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). Categorical 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;

TABLE 1. Demographic comparison between 45 patients with and 289 patients without infections occurring during extracorporeal membrane oxygenation use

Characteristics	Total	Infections	No infections	P value
Patient no.	334	45	289	
Men, % (n)	68.0 (227)	73.3 (33)	67.1 (194)	.407
Age, y (mean $\pm$ SD)	51 $\pm$ 17	47 $\pm$ 15	52 $\pm$ 17	.099
16–35 y, % (n)	21.6 (72)	28.9 (13)	20.4 (59)	.140
36–55 y	35.0 (117)	35.6 (16)	34.9 (101)	
56–75 y	38.6 (129)	35.6 (16)	39.1 (113)	
≥ 76 y	4.8 (16)	0 (0)	5.5 (16)	
Underlying diseases, % (n)				
Coronary artery disease	45.2 (151)	40.0 (18)	46.0 (133)	.450
Hypertension	28.7 (96)	28.9 (13)	28.7 (83)	.981
Diabetes mellitus	26.3 (88)	26.7 (12)	26.3 (76)	.958
Valvular heart disease	13.2 (44)	8.9 (4)	13.8 (40)	.361
Cardiomyopathy	11.1 (37)	11.1 (5)	11.1 (32)	.999
Transplantation	9.3 (31)	6.7 (3)	9.7 (28)	.709
Cerebrovascular accident	6.9 (23)	4.4 (2)	7.3 (21)	.705
Malignancy	6.6 (22)	8.9 (4)	6.2 (18)	.729
Congenital heart disease	4.5 (15)	4.4 (2)	4.5 (13)	.999
End-stage renal disease	4.2 (14)	8.9 (4)	3.5 (10)	.197
Autoimmune disease*	3.0 (10)	11.1 (5)	1.7 (5)	.003
Others†	7.2 (24)	13.3 (6)	6.2 (18)	.160
Indication of ECMO use, % (n)				
Respiratory support	20.4 (68)	37.8 (17)	17.6 (51)	.002
Infection associated	60.3 (41/68)	70.6 (12/17)	56.9 (29/51)	.317
Non-infection associated	39.7 (27/68)	29.4 (5/17)	43.1 (22/51)	
Cardiac support	79.6 (266)	62.2 (28)	82.4 (238)	.002
Postcardiotomy‡	30.1 (80/266)	17.9 (5/28)	31.5 (75/238)	.136
Acute myocardial infarction	29.7 (79/266)	32.1 (9/28)	29.4 (70/238)	.765
Cardiomyopathy	15.4 (41/266)	28.6 (8/28)	13.9 (33/238)	.078
Acute myocarditis	10.5 (28/266)	3.6 (1/28)	11.3 (27/238)	.346
PH and RH failure	2.3 (6/266)	10.7 (3/28)	1.3 (3/238)	.017
Septic shock	3.0 (8/266)	7.1 (2/28)	2.5 (6/238)	.201
Others§	9.0 (24/266)	0 (0/28)	10.1 (24/238)	.158

SD, Standard deviation; ECMO, extracorporeal membrane oxygenation; PH, pulmonary hypertension; RH, right heart. *Autoimmune disease included systemic lupus erythematosus, Wegener's granulomatosis, dermatomyositis, antiphospholipid syndrome, and scleroderma with vasculitis. †Others included trauma, primary pulmonary hypertension, liver cirrhosis, and chronic obstructive pulmonary disease. ‡Postcardiotomy = ECMO use for postcardiotomy cardiogenic shock in patients undergoing cardiac operations, including coronary bypass grafting in 40% (32/80), heart transplantation in 25% (20/80), heart valvular operations in 18.8% (15/80), and others in 16.2% (13/80, including pericardiotomy/pericardiectomy, correction of congenital heart disease, aortic operation, and pulmonary artery endarterectomy). §Others included acute rejection, congenital heart disease, and unidentified cardiac diseases.

and 40% (2/5) were resistant to carbapenem. Of the 5 isolates of *Acinetobacter baumannii*, 60% (3/5) were nonsusceptible to carbapenem; 80% (4/5) were nonsusceptible to ceftazidime, cefepime, or ciprofloxacin; and all (5/5) were resistant to gentamicin.

Of the 21 isolates of enteric bacteria that included 7 *Enterobacter* species, 6 *Klebsiella pneumoniae*, 6 *E coli*, 1 *Aeromonas caviae*, and 1 *Serratia marcescens*, 62% (13/21) were nonsusceptible to cefotaxime, 33.3% (7/21) were resistant to gentamicin, 19% (4/21) were resistant to fluoroquinolone, 14.3% (3/21) were resistant to cefepime, and none (0/21) were resistant to carbapenem. Of the 7 isolates of *S aureus*, 85.7% (6/7) were resistant to oxacillin and gentamicin, and 42.9% (3/7) were resistant to trimethoprim/sulfamethoxazole. All 3 isolates of coagulase negative

staphylococci were resistant to oxacillin, and the 2 isolates of *Enterococcus faecalis* were both susceptible to penicillin.

Compared with patients without infections occurring during ECMO use, those with infections were more likely to have autoimmune disease as the underlying disease (11.1% vs 1.7%, $P = .003$); to undergo ECMO for respiratory support (37.8% vs 17.6%, $P = .002$) or pulmonary hypertension and right-sided heart failure as indication of cardiac support (10.7% vs 1.3%, $P = .017$); to have infections before ECMO initiation (37.8% vs 17.0%, $P = .001$); to receive venovenous (VV) mode (37.8% vs 14.0%, $P < .001$); to have a longer duration of ECMO use (360 ± 237 vs 157 ± 165 hours, $P < .001$); and to develop mechanical (91.1% vs 56.4%, $P < .001$) or pulmonary complications (17.8% vs 5.2%, $P = .005$) (Tables 1 and 3).

TABLE 2. Isolates of bloodstream, surgical site, respiratory tract, and urinary tract infections during extracorporeal membrane oxygenation use

BSI (48 isolates)	% (n)	SSI (10 isolates)	% (n)	RTI (5 isolates)	% (n)	UTI (3 isolates)	% (n)
Gram-negative bacteria	68.8 (33)		70.0 (7)		80 (4)		33.3 (1)
<i>Stenotrophomonas maltophilia</i>	16.7 (8)	<i>Enterobacter cloacae</i>	30.0 (3)	<i>Burkholderia cepacia</i> complex	40.0 (2)	<i>E coli</i>	33.3 (1)
<i>Pseudomonas aeruginosa</i>	12.5 (6)	<i>Klebsiella oxytoca</i>	10.0 (1)	<i>Sphingomonas paucimobilis</i>	20.0 (1)		
<i>Klebsiella pneumoniae</i>	10.4 (5)	<i>E coli</i>	10.0 (1)	<i>Serratia marcescens</i>	20.0 (1)		
<i>Acinetobacter baumannii</i>	10.4 (5)	<i>Aeromonas caviae</i>	10.0 (1)				
<i>Enterobacter</i> species	8.3 (4)	<i>S maltophilia</i>	10.0 (1)				
<i>Escherichia coli</i>	6.3 (3)						
<i>Burkholderia cepacia</i> complex	2.1 (1)						
<i>Bacteroides thetaiotaomicron</i>	2.1 (1)						
Gram-positive bacteria	16.7 (8)		20.0 (2)		20 (1)		0 (0)
<i>Staphylococcus aureus</i>	8.3 (4)	<i>S aureus</i>	20.0 (2)	<i>S aureus</i>	20.0 (1)		
<i>Enterococcus faecalis</i>	4.2 (2)						
Coagulase-negative staphylococci	4.2 (2)						
Fungi	14.6 (7)		10.0 (1)		0 (0)		66.7 (2)
<i>Candida albicans</i>	8.3 (4)	<i>Candida parapsilosis</i>	10.0 (1)			Yeast-like organism	66.7 (2)
<i>Candida tropicalis</i>	4.2 (2)						
<i>Candida glabrata</i>	2.1 (1)						

BSI, Bloodstream infection; SSI, surgical site infection; RTI, respiratory tract infection; UTI, urinary tract infection.

A stepwise logistic regression model was constructed to determine the independent role of duration of ECMO use, infection before ECMO initiation, ECMO use as respiratory support, receipt of VV mode, development of mechanical or pulmonary complications, and underlying disease with autoimmune disease as contributors to occurrence of infections during ECMO use (Table 4). Longer duration of ECMO use (odds ratio [OR], 1.003; 95% confidence interval [CI], 1.001–1.005; $P = .004$), mechanical complication

(OR, 4.849; 95% CI, 1.569–14.991; $P = .006$), receipt of VV mode (OR, 4.473; 95% CI, 1.001–19.977; $P = .050$), and autoimmune disease (OR, 6.997; 95% CI, 1.541–31.766; $P = .012$) were independently associated with a higher risk for infections occurring during ECMO use (Table 4). Infections before ECMO initiation, ECMO use for respiratory support, and development of pulmonary complications were not independently associated with occurrence of infections during ECMO use.

FIGURE 1. Rates of bloodstream infection among patients undergoing ECMO who were stratified by duration of ECMO. ECMO, Extracorporeal membrane oxygenation.

TABLE 3. Comparison of extracorporeal membrane oxygenation use between patients with and without infections occurring during extracorporeal membrane oxygenation use

	Total	Infections	No infections	P value
Patient no.	334	45	289	
IABP during hospitalization, % (n)	58.4 (195)	46.7 (21)	60.2 (174)	.086
CPR during hospitalization, % (n)	49.4 (165)	40.0 (18)	50.9 (147)	.175
Infection before ECMO initiation, % (n)	19.8 (66)	37.8 (17)	17.0 (49)	.001
Severity of disease at ECMO initiation				
APACHE II score, mean $\pm$ SD	17 $\pm$ 7	16 $\pm$ 7	17 $\pm$ 7	.504
≥ 20 , % (n)	31.4 (105)	28.9 (13)	31.8 (92)	.692
Duration of hospitalization before ECMO initiation, d, mean $\pm$ SD	11.3 $\pm$ 26.0	13.2 $\pm$ 17.8	11.0 $\pm$ 27.0	.595
ECMO use at admission, % (n)	26.9 (90)	17.8 (8)	28.4 (82)	.136
≤ 1 wk of hospitalization	68.3 (228)	57.8 (26)	69.9 (202)	.134
≤ 2 and > 1 wk of hospitalization	10.2 (34)	8.9 (4)	10.4 (30)	
> 2 wk of hospitalization	21.6 (72)	33.3 (15)	19.7 (57)	
Mode of ECMO, % (n)				
Venoarterial	80.3 (265/330)	60.0 (27/45)	83.5 (238/285)	$< .001$
Venovenous	17.3 (57/330)	37.8 (17/45)	14.0 (40/285)	$< .001$
Duration of ECMO, h, mean $\pm$ SD	184 $\pm$ 188	360 $\pm$ 237	157 $\pm$ 163	$< .001$
≤ 184 h and > 48 h, % (n)	69.2 (231)	26.7 (12)	75.8 (219)	$< .001$
> 184 h	30.8 (103)	73.3 (33)	24.2 (70)	
Complications, % (n)				
Mechanical*	61.1 (204)	91.1 (41)	56.4 (163)	$< .001$
Hemorrhage†	49.4 (165)	62.2 (28)	47.4 (137)	.064
Pulmonary‡	6.9 (23)	17.8 (8)	5.2 (15)	.005
Cardiac tamponade	9.9 (33)	4.4 (2)	10.7 (31)	.296
Vascular§	41.6 (139)	37.8 (17)	42.2 (122)	.574
Outcomes of ECMO, % (n)				
ECMO removal and discharge	27.8 (93)	24.4 (11)	28.4 (82)	.075
Bridge to VAD or heart transplantation	7.5 (25)	2.2 (1)	8.3 (24)	
Death with ECMO use	40.7 (136)	57.8 (26)	38.1 (110)	
Death after ECMO removal	24.0 (80)	15.6 (7)	25.3 (73)	
Death, % (n)	68.3 (228)	75.6 (34)	67.1 (194)	.259
≤ 1 wk of ECMO initiation	38.6 (88/228)	23.5 (8/34)	41.2 (80/194)	.147
≤ 2 and > 1 wk of ECMO initiation	26.3 (60/228)	32.4 (11/34)	25.3 (49/194)	
> 2 wk of ECMO initiation	35.1 (80/228)	44.1 (15/34)	33.5 (65/194)	

IABP, Intra-aortic balloon pump; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; SD, standard deviation; VAD, ventricular assist device.

*Mechanical complications included oxygenator failure; pump malfunction; heater dysfunction; clot of oxygenator, hemofilter, and other sites; connector crack; and so forth.

†Hemorrhage complications included gastrointestinal hemorrhage, cannulation site bleeding, surgical site bleeding, and hemolysis. ‡Pulmonary complications included pneumothorax and pulmonary hemorrhage. §Vascular complications included digital gangrene, dysfunction of reperfusion catheter, and fasciotomy.

Outcome

At the end of follow-up, overall mortality was 68.3%: 75.6% in patients with infections and 67.1% in patients without infections occurring during ECMO use ($P = .259$) (Table 4). The death rate of patients with bloodstream, surgical site, and respiratory tract infections was 88.2% (30/34), 83.3% (5/6), and 75.0% (3/4), respectively. Compared with patients who survived, patients who died at the end of follow-up were older and more likely to have coronary artery disease or diabetes mellitus; to undergo ECMO with the indication of cardiac support for acute myocardial infarction; to require CPR during hospitalization; to initiate ECMO in the second week of hospitalization; to have higher APACHE II score; and to have neurologic, metabolic, or vascular complications (Tables E1 and E2). In addition, patients who died

were less likely to have cardiomyopathy as the underlying disease, to have a baseline heart function of New York Heart Association class I, to have acute myocarditis as an indication of ECMO support, or to undergo ECMO in the first week of hospitalization than patients who survived (Tables E1 and E2). Infections before or during ECMO use were not associated with in-hospital mortality.

By using stepwise logistic regression analysis with variables in Tables E1 and E2 significant at P less than .05 in the model (ie, age, underlying diseases, baseline heart function, ECMO indications, CPR during hospitalization, APACHE II score, duration of hospitalization before ECMO initiation, and complications of ECMO use), only older age (OR, 1.037; 95% CI, 1.021–1.054; $P < .001$), neurologic complications (OR, 51.153; 95% CI, 6.773–386.329;

TABLE 4. Variables associated with infections occurring during extracorporeal membrane oxygenation use by stepwise logistic regression model

Variables	Reference	OR (95% CI)	P value
Duration of ECMO use	Continuous variable	1.003 (1.001–1.005)	.004
Infections before ECMO initiation	No infections before ECMO initiation	1.782 (0.721–4.402)	.211
Respiratory support	Cardiac support	0.350 (0.072–1.688)	.191
Venovenous mode	Venoarterial mode	4.473 (1.001–19.977)	.050
Mechanical complication*	No mechanical complication	4.849 (1.569–14.991)	.006
Pulmonary complication†	No pulmonary complication	1.694 (0.545–5.264)	.362
Autoimmune disease‡	No autoimmune disease	6.997 (1.541–31.766)	.012

OR, Odds ratio; CI, confidence interval; ECMO, extracorporeal membrane oxygenation. *Mechanical complications included oxygenator failure; pump malfunction; heater dysfunction; clot of oxygenator, hemofilter, and other sites; connector crack; and so forth. †Pulmonary complications included pneumothorax and pulmonary hemorrhage.

‡Autoimmune disease included systemic lupus erythematosus, Wegener's granulomatosis, dermatomyositis, antiphospholipid syndrome, and scleroderma with vasculitis.

$P < .001$), and vascular complications (OR, 1.922; 95% CI, 1.112–3.320; $P < .001$) were independently associated with a higher risk for death, whereas ECMO initiation within 1 week of hospitalization (OR, 0.291; 95% CI, 0.160–0.530; $P < .001$) was significantly associated with a lower risk for mortality. Underlying diseases, baseline heart function, indications of ECMO use, CPR during hospitalization, and higher APACHE II score were not independently associated with death at the end of follow-up.

DISCUSSION

In the literature, incidence of infections occurring during ECMO use ranges widely from 3.5% to 45.1%,^{8-10,14,15} and bloodstream infection is most common, occurring in 32.6% to 89.4% of these infections.^{10,15,16} Gram-positive cocci, particularly coagulase-negative staphylococci, are reported to be the predominant blood isolates.^{10,16-18} Likewise, 13.5% of our patients developed infections during ECMO use, and 69.1% of these infections were bloodstream infection. However, *S maltophilia* and *Candida* species were the most common blood isolates. Because a single blood isolate of coagulase-negative staphylococci without compatible clinical conditions defined by the Centers for Disease Control was not regarded as a bloodstream infection, this may explain why coagulase-negative staphylococci were not the most common blood isolate in our study. In addition, our practice of antibiotic prophylaxis with vancomycin may contribute to this finding.

Risk factors for infections caused by *S maltophilia* and *Candida* species include prolonged hospitalization or intensive care unit stay,¹⁹⁻²¹ exposure to broad-spectrum antibiotics,²⁰⁻²³ and use of central venous catheters.²¹⁻²³ Thus, it is not surprising that *S maltophilia* and *Candida* species were the predominant blood isolates in this study, and significant proportions of causative pathogens of infections during ECMO use had antibiotic resistance given the fact that our patients with infections during ECMO use had a mean duration of hospitalization of 13.2 days before ECMO initiation. In addition, 37.8% of them had infections before ECMO initiation, 40.0% required CPR, and 46.7% required IABP. These clinical conditions

further predisposed patients to prolonged hospital or intensive care unit stay, broad-spectrum antibiotic exposure, and placement of multiple central catheters, which subsequently led to increased risk of acquiring infections caused by resistant organisms.

Given highly invasive procedures (eg, ECMO or IABP) in emergency situations (eg, sudden collapse or worsening respiratory conditions despite full ventilator support), compliance of infection-control precautions might not be perfect. In addition, immunologic responses of patients with sepsis may be inappropriate. The use of steroids for acute respiratory distress syndrome or adrenal insufficiency, body temperature control, and multiple blood transfusions after cardiac operations or for coagulopathy during ECMO use can also interfere with the presentations of infection in patients undergoing ECMO. Thus, we routinely prescribed antimicrobial prophylaxis after ECMO initiation, and it is common to escalate antibiotics immediately and empirically whenever infections are suspected. Although these practices might decrease the occurrence of infections during ECMO use, they also contribute to the subsequent infections caused by drug-resistant bacteria and *Candida* species as a result of antibiotic selection pressure.

Duration of ECMO use and mechanical complications have been reported as risk factors for occurrence of infections during ECMO use,^{7,8,10,15,16,18,24} and we also had similar observations. Our patients with autoimmune disease and receipt of VV mode also had greater likelihood of infections (Table 4). The association between autoimmune disease and infections has not been previously described. Nevertheless, it is plausible that the immunity of these patients was severely compromised by immunosuppressive agents or their diseases, which predispose them to infections during ECMO use. Before ECMO initiation, 8 of our 10 patients with autoimmune disease received intensified immunosuppression with corticosteroid or cyclophosphamide to control their disease exacerbation.

Compared with VV mode, venoarterial mode has long been considered as a more complex cannulation and associated with more complications, such as vascular trauma, systemic embolization, and ischemia.²⁵ It is not clear why VV

mode was associated with a higher risk for infection in the present study. However, because our patients with VV mode were more likely to require respiratory support, have infections before ECMO use, and undergo ECMO longer than those with venoarterial mode (data not shown), it is possible that the characteristics of patients with VV mode rendered them vulnerable to infections, or that other unknown or unassessed factors influenced the risk of infections.

Infections during ECMO use have also been identified as a risk factor for death.^{7-9,18} However, older age, neurologic, and vascular complications, but not infections during ECMO use, were associated with a higher risk for in-hospital death in our study. Elderly patients usually had more comorbidities and were more fragile. Therapeutic strategies tended to be supportive in patients in whom neurologic complications developed during ECMO use (eg, intracranial hemorrhage or brain death), which might explain why the likelihood of in-hospital death in older patients or patients with neurologic complications was greater. Because vascular complications included dysfunction of distal reperfusion catheter (91.4%), digital gangrene (12.2%), and requirement of fasciotomy (4.3%) (data not shown), the association between vascular complications and mortality might be due to inadequate perfusion of distal limbs and its associated complications.

It should be noted that several studies have described infections occurring during ECMO use in neonatal and pediatric populations,^{9,14-18} whereas in adults, only 1 study explicitly addressed this issue, and its study population was different from ours.¹⁰ Our patient population was larger (334 patients with a total of 2559 ECMO days vs 71 patients with a total of 799 ECMO days), was older (mean 51 vs 36.0 years in infected group and 33.3 years in uninfected group), was hospitalized longer before ECMO initiation (mean 11.3 vs 2.3 days in infected group and 1.6 days in uninfected group), and underwent ECMO in recent years (1996–2007 vs 1985–1995), primarily for cardiac support (79.6% vs 9.9%). Nevertheless, there were less bloodstream infections in the present study in terms of both overall rate (14.85 vs 18.8 episodes per 1000 ECMO days) and rates stratified by the duration of ECMO use (13.83, 23.78, 24.45, and 14.65 vs 9.5, 27.2, 64.5, and 90.9 episodes per 1000 ECMO days for ECMO duration of >2–10, >10–20, >20–30, and >30 days, respectively). These differences may be attributable to advances of ECMO technology and critical care in the current era, different definitions of infections during ECMO use (ours was from ECMO initiation to removal and theirs¹⁰ was from 24 hours after initiation to 48 hours after removal), and multidiscipline experience in our ECMO team.

Study Limitations

Several weaknesses of our study deserve to be acknowledged. First, information regarding antibiotic use and dura-

tion in patients undergoing ECMO was not available, so we could not evaluate the effects of antibiotics on the occurrence of infections or resistance of causative pathogens. In addition, variables such as surveillance cultures, nutritional support, need for and amount of blood transfusion, and ventilation times were not assessed, so their impact on the incidence of infection in the patients receiving ECMO is beyond the scope of this report. Second, because the lung parenchyma could be affected by patients' underlying pulmonary or cardiac diseases, it is difficult to distinguish whether superimposed respiratory tract infections occurred. Thus, the rate of respiratory tract infections might be underestimated in our surveillance system. Third, data regarding nosocomial infections in intensive care unit patients without ECMO use who had similar disease severity were not available, and this precludes our ability to further analyze the impact of ECMO use on the occurrence of infections. Last, the present study was limited to a single center.

CONCLUSIONS

Our study showed that infections during ECMO use occurred in 13.5% of an adult population. Bloodstream infection was most common and primarily caused by *S. maltophilia* and *Candida* species. The majority of the causative pathogens carried antimicrobial resistance. We demonstrated substantial advancement of ECMO care in adults in the current era and identified several risk factors associated with occurrence of infections during ECMO use and in-hospital mortality. These warrant prospective randomized studies to confirm our findings.

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TABLE E1. Demographic comparison between patients who died during hospitalization and patients who survived to be discharged

Characteristics	Total	Death	Survival	P value
Patient no.	334	228	106	
Men, % (n)	68.0 (227)	69.3 (158)	65.1 (69)	.443
Age, y (mean $\pm$ SD)	51 $\pm$ 17	54 $\pm$ 17	45 $\pm$ 16	<.001
16–35 y, % (n)	21.6 (72)	15.8 (36)	34.0 (36)	<.001
36–55 y	35.0 (117)	34.2 (78)	36.8 (39)	.645
56–75 y	38.6 (129)	43.4 (99)	28.3 (30)	.008
$\geq$ 76 y	4.8 (16)	6.6 (15)	0.9 (1)	.025
Underlying diseases, % (n)				
Coronary artery disease	45.2 (151)	52.2 (119)	30.2 (32)	<.001
Hypertension	28.7 (96)	32.0 (73)	21.7 (23)	.052
Diabetes mellitus	26.3 (88)	30.3 (69)	17.9 (19)	.017
Valvular heart disease	13.2 (44)	13.6 (31)	12.3 (13)	.738
Cardiomyopathy	11.1 (37)	8.8 (20)	16.0 (17)	.049
Transplantation	9.3 (31)	8.8 (20)	10.4 (11)	.638
Cerebrovascular accident	6.9 (23)	7.9 (18)	4.7 (5)	.286
Malignancy	6.6 (22)	6.6 (15)	6.6 (7)	.993
Congenital heart disease	4.5 (15)	4.4 (10)	4.7 (5)	.999
End-stage renal disease	4.2 (14)	4.8 (11)	2.8 (3)	.580
Autoimmune disease*	3.0 (10)	4.4 (10)	0 (0)	.065
Others†	7.2 (24)	7.5 (17)	6.6 (7)	.779
Baseline heart function				
NYHA class I	32.5 (82/252)	27.5 (47/171)	43.2 (35/81)	.015
NYHA class II	29.0 (73/252)	32.2 (55/171)	22.2 (18/81)	
NYHA class III	18.7 (47/252)	22.2 (38/171)	11.1 (9/81)	
NYHA class IV	19.8 (50/252)	18.1 (31/171)	23.5 (19/81)	
Indication of ECMO use, % (n)				
Respiratory support	20.4 (68)	20.6 (47)	19.8 (21)	.865
Infection associated	60.3 (41/68)	63.8 (30)	52.4 (11)	.373
Non-infection associated	39.7 (27/68)	36.2 (17)	47.6 (10)	
Cardiac support	79.6 (266)	79.4 (181)	80.2 (85)	.865
Postcardiotomy‡	30.1 (80/266)	28.7 (52/181)	32.9 (28/85)	.485
Acute myocardial infarction	29.7 (79/266)	35.4 (64/181)	17.6 (15/85)	.003
Cardiomyopathy	15.4 (41/266)	13.3 (24/181)	20.0 (17/85)	.156
Acute myocarditis	10.5 (28/266)	5.5 (10/181)	21.2 (18/85)	<.001
PH and RH failure	2.3 (6/266)	2.8 (5/181)	1.2 (1/85)	.712
Septic shock	3.0 (8/266)	3.9 (7/181)	1.2 (1/85)	.416
Others§	9.0 (24/266)	10.5 (19/181)	5.9 (5/85)	.221

SD, Standard deviation; NYHA, New York Heart Association; ECMO, extracorporeal membrane oxygenation; PH, pulmonary hypertension; RH, right heart. *Autoimmune disease included systemic lupus erythematosus, Wegener's granulomatosis, dermatomyositis, antiphospholipid syndrome, and scleroderma with vasculitis. †Others included trauma, primary pulmonary hypertension, liver cirrhosis, and chronic obstructive pulmonary disease. ‡Postcardiotomy = ECMO use for postcardiotomy cardiogenic shock in patients undergoing cardiac operations, including coronary bypass grafting in 40% (32/80), heart transplantation in 25% (20/80), heart valvular operations in 18.8% (15/80), and others in 16.2% (13/80, including pericardiotomy/pericardiectomy, correction of congenital heart disease, aortic operation, and pulmonary artery endarterectomy); in-hospital mortality of patients with postcardiotomy ECMO use and those without was 65% (52/80) and 69.4% (129/186), respectively ($P = .485$); of 52 patients with postcardiotomy ECMO who died, causes of in-hospital death were worsening heart function in 46.2% (24/52), sepsis after ECMO removal in 13.5% (7/52), bleeding in 11.5% (6/52), and miscellaneous causes in 28.8% (15/52, including respiratory failure in 4, ventricular tachycardia in 3, unidentifiable causes in 3, hepatic failure in 2, acidosis in 1, compartment syndrome in 1, and refractory acidosis in 1). §Others included acute rejection, congenital heart disease, and unidentified cardiac disease

TABLE E2. Comparison of extracorporeal membrane oxygenation use between patients who died during hospitalization and those who survived to be discharged

	Total	Death	Survival	P value
Patient No.	334	228	106	
IABP during hospitalization, % (n)	58.4 (195)	60.1 (137)	54.7 (58)	.354
CPR during hospitalization, % (n)	49.4 (165)	54.4 (124)	38.7 (41)	.008
Infection < 1 wk before ECMO, % (n)	19.8 (66)	21.9 (50)	15.1 (16)	.144
Severity of disease at ECMO initiation				
APACHE II score, mean $\pm$ SD	17 $\pm$ 7	18 $\pm$ 7	15 $\pm$ 7	<.001
≥ 20 , % (n)	31.4 (105)	37.3 (85)	18.9 (20)	.001
Duration of hospitalization before ECMO initiation, d, mean $\pm$ SD	11.3 $\pm$ 26.0	12 $\pm$ 24	10 $\pm$ 30	.522
ECMO use at admission, % (n)	26.9 (90)	25.9 (59)	29.2 (31)	.518
≤ 1 wk of hospitalization	68.3 (228)	64.0 (146)	77.4 (82)	.015
≤ 2 and > 1 wk of hospitalization	10.2 (34)	13.2 (30)	3.8 (4)	.008
> 2 wk of hospitalization	21.6 (72)	22.8 (52)	18.9 (20)	.415
Mode of ECMO, % (n)				
Venoarterial	80.3 (265/330)	81.4 (184)	77.9 (81)	.454
Venovenous	17.3 (57/330)	15.5 (35)	21.2 (22)	.206
Duration of ECMO, h, mean $\pm$ SD	184 $\pm$ 188	185 $\pm$ 191	182 $\pm$ 182	.908
≤ 184 h and > 48 h, % (n)	69.2 (231)	68.4 (156)	70.8 (75)	.667
> 184 h	30.8 (103)	31.6 (72)	29.2 (31)	
Complications, % (n)				
Infection	13.5 (45)	14.9 (34)	10.4 (11)	.259
Mechanical*	61.1 (204)	62.3 (142)	58.5 (62)	.508
Hemorrhage†	49.4 (165)	52.2 (119)	43.4 (46)	.134
Neurologic‡	17.7 (59)	25.4 (58)	0.9 (1)	<.001
Pulmonary§	6.9 (23)	6.1 (14)	8.5 (9)	.430
Cardiac tamponade	9.9 (33)	11.8 (27)	5.7 (6)	.078
Metabolic	75.1 (251)	81.1 (185)	62.3 (66)	<.001
Vascular¶	41.6 (139)	46.1 (105)	32.1 (34)	.016

IABP, Intra-aortic balloon pump; CPR, cardiopulmonary resuscitation; APACHE II, Acute Physiology and Chronic Health Evaluation II; ECMO, extracorporeal membrane oxygenation; SD, standard deviation. *Mechanical complications included oxygenator failure; pump malfunction; heater dysfunction; clot of oxygenator, hemofilter, and other sites; connector crack; and so forth. †Hemorrhage complications included gastrointestinal hemorrhage, cannulation site bleeding, surgical site bleeding, and hemolysis. ‡Neurologic complications included brain death, seizure, and cerebrovascular accident. §Pulmonary complications included pneumothorax and pulmonary hemorrhage. ||Metabolic complications included blood glucose level < 40 mg/dL or > 240 mg/dL, serum pH < 7.2 or > 7.6 , or serum bilirubin level > 15 mg/dL. ¶Vascular complications included digital gangrene, dysfunction of reperfusion catheter, and fasciotomy.