Patients who were taking terlipressin received the last dose until the OLT to treat the hepatorenal syndrome that could be a risk factor by itself. The authors did not refer to clinical and laboratory parameters as they are included in other scores. Some patients received other vasopressors during the OLT, but there were no statistically significant differences between the two groups. As the authors remarked in the discussion, further studies are needed to clarify this finding.

Applications

The application of the authors' results aims to individualize patients at major risk, to apply earlier intensive treatment and several strategies to prevent VAP.

Peer-review

The authors performed a study on a very important infectious complication in post-operative OLT setting. The paper is well written and the aim is clear.

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