Nosocomial infections in a cohort of extracorporeal life support patients*

Ian Conrick-Martin, Joanne O'Gorman, Deirdre Lenehan, Daniel Oshodi, Nuala Scanlon, Serena O'Brien, Margaret Hannan, Maureen Lynch and Edmund Carton

ABSTRACT

Objectives: To examine nosocomial infections in a cohort of patients receiving extracorporeal life support (ECLS) at our institution and to identify the types of infections, impact of prophylaxis, and any apparent risk factors for infection.

Methods: In a retrospective cohort study, we examined the records of all patients who received ECLS at our institution between August 2009 and March 2011. A prospective, daily, multidisciplinary assessment of all microbiological issues in these patients was carried out, including assessment of microbiological culture positivity and clinical evidence of infection. The results of these assessments were analysed in relation to HELICS (Hospital in Europe Link for Infection Control through Surveillance) and CDC (Centers for Disease Control and Prevention) diagnostic criteria. The use of antimicrobials in these patients was also assessed, as well as the overall bloodstream infection rate in ICU patients.

Results: Seventeen patients received ECLS during the study period, with a total of 445 ECLS days. Of these patients, 13 received respiratory (venovenous) ECLS and four received cardiac (venoarterial) ECLS. There were 17 infections in the cohort: 11 ventilator-associated pneumonias; four bloodstream infections (likely all catheter-related, yielding a rate of 9.0 infections/1000 ECLS days); one skin and soft tissue infection; and one urinary tract infection. The bloodstream infection rate in the ICU population as a whole was 9.30/1000 bed-days in 2009 and 7.21/1000 bed-days in 2010. Resistant organisms were identified in 3/17 infections: one methicillin-resistant *Staphylococcus aureus*, one multidrug-resistant strain of *Pseudomonas* and one extended-spectrum β-lactamase-producing *Escherichia coli*. The median time to acquiring nosocomial infection was 25 days (interquartile range, 13–33 days). The first four ECLS patients received antibacterial (vancomycin) and antifungal (caspofungin) prophylaxis for the duration of ECLS, whereas the later cohort of 13 did not. In patients who received prophylactic antimicrobials, the defined daily dose (DDD) per 100 ECLS days was 49.54 for vancomycin and 49.63 for meropenem. In patients who did not receive prophylaxis, the corresponding DDDs were 25.31 and 37.73, respectively. In ICU patients overall, the DDD per 100 bed-days over the same time period was 13.60 for vancomycin and 19.75 for meropenem. There were 21/445 ECLS days on which antimicrobials were not used.

Conclusion: Although ECLS patients are at high risk of acquiring nosocomial infections, the infection rate in our cohort was low. The bloodstream infection rate compared favourably with previously published rates, and was comparable with the bloodstream infection rate among ICU patients as a whole over the same time period. Increased duration of ECLS in this cohort may correlate with an increased rate of infection, consistent with data from other ECLS centres. Antimicrobial use in ECLS patients was high relative to overall use in ICU patients. Larger studies are warranted to evaluate the diagnosis, treatment and overall approach to managing nosocomial infection in ECLS patients.

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Extracorporeal life support (ECLS) is a method of organ support used in intensive care units to treat patients with severe respiratory and/or cardiac failure refractory to conventional modes of therapy.[1,2] Nosocomial infections in these patients are associated with increased morbidity and mortality, as well as increased lengths of ICU and hospital stay.[3] The large-bore cannulae used for vascular access for the extracorporeal circuit disrupt the normal protective mechanism of the skin barrier and therefore, as is the case with all invasive vascular devices, they constitute a risk factor for nosocomial infection.[4]

The respiratory ECLS program at our institution began in 2009, and since then, an increasing number of patients have been treated using this form of therapy. However, the data available on nosocomial infections in ECLS patients are limited, and there are no international guidelines on the use of antimicrobial therapies for treatment of, or prophylaxis against, these infections.

The use of antimicrobial prophylaxis in ECLS patients is without a robust evidence base. Some ECLS centres routinely use broad-spectrum antimicrobials (including antifungals) and others use no prophylactic agents.[5] The Extracorporeal Life Support Organization (ELSO) provides no guidelines on antimicrobial prophylaxis.[6]

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Published work to date regarding risk factors for nosocomial infection in ECLS patients has identified duration of ECLS therapy as an independent risk factor.[7] This appears to be the most consistently reported factor in the literature.[8-10]

We therefore decided to examine nosocomial infections in the cohort of ECLS patients treated at our institution in order to identify the types of infections, possible impact of prophylaxis, and any apparent risk factors for infection.

Methods

Our study was conducted in an 18-bed, university-affiliated, tertiary referral combined medical and surgical ICU. This unit is located in a 570-bed, inner-city hospital that serves as the national referral centre for cardiothoracic surgery (including cardiac and lung transplantation). It is also the only institution nationally that offers an adult ECLS service, with associated multidisciplinary inputs from critical care medicine, critical care nursing, cardiothoracic surgery, vascular surgery and the perfusion service.

A prospectively recorded electronic database of ICU admissions was used to identify all ECLS cases from the initiation of our adult respiratory ECLS service in August 2009 to March 2011. We conducted a prospective multidisciplinary (critical care medicine, critical care nursing, clinical microbiology and clinical pharmacy) assessment of all microbiological issues in these patients, including assessment of culture positivity and clinical evidence of infection.

From a retrospective analysis of these data, we recorded the types of nosocomial infection, associated microorganisms, patterns of resistance, antimicrobial treatment regimen and use of prophylactic antimicrobial agents. We also retrospectively examined the bloodstream infection rate of *all* patients in the ICU over the same time period, to provide a context in which to interpret the bloodstream infection rate of the ECLS cohort.

We used diagnostic criteria from HELICS (Hospital in Europe Link for Infection Control through Surveillance)[11] and the Centers for Disease Control and Prevention[12] to facilitate diagnosis of the underlying infection. If specific diagnostic criteria for a given infection were not met, but the clinical context was such that the likelihood of source-specific infection was high (and a therapeutic strategy was directed at same), this was accepted as positive evidence of infection.

The use of antimicrobials in these patients was also assessed. As well as assessing quantitative use, we used the concept of defined daily dose (DDD), which is a World Health Organization statistical measure of drug consumption. The DDD of a drug is its assumed average maintenance dose per day, when used for its main indication in adults. DDDs are used to standardise the comparative usage of drugs of different strengths and potencies.[13] The WHO have assigned a DDD of 2 (ie, 2 g/day) to meropenem, and a DDD of 2 has also been assigned to vancomycin.

Informed consent for demographic, physiological and microbiological data, as well as ICU and hospital-outcome data was not required, because this retrospective, observational study did not modify existing diagnostic or therapeutic strategies.

Results

A total of 17 patients received ECLS during the study period, yielding 445 ECLS days. Of these patients, 13 received respiratory (venovenous) ECLS and four received cardiac (venoarterial) ECLS, yielding 432 and 13 ECLS days, respectively. All four venoarterial ECLS patients were cannulated peripherally (ie, via the femoral artery and vein). Of the 13 venovenous ECLS patients, 11 were cannulated with internal jugular venous cannulae and six with femoral venous cannulae (four patients had both femoral *and* internal jugular cannulae during their ECLS "run").

In total, there were 17 infections in the cohort: 11 ventilator-associated pneumonias; four bloodstream infections (likely all catheter-related, yielding a rate of 9.0 infections/1000 ECLS days); one skin and soft tissue infection; and one urinary tract infection. All catheter-related infections were attributable to central venous catheters and not ECLS cannulae. The bloodstream infection rate in the ICU population as a whole was 9.30/1000 bed-days in 2009 and 7.21/1000 bed-days in 2010.

The characteristics of patients who developed nosocomial infections during ECLS use are outlined in Table 1. It should be noted that for the four reported bloodstream infections, only one microorganism was isolated, with clinical evidence of bacteraemia supporting the diagnosis in the other three cases (eg, fever, raised white cell count, increasing doses of vasoactive medications, visible erythema and/or pus at the infected catheter site). These bloodstream infections were treated as catheter-related in origin (although standard diagnostic criteria were not met, there was clinical evidence of improvement after catheter removal).

Sensitivity testing revealed resistant organisms in three of the 17 infections: one methicillin-resistant *Staphylococcus aureus*, one multidrug-resistant strain of *Pseudomonas*, and one extended-spectrum β-lactamase-producing *Escherichia coli*). Additionally, *Candida parapsilosis* was isolated from a catheter specimen of urine in one patient. This organism is known to have intrinsically high minimum inhibitory concentrations to echinocandin antifungals. The median time to acquiring nosocomial infection was 25 days (interquartile range, 13–33 days). Our first four ECLS patients received antibacterial (vancomycin) and antifungal (caspofungin) prophylaxis, whereas the later cohort of 13 did not.

Antimicrobial use in ECLS patients (prophylaxis and non-prophylaxis cohorts) and in ICU patients overall are outlined in Table 2. There were 21/445 ECLS days on which antimicrobials were not used (ie, 21 antimicrobial-free ECLS days).

Table 1. Characteristics of patients who developed nosocomial infections during ECLS use

Case	Age (years)	Sex	ECLS mode	ECLS duration (days)	Prophylaxis	Influenza A H1N1 infection	Nosocomial infection	Pathogen	Survival to ECLS decannulation	Survival to hospital discharge
1	26	F	VV, VA	61	Y	Y	VAP	*Enterobacter* and *Proteus* spp	Y	Y
							CRBSI?	*Enterobacter*		
2	31	F	VV, VA	120	Y	Y	VAP	No pathogen isolated	N	N
							CRBSI?	No pathogen isolated		
							SSTI	*Escherichia coli*		
							VAP*	No pathogen isolated		
3	52	F	VV	15	Y	Y	VAP	*E. coli*	Y	Y
4	22	F	VV	11	N	Y	None		Y	Y
5	29	F	VV	18	N	Y	CRBSI?	No pathogen isolated	Y	Y
6	31	M	VV	12	N	Y	None		N	N
7	35	M	VV	34	N	Y	VAP	*Klebsiella oxytoca*	Y	Y
							UTI	*Pseudomonas aeruginosa*		
8	25	M	VV	17	N	Y	VAP	No pathogen isolated	Y	Y
9	36	F	VV	32	N	Y	VAP	*E. coli* (ESBL)	N	N
10	54	M	VV	16	N	Y	CRBSI?	No pathogen isolated	Y	Y
							VAP	*Enterobacter*		
11	61	M	VV	71	Y	N	VAP	No pathogen isolated	N	N
							VAP	No pathogen isolated		
							VAP	MRSA		
12	37	M	VA	3	N	N	None		N	N
13	33	M	VV	12	N	N	None		Y	Y
14	64	M	VA	4	N	N	None		Y	Remains in hospital
15	43	M	VA	5	N	N	None		Y	Y
16	22	F	VA	0.5	N	N	None		N	N
17	29	M	VV	13	N	N	None		Y	Y

CRBSI = catheter-related bloodstream infection. ESBL = extended-spectrum β-lactamase-producing. ECLS = extracorporeal life support. MRSA = methicillin-resistant *Staphylococcus aureus*. N = no. SSTI = skin/soft tissue infection. UTI = urinary tract infection. VA = venoarterial. VAP = ventilator-associated pneumonia. VV = venovenous. Y = yes. * Evidence of pleural collection on imaging.

Discussion

Although ECLS patients are at high risk of acquiring nosocomial infections, the infection rate in our cohort was low. In particular, the bloodstream infection rate compared favourably with previously published rates, and was comparable with the "background" bloodstream infection rate in the ICU population as a whole over the same time period.

Regarding the issue of catheter-related infection, our unit now inserts antimicrobial-impregnated central venous catheters, if possible, before ECLS cannulation. The aim of this is to minimise the risk of catheter-related infection in patients who would likely be receiving anticoagulation treatment for a prolonged period to facilitate ECLS and would therefore have a relative contraindication to the placement of new central venous catheters. Our central line care protocols are otherwise unchanged from the "standard" line care protocols.

With respect to timing of infection, increased duration of ECLS in this cohort may correlate with an increased rate of infection, consistent with previously published data from other ECLS centres. No infections were identified in patients with an ECLS duration of less than 14 days. The lack of infection in patients with a shorter ECLS duration would suggest, for those who require it, that an earlier start with a shorter duration of ECLS might predispose to a lower risk of infection.

Our first four ECLS patients received antimicrobial prophylaxis in the form of vancomycin and caspofungin. This practice was in place following advice from colleagues in a high-volume ECLS centre in Europe. We later decided to discontinue antimicrobial prophylaxis based on a clinical consensus between treating physicians. There was no significant difference in outcome between the prophylaxis and non-prophylaxis cohorts to precipitate the discontinuation of antimicrobial prophlyaxis. Our study does not lend support to the routine

Table 2. Antimicrobial use in patients receiving ECLS (prophylaxis and non-prophylaxis cohorts) and in ICU patients overall

DDD*	ECLS with prophylaxis†	ECLS without prophylaxis†	Overall ICU use‡
DDD (vancomycin)	49.54	25.31	13.60
DDD (meropenem)	49.63	37.73	19.75

DDD = defined daily dose. * Average maintenance dose per day, standardised for meropenem and vancomycin, which have both been assigned a DDD of 2 (ie, 2 g/day). ECLS = extracorporeal life support. ICU = intensive care unit. † Per 100 ECLS days. ‡ Per 100 bed-days.

use of antimicrobial prophylaxis. As mentioned previously, the ELSO guidelines contain no recommendations on the use (or non-use) of such prophylaxis and there are, to our knowledge, no published data in the literature to support its use.

Antimicrobial use in ECLS patients was high relative to overall antimicrobial use in ICU patients. This has major clinical implications in terms of the potential for promoting antimicrobial resistance and the consequences of adverse effects of these antimicrobial agents. The financial cost of such agents is also a major consideration.

ECLS was used in the context of influenza A H1N1 pneumonitis with refractory respiratory failure in 10 patients. Nosocomial infections developed in 8 out of 10 of these patients. Given the small volume of our data, the explanation for this is unclear. To our knowledge, no published data exist with respect to influenza A H1N1 as a potential risk factor for acquiring nosocomial infection while receiving ECLS.

Our study has a number of limitations that should be considered when interpreting the results. Our data reflect practice at a single ECLS centre (carrying out a relatively novel practice) and are derived from a somewhat heterogeneous study population. The number of patients is small, thus precluding any ability to attach statistical significance to our results. We are continuing to audit ECLS-associated infections at our institution, and hope to present more extensive data on these infections in the future. With respect to the diagnosis of individual infections, some did not meet the appropriate internationally accepted diagnostic criteria but were, for the purposes of our study, considered bona fide infections. We felt that this was an appropriate way to interpret the data, given that a multidisciplinary consensus had been reached, in each case of infection, that the clinical and therapeutic strategy be directed at that specific infection on the basis of clinical, radiological and/or other data available to the treating clinicians at the time. Where differing opinions on this strategy were present, consensus was established after discussion.

In conclusion, further robust large-scale study is warranted to evaluate the diagnosis, treatment and overall approach to the management of nosocomial infection in patients receiving ECLS. Likewise, ELSO guidelines regarding the use (or non-use) of prophylactic antimicrobials would be welcome.

Author details

Ian Conrick-Martin, Clinical Fellow[1]
Joanne O'Gorman, Specialist Registrar[2]
Deirdre Lenehan, Antimicrobial Pharmacist[3]
Daniel Oshodi, Senior Registrar[1]
Nuala Scanlon, Antimicrobial Pharmacist[3]
Serena O'Brien, ECLS Coordinator[1]
Margaret Hannan, Consultant in Clinical Microbiology[2]
Maureen Lynch, Consultant in Clinical Microbiology[2]
Edmund Carton, Consultant in Critical Care Medicine[1]

1 Department of Critical Care Medicine, Mater Misericordiae University Hospital, Dublin, Ireland.
2 Department of Clinical Microbiology, Mater Misericordiae University Hospital, Dublin, Ireland.
3 Department of Clinical Pharmacy, Mater Misericordiae University Hospital, Dublin, Ireland.

Correspondence: iancm25@hotmail.com

References

1 Peek GJ, Moore HM, Moore N, et al. Extracorporeal membrane oxygenation for adult respiratory failure. *Chest* 1997; 112: 759-64.
2 Combes A, Leprince P, Luyt CE, et al. Outcomes and long-term quality-of-life of patients supported by extracorporeal membrane oxygenation for refractory cardiogenic shock. *Crit Care Med* 2008; 36: 1404-11.
3 Extracorporeal Life Support Organization. Registry report: international summary. Ann Arbor, Michigan: ELSO, 2010.
4 O'Neill JM, Schutze GE, Heulitt MJ, et al. Nosocomial infections during extracorporeal membrane oxygenation. *Intensive Care Med* 2001; 27: 1247-53.
5 Brown KL, Ridout DA, Shaw M, et al. Healthcare-associated infection in pediatric patients on extracorporeal life-support: the role of multidisciplinary surveillance. *Pediatr Crit Care Med* 2006; 7: 546-50.
6 Extracorporeal Life Support Organization. Guidelines. http://www.elso.med.umich.edu/Guidelines.html (accessed Nov 2011).
7 Hsu M-S, Chiu K-M, Huang Y-T, et al. Risk factors for nosocomial infection during extracorporeal membrane oxygenation. *J Hosp Infect* 2009; 73: 210-5.
8 Burket JS, Bartlett RH, Vander Hyde K, Chenoweth CE. Nosocomial infections in adult patients undergoing extracorporeal membrane oxygenation. *Clin Infect Dis* 1999; 28: 828-33.
9 Sun H-Y, Ko W-J, Tsai P-R, et al. Infections occurring during extracorporeal membrane oxygenation use in adult patients. *J Thorac Cardiovasc Surg* 2010; 140: 1125-32.e2.
10 Bizzarro MJ, Conrad SA, Kaufman DA, Rycus P. Infections acquired during extracorporeal membrane oxygenation in neonates, children and adults. *Pediatr Crit Care Med* 2011; 12: 277-81.
11 Hospital in Europe Link for Infection Control through Surveillance (HELICS). Surveillance of nosocomial infections in intensive care units. Protocol. Version 6.1, Sep 2004. http://helics.univ-lyon1.fr/protocols/icu_protocol.pdf (accessed Nov 2011).
12 Centers for Disease Control and Prevention (CDC). http://www.cdc.gov (accessed Nov 2011).
13 Hanberger H, Arman D, Gill H, et al. Surveillance of microbial resistance in European intensive care units: a first report from the Care-ICU programme for improved infection control. *Intensive Care Med* 2009; 35: 91-100. ❑