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Analysis of Nosocomial Infections in Post–Cardiac Surgery Extracorporeal Membrane Oxygenation Support Therapy

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ABSTRACT

Objectives: This study aims to analyze the nosocomial infection factors in post–cardiac surgery extracorporeal membrane oxygenation (ECMO) supportive treatment (pCS-ECMO).

Methods: The clinical data of the pCS-ECMO patients who obtained nosocomial infections (NI) were collected and analyzed retrospectively. Among the 74 pCS-ECMO patients, 30 occurred with NI, accounting for 40.5%; a total of 38 pathogens were isolated, including 22 strains of Gram-negative bacteria (57.9%), 15 strains of Gram-positive bacteria (39.5%), and 1 fungus (2.6%).

Results: Multidrug-resistant strains were highly concentrated, among which *Acinetobacter baumannii* and various coagulase-negative staphylococci were the main types; NI was related to mechanical ventilation time, intensive care unit (ICU) residence, ECMO duration, and total hospital stay, and the differences were statistically significant ($P < .05$). The binary logistic regression analysis indicated that ECMO duration was a potential independent risk factor (OR = 0.992, $P = .045$, 95.0% CI = 0.984-1.000).

Conclusions: There existed significant correlations between the secondary infections of pCS-ECMO and mechanical ventilation time, ICU residence, ECMO duration, and total hospital stay; therefore, hospitals should prepare appropriate preventive measures to reduce the incidence of ECMO secondary infections.

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass device that supports patients with respiratory and/or cardiac failure [Sherwin 2016], which is also known as artificial heart and lung. About 1.0% of the patients who had cardiac surgery needs ECMO to support the life circulation [Smith 2001; Allen 2011; Mirabel 2011]. However, the data from extracorporeal life support organization (ELSO) showed that the success rate of post–cardiac surgery ECMO supportive treatment (pCS-ECMO) was significantly low for a long period [Annich 2012; Paden 2013]. In fact, complication rates with ECMO are high. This is true during both cannulation and ongoing management [Zangrillo 2013]. Complications include hemorrhage, stroke, thrombosis, and infection from the indwelling lines/tubes, and over half of the ECMO patients had at least one complication occurring [Combes 2008]. ECMO secondary infections are such common complications, which affected about 31% patients [Cheng 2014], that not only increase patients' suffering, with some studies reporting neurologic injury and long-term neurocognitive abnormalities in over 50% of cases [Mateen 2011], and affect their prognosis, but also lead to death [Liu 2016]. In recent years, with the continuous promotion of ECMO clinical application, much literature has reported that the risk factors of the infections occurred in the patients receiving ECMO; for example, Yan, Care Unit of the Affiliated Beijing Anzhen Hospital, Capital Medical University, analyzed the situations of nosocomial infections (NI) in the pCS-ECMO patients [Kumar 2012]; different scholars reported different infection risk factors of ECMO in newborns, children, and adults [Bizzarro 2011; Müller 2011; Bowman 2013; Cheng 2013; Harder 2013; Pieri 2013], but none of them ever analyzed the risk factors from the aspect of drug-resistance phenotype. As time changes and there are medical developments, the risk factors and pathogens of NI also gradually change; because there was no study in this field in the Zhongshan People's Hospital, the authors retrospectively analyzed the NI situations of the pCS-ECMO patients in Zhongshan People's Hospital from June 2010 to August 2015 with the aim to provide basis and reference for the clinical prevention of ECMO secondary infections, to reduce the infection incidence, and to improve the post-ECMO survival rate.

MATERIALS AND METHODS

Setting and Study Population

The clinical data and test results of 74 pCS-ECMO patients in Zhongshan People's Hospital were obtained from December 2012 to August 2015, including 39 males (53%) and 35 females (47%). The related conditions are shown in Table 1. This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Sun Yat-sen University. Written informed consent was obtained from all participants.

The clinical data and test results of these 74 pCS-ECMO patients were retrospectively analyzed. The clinical data included sex, age, ECMO model, ECMO duration, total

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Table 1. Postoperative Data of the NI Group and the Non-NI Group

Item	NI Group (n = 30)	Non-NI Group (n = 44)	*P*
Sex			
M (cases)	15	24	.64
F (cases)	15	20	
Age (years)	51.3 ± 13.1	46.7 ± 18.3	.983
ECMO mode			
V/V (cases)	3	5	.827
V/A (cases)	27	38	
ECMO duration (hours)	142.2 ± 140.9	73.8 ± 68.4	.045
Total hospital stay (days)	78.0 ± 244.4	23.0 ± 20.4	.269
NYHA heart function grade III or above (cases)	20	24	.297
Mechanical ventilation time (hours)	325.4 ± 375.0	104.2 ± 156.5	.400
ICU residence (hours)	298.0 ± 268.4	172.8 ± 210.7	.532

hospital stay, duration of ventilator-assisted time, and duration of ICU residence. The test results included distribution of pathogenic bacteria and drug susceptibility. The diagnosis of NI referred to the "diagnostic criteria of NI (Trial)" issued by the Ministry of Health in 2001, and the NI cases that occurred from the first 24 hours after ECMO was started to the first 48 hours after it was completed and defined as ECMO secondary infections [Hsu 2009]; according to the post-ECMO NI conditions, the patients were divided into the NI group and the non-NI group for the comparison and analysis. The distribution of pathogenic bacteria was analyzed, and the pathogenic bacteria of multidrug-resistant bacteria were analyzed.

Statistical Analysis

IBM SPSS Statistics 22 (Armonk, NY, USA) was used to sort the input data for the related analysis and processing. The intergroup comparison of the measurement data used the 2-independent-samples nonparametric test (Mann-Whitney *U*), and the counting data were compared by using the chi-square test or the Fisher exact test; the factors showing statistically significant difference in the univariate analysis of ECMO secondary infections were then analyzed by using the binary logistic regression analysis to verify the independent risk factor(s) of ECMO secondary infections. The binary logistic regression analysis offers several methods for selection of the best predictors to include in the model. When performing regression, the specify dependent variable in title, provide full range of parameters and provide reference group for each of independent variable were included. In the present study, a forward stepwise analysis has been done. This method starts with a model that does not include any predictor variables. At each step, the predictor with the largest score statistic whose significance value is less than the specified value (0.05, for 95% confidence interval [CI]) is added to the model. The variables left out of the analysis at the last step all have significance values larger than 0.05, so no more are added. $P < .05$ is considered as statistically significant.

Table 2. Distribution and Composition Ratio of Main Pathogens

Bacterial Name	Strain	Composition Ratio (%)
Gram-negative bacteria	22	57.9
Acinetobacter baumannii	6	15.8
Pseudomonas aeruginosa	4	10.5
Stenotrophomonas maltophilia	4	10.5
Klebsiella pneumoniae	3	7.9
Others	5	13.2
Gram-positive bacteria	15	39.5
Staphylococcus aureus	3	7.9
Unclassified coagulase-negative staphylococci	3	7.9
Staphylococcus epidermidis	2	5.3
Staphylococcus haemolyticus	2	5.3
Enterococcus faecalis	2	5.3
Staphylococcus warneri	1	2.6
Others	2	5.3
Fungus	1	2.6
Monilia krusei	1	2.6
Sum	38	100

RESULTS

NI Situations

Among the 74 patients, 30 occurred ECMO secondary infections, accounting for 40.5%; the respiratory tract infection was the main infection mode (13 cases, 43.3%), followed by hematogenous infection (11 cases, 36.7%), surgical site infection (5 cases, 16.7%), and urinary tract infection (1 cases, 3.3%).

Risk Factors of NI

It can be seen from Table 1 that the ECMO duration ($P = .001$), mechanical ventilation time ($P < .400$), ICU residence ($P = .004$), and total hospital stay ($P = .011$) showed statistically significant difference in the incidence of ECMO secondary infections; the binary logistic regression analysis generates OR = 0.992 ($P = .045$, 95.0% CI = 0.984-1.000) for ECMO duration, an independent risk factor. The data in Table 1 reveals that the ECMO duration, mechanical ventilation time, and ICU residence in the NI group were higher than the non-NI group.

Pathogens

A total of 38 strains of pathogens were isolated, among which the Gram-negative bacteria were dominant (22 strains,

Table 3. Drug Resistance of the 5 Strains of 5 *Acinetobacter baumannii*

Antibiotics	Drug-Resistant Strains	Drug-Resistance Rate (%)	Sensitive Strains	Sensitivity Rate (%)
Ampicillin	5	100	0	0
Ampicillin/sulbactam	5	100	0	0
Aztreonam	4	80	0	0
Ciprofloxacin	4	80	0	0
Cefotetan	5	100	0	0
Ceftriaxone	4	80	1	20
Cefazolin	5	100	0	0
Cefepime	4	80	1	20
Nitrofurantoin	5	100	0	0
Gentamicin	4	80	1	20
Imipenem	4	80	1	20
Levofloxacin	2	40	1	20
Cotrimoxazole	3	60	2	40
Ceftazidime	3	60	2	40
Tobramycin	3	60	2	40
Piperacillin/tazobactam	3	60	1	20

57.9%), mainly including *Acinetobacter baumannii* (6 strains), *Pseudomonas aeruginosa* (4 strains), and *Stenotrophomonas maltophilia* (4 strains), followed by Gram-positive bacteria (15 strains, 39.5%), mainly including *Staphylococcus aureus* (4 strains) and 1 fungus (2.6%). The distribution and the composition ratio of the main pathogens are shown in Table 2; among the 6 strains of *Acinetobacter baumannii*, the susceptibility results of 1 strain was incomplete, and 4 strains showed multidrug resistance towards most carbapenems (including imipenem). The detailed drug resistance information are shown in Table 3; the 4 strains of *Pseudomonas aeruginosa* showed no multidrug resistance; 8 strains of various coagulase-negative staphylococci were also isolated, among which the 3 strains of unclassified coagulase-negative staphylococci were not tested for their drug susceptibility, but 4 strains exhibited methicillin resistance.

DISCUSSION

As a bridge of adjuvant cardiopulmonary treatment, ECMO could replace the lung's gas exchange task and the heart's blood pump function, and it could provide sustained and effective respiratory and circulatory support, thus providing a chance for the rehabilitation of cardiopulmonary functions. However, due to preoperative malnutrition and lung congestion accompanying in some patients, as well as longer operative time and various invasive procedures, postoperative complicated infections are also common. According to literature, the overall prevalence of documented infections was 33%. Bloodstream infection represented the most frequently documented (53%), followed by pneumonia (40%). Coagulase-negative staphylococci and *P. aeruginosa* prevailed as isolated pathogens. Overall survival was 46% among those developing infections during ECMO [Castagnola 2018]. Among which NI, as one complication of ECMO, would significantly increase postoperative mortality [Haneke 2016].

The results showed that the ECMO duration, mechanical ventilation time, ICU residence, and total hospital stay were 4 risk factors of NI, thus providing the basis for preventing the ECMO secondary infections in our hospital. The study results were consistent with our expectations.

This study showed that the NI rate of pCS-ECMO in Zhongshan People's Hospital was 40.5%, which mainly was respiratory tract infection (43.3%), followed by hematogenous infection (this might be related to endotracheal intubation or incision, ventilator usage, or low immunity). It was reported that the NI cases in Chinese ICU were mainly lung infection, up to 8.0%-54.0%, consistent with the results of this study; and lung infection is the characteristic of Chinese ECMO secondary infections (mainly respiratory tract infections). A certain foreign study reported that the main NI mode of ECMO was hematogenous infection, indicating that the ECMO–secondary infection sites in China and abroad were different.

In this study, the ECMO duration, mechanical ventilation time, and ICU residence of the NI group were significantly higher than the non-NI group; namely the post-ECMO secondary infections were related to the ECMO duration, mechanical ventilation time, and ICU residence. During the process of ECMO, a large number of invasive procedures were necessary, such as inserting a variety of intravascular ECMO catheters, central venous catheters, arterial catheters, endotracheal catheters, urinary catheter, and abdominal drainage catheters, etc. This would undoubtedly result in the patients to face the high risk of NI. Moreover, the patients receiving ECMO are more in high-risk status; their low immunity, therapeutic blood products (such as platelets), and application of glucocorticoids would inhibit the patients' own immune functions and increase the risk of NI. Hsin-Yun Sun, MD, confirmed that ECMO time was an independent risk factor of ECMO secondary infections [Sun 2010]. Long-term mechanical ventilation weakens the normal mucosal barrier and diminishes the movement capability of respiratory cilia, so the defensive functions would be weakened, thus providing favorable conditions for the breeding and reproduction of oral bacteria. Meanwhile, with the extension of the ventilator tubing time, the number of pathogens would be significantly increased, and the incidence of NI, especially respiratory infection, would be increased significantly. Yan pointed out the significant difference in the mechanical ventilation time between the NI group and the non-NI group [Hsu 2009]. It was also reported that the ICU residence was a major risk factor of all NI cases, and the risk of NI in the patients staying in ICU for 3 to 4 days was 3 times higher than those staying for 1 to 2 days, and the risk of NI in the patients staying in ICU for more than 3 weeks was as high as 33 times than other NI cases [Aubron 2013b; Lunz 2014]. The evidence strongly supported the results obtained in this study, proving the consistence among these studies.

A certain study had reported that clinical detection rate of *Acinetobacter baumannii* had risen in recent years [Fu 2012], and this study detected 6 strains of *Acinetobacter baumannii* and 4 strains of *Pseudomonas aeruginosa*, consistent with the literature. The reason for the highly concentrated multidrug resistant bacteria found in this study might be that preventive antibiotics administration was not the routine use in ECMO and that the indications of preventive antibiotics usage in ECMO were cardiac surgery and sepsis [Aubron 2013a]. Numerous studies had shown that preventive antibiotics application could significantly decrease the NI rate; therefore, antibiotics are now appropriately applied in the perioperative period of such surgeries because ECMO will have greater risk of infections; but using antibiotics in this way also leads to another problem: pathogens would produce self-mutation under the pressure of antibiotics, so that the drug-resistant strains would be highly concentrated. Of course, it is also related to the irrational use of antibiotics in China currently.

NI is a common complication during ECMO, and this study showed that reducing the ECMO duration, mechanical ventilation time, and ICU residence, as well as stopping the respiratory and circulatory assistance as early as possible and reducing the ICU residence, could reduce the occurrence risk of NI. On the other hand, based on strict aseptic operations in all the aspects of ECMO, antibiotics could be used empirically, and then promptly and reasonably adjusted according to bacterial culture and sensitivity test to prevent the irrational use of antibiotics and the occurrence of multidrug resistance, and to reduce the incidence of infectious complications. The limitation of this study was that the number of the patients was not sufficient.

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