Infections occurring during extracorporeal membrane oxygenation use in adult patients

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Objective: The application of extracorporeal membrane oxygenation in adults has been increasing, but infections occurring during extracorporeal membrane oxygenation use are rarely described.

Methods: We retrospectively analyzed the prospectively collected data on nosocomial infection surveillance of 334 patients aged 16 years or more undergoing their first extracorporeal membrane oxygenation for more than 48 hours at a university hospital from 1996 to 2007 for respiratory (20.4%) and cardiac (79.6%) support.

Results: During a total of 2559 extracorporeal membrane oxygenation days, 55 episodes of infections occurred in 45 patients (13.5%), including 38 bloodstream (14.85 per 1000 extracorporeal membrane oxygenation days), 6 surgical site, 4 respiratory tract, 3 urinary tract, and 4 other infections. *Stenotrophomonas maltophilia* (16.7%) and *Candida* species (14.6%) were the predominant blood isolates. In stepwise logistic regression analysis, longer duration of extracorporeal membrane oxygenation use (odds ratio 1.003; 95% confidence interval, 1.001–1.005; $P = .004$), mechanical complications (odds ratio, 4.849; 95% confidence interval, 1.569–14.991; $P = .006$), autoimmune disease (odds ratio, 6.997; 95% confidence interval, 1.541–31.766; $P = .012$), and venovenous mode (odds ratio, 4.473; 95% confidence interval, 1.001–19.977; $P = .050$) were independently associated with a higher risk for infections during extracorporeal membrane oxygenation use. Overall in-hospital mortality was 68.3%, and its independent risk factors included older age (odds ratio, 1.037; 95% confidence interval, 1.021–1.054; $P < .001$), neurologic complications (odds ratio, 51.153; 95% confidence interval, 6.773–386.329; $P < .001$), and vascular complications (odds ratio, 1.922; 95% confidence interval, 1.112–3.320; $P < .001$), but not infections during extracorporeal membrane oxygenation use.

Conclusions: Bloodstream infection was the most common infection during extracorporeal membrane oxygenation use. Duration of extracorporeal membrane oxygenation, mechanical complications, autoimmune disease, and venovenous mode seemed to be independently associated with infections. (J Thorac Cardiovasc Surg 2010;140:1125-32)

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Extracorporeal membrane oxygenation (ECMO) was first reported for adult respiratory distress syndrome in 1972.[1] Subsequently, ECMO was gradually accepted as a treatment modality for neonatal, pediatric, and adult patients with respiratory or cardiac failure who fail to respond to maximal medical therapy. Currently, more than 24,000 neonates, 7000 children, and 2000 adults have been treated with ECMO.[2] Although its use is relatively controversial in adults, ECMO has been gradually used as cardiac support in various clinical settings, such as postcardiotomy cardiogenic shock after cardiac surgery,[3] bridge to heart transplantation,[4] fulminant myocarditis,[5] and assistance for cardiopulmonary resuscitation (CPR).[6]

Infections occurring during ECMO use increase mortality in neonatal or pediatric populations, but whether they have a similar impact on adults has rarely been reported.[7-10] Thus, we assessed the occurrence, type, causative pathogens, and risk factors of infections during ECMO use as respiratory or cardiac support in adults at an extracorporeal life-support referral center. Risk factors associated with in-hospital mortality were also analyzed.

MATERIALS AND METHODS

Setting and Study Population

National Taiwan University Hospital, a university hospital with a 2200-bed capacity, provides both primary and tertiary referral care. It is also an extracorporeal life-support referral center.[4,11] The first ECMO at this hospital was in August of 1994.[3] In the following years, ECMO was performed approximately 30 to 60 times per year before 2003 and approximately 100 or more times per year since 2003. A computerized case

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Abbreviations and Acronyms

APACHE II = Acute Physiology and Chronic Health Evaluation II
CI = confidence interval
CPR = cardiopulmonary resuscitation
ECMO = extracorporeal membrane oxygenation
IABP = intra-aortic balloon pump
OR = odds ratio
VV = venovenous

record form was used to prospectively collect the demographic and clinical data of patients undergoing ECMO, including age, gender, underlying diseases, baseline heart function by New York Heart Association classification, dates of admission, infections before ECMO initiation, and conditions during ECMO use (Acute Physiology and Chronic Health Evaluation II [APACHE II] at ECMO initiation and dates, locations, indications, modes, complications, and outcomes of ECMO use). We also recorded the requirement of an intra-aortic balloon pump (IABP) or CPR during hospitalization and dates of discharge or in-hospital death.

Patients were eligible for the present study if they (1) were aged 16 years or more; (2) underwent ECMO between January 1, 1996, and December 31, 2007; and (3) underwent ECMO for respiratory or circulatory support. Patients were excluded if (1) ECMO was initiated at other hospitals, (2) ECMO use was less than 48 hours because of inadequate ECMO exposure for evaluation of infections during ECMO use, or (3) this was not their first-time ECMO use. After ECMO initiation, patients were followed until discharge or death during hospitalization. Infections before ECMO initiation were defined as newly emerging or uncontrolled infections within 7 days before ECMO initiation.

Hospital-wide active surveillance of nosocomial infections at National Taiwan University Hospital has been conducted since 1981.[12] Nosocomial infections were defined as the criteria proposed by the Centers for Disease Control and Prevention definition.[13] A computerized case record form was used to prospectively collect the data of patients with nosocomial infections, including age; gender; and dates, sites, and causative pathogens of nosocomial infections. The data of infections occurring in the period from the initiation to the removal of ECMO and caused by pathogens different from those of infections within 7 days before ECMO initiation were extracted for analysis. Patients' medical charts were also reviewed to ensure completeness of data collection.

At ECMO initiation, antibiotic prophylaxis with ceftazidime and vancomycin was prescribed to patients without antibiotic use. In patients who had already been taking antibiotics, antimicrobial agents were maintained or modified empirically at the discretion of the attending clinical team. During ECMO use, antibiotics were adjusted according to clinical situations or culture results. The institutional review board of the hospitals approved the study and waived for the need of informed consent.

Statistical Analysis

All statistical analyses were performed using SPSS software version 16.0 (SPSS Inc, Chicago, Ill). Categoric variables were compared using the chi-square or Fisher's exact test, whereas continuous variables were compared using the Student t test or Mann–Whitney U test and were expressed as mean $\pm$ standard deviation or median with range. A stepwise logistic regression model was built to identify independent variables associated with infections occurring during ECMO use and in-hospital death, respectively. All tests were 2-tailed.

RESULTS

A total of 569 adults underwent 594 cases of ECMO for respiratory or cardiac support during the study period. Of the 594 cases of ECMO, 260 were excluded for the following reasons: ECMO use for less than 48 hours in 166, ECMO initiated at other hospitals in 62, and not the first-time use of ECMO in 32. The demographics of the remaining 334 ECMO cases in 334 patients are presented in Table 1. Fifty-five episodes of infection occurred in 45 patients (13.5%, 45/334) during ECMO use, including 38 episodes (69.1%, 38/55) of bloodstream infections, 6 (10.9%, 6/55) surgical site infections, 4 (7.3%, 4/55) respiratory tract infections, 3 (5.5%, 3/55) urinary tract infections, 2 (3.6%, 2/55) skin and soft tissue infections, and 2 (3.6%, 2/55) catheter infections.

A total of 48 pathogens were isolated from the blood, and gram-negative bacteria (68.8%, 33/48) were most common, followed by gram-positive bacteria (16.7%, 8/48) and fungi (14.6%, 7/48) (Table 2). *Stenotrophomonas maltophilia*, *Candida* species, and *Pseudomonas aeruginosa* were the 3 predominant blood isolates; *Staphylococcus aureus* was the main gram-positive pathogen. The median interval from ECMO initiation to the onset of bloodstream infections was 8 days (range, 2–32 days). At the onset of bloodstream infections, patients had been hospitalized for a median duration of 20 days (range, 2–89 days).

In the 334 patients, the total duration of ECMO use was 61,424 hours (or 2559 days) and overall rate of bloodstream infection was 14.85 episodes per 1000 ECMO days. Rate of bloodstream infection was 13.83, 23.78, 24.45, and 14.65 episodes per 1000 ECMO days in patients undergoing ECMO for more than 2 to 10 days, more than 10 to 20 days, more than 20 to 30 days, and more than 30 days, respectively (Figure 1).

Surgical site infection developed a median of 23 days (range, 8–35 days) after ECMO initiation, and gram-negative bacteria accounted for 70% of the causative pathogens (Table 2). Respiratory tract infections occurred at a median of 5 days (range, 5–6 days) of ECMO use, and 80% were caused by gram-negative bacteria. Urinary tract infection developed on days 10, 13, and 13 of ECMO use, respectively. Infections were due to *Escherichia coli* in 1 episode and yeast-organisms in 2 episodes. Skin and soft tissue infection occurred on days 2 and 22 of ECMO use, respectively, and both patients survived. Catheter infection developed in 2 patients on days 6 and 14 of ECMO use.

Of the 9 isolates of *S maltophilia*, 11.1% (1/9) were resistant to trimethoprim/sulfamethoxazole, 28.5% (2/7) were resistant to ticarcillin/clavulanate, 33.3% (3/9) were nonsusceptible to ciprofloxacin, 44.4% (4/9) were nonsusceptible to ceftazidime, and all were nonsusceptible to cefepime (9/9). Of the 6 isolates of *P aeruginosa*, none were resistant to gentamicin; 16.7% (1/6) were resistant to ciprofloxacin; 20% (1/5) were resistant to piperacillin/tazobactam; 33.3% (2/6) were resistant to ceftazidime, cefepime, or aztreonam;