Nosocomial Infections During Extracorporeal Membrane Oxygenation: Incidence, Etiology, and Impact on Patients' Outcome

Giacomo Grasselli, MD[1]; Vittorio Scaravilli, MD[1]; Stefano Di Bella, MD[2]; Stefano Biffi, MD[3]; Michela Bombino, MD[4]; Nicolò Patroniti, MD[3,4]; Luca Bisi, MD[5]; Anna Maria Peri, MD[5]; Antonio Pesenti, MD[1,6]; Andrea Gori, MD[3,5]; Laura Alagna, MD[5]

[1]Department of Anesthesia, Critical Care and Emergency, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan (MI), Italy.

[2]Infectious Disease Unit, University Hospital of Trieste, Trieste (TS), Italy.

[3]School of Medicine and Surgery, University of Milan-Bicocca, Milan (MI), Italy.

[4]Department of Anesthesia, Critical Care and Emergency, ASST Monza San Gerardo Hospital, Monza (MB), Italy.

[5]Infectious Disease Clinics, ASST Monza San Gerardo Hospital, Monza (MB), Italy.

[6]Department of Pathophysiology and Transplantation, University of Milan, Milan (MI), Italy.

The work was performed in the Department of Anesthesia, Critical Care and Emergency, ASST Monza San Gerardo Hospital, Monza (MB), Italy.

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For information regarding this article, E-mail: jaku71@gmail.com

Objective: To study incidence, type, etiology, risk factors, and impact on outcome of nosocomial infections during extracorporeal membrane oxygenation.

Design: Retrospective analysis of prospectively collected data.

Setting: Italian tertiary referral center medical-surgical ICU.

Patients: One hundred five consecutive patients who were treated with extracorporeal membrane oxygenation from January 2010 to November 2015.

Interventions: None.

Measurements and Main Results: Ninety-two patients were included in the analysis (48.5 [37–56] years old, simplified acute physiology score II 37 [32–47]) who underwent peripheral extracorporeal membrane oxygenation (87% veno-venous) for medical indications (78% acute respiratory distress syndrome). Fifty-two patients (55%) were infected (50.4 infections/1,000 person-days of extracorporeal membrane oxygenation). We identified 32 ventilator-associated pneumonia, eight urinary tract infections, five blood stream infections, three catheter-related blood stream infections, two colitis, one extracorporeal membrane oxygenation cannula infection, and one pulmonary-catheter infection. G+ infections (35%) occurred earlier compared with G– (48%) (4 [2–10] vs. 13 [7–23] days from extracorporeal membrane oxygenation initiation; $p < 0.001$). Multidrug-resistant organisms caused 56% of bacterial infections. Younger age (2–35 years old) was independently associated with higher risk for nosocomial infections. Twenty-nine patients (31.5%) died (13.0 deaths/1,000 person-days of extracorporeal membrane oxygenation). Infected patients had higher risk for death (18 vs. 8 deaths/1,000 person-days of extracorporeal membrane oxygenation; $p = 0.037$) and longer ICU stay (32.5 [19.5–78] vs. 19 [10.5–27.5] days; $p = 0.003$), mechanical ventilation (36.5 [20–80.5] vs. 16.5 [9–25.5] days; $p < 0.001$), and extracorporeal membrane oxygenation (25.5 [10.75–54] vs. 10 [5–13] days; $p < 0.001$). Older age (> 50 years old), reason for connection different from acute respiratory distress syndrome, higher simplified acute physiology score II, diagnosis of ventilator-associated pneumonia, and infection by multidrug-resistant bacteria were independently associated to increased death rate.

Conclusions: Infections (especially ventilator-associated pneumonia) during extracorporeal membrane oxygenation therapy are common and frequently involve multidrug-resistant organisms. In addition, they have a negative impact on patients' outcomes. (*Crit Care Med* 2017; 45:1726–1733)

Key Words: extracorporeal membrane oxygenation; health care–associated infection; intensive care unit; multidrug resistance; retrospective study

Extracorporeal membrane oxygenation (ECMO) is a life-support technique utilized in patients with reversible refractory respiratory and/or circulatory failure (1). In the last decade, ECMO use has increased worldwide. Nosocomial infections (NIs) are common complications in ECMO patients (2–5) due to predisposing factors such as patients' comorbidities, immunocompromise associated with the critical illness, and invasiveness of ECMO and of other life-support procedures (e.g., invasive mechanical ventilation [IMV], renal replacement therapies [RRT]).

To date, relatively few studies have assessed the incidence, risk factors, microbial etiology, and antibiotic resistance patterns of NIs during ECMO (3–7). Furthermore, literature data on the impact of NIs on ECMO patients' outcome and mortality are conflicting and inconclusive.

The aim of this study was to evaluate the incidence, microbial etiology, resistance patterns, risk factors, and impact on survival of NIs in a large cohort of nonsurgical patients undergoing ECMO for respiratory and/or circulatory failure.

MATERIALS AND METHODS

This is a retrospective analysis of prospectively collected data of all consecutive ECMO patients admitted to the General ICU of San Gerardo Hospital (Monza, Italy) from January 2010 to November 2015. For further details on ECMO setting and patients' standard of care, see Setting and Standard of Care, see **Supplementary Material, Additional Methods** (Supplemental Digital Content 1, http://links.lww.com/CCM/C779).

The study was approved by the Institutional Ethical Committee. All patients receiving ECMO support for more than 24 hours were included in the study. Exclusion criteria were 1) ICU length of stay (LOS) less than 24 hours; 2) ECMO use less than 24 hours; 3) occurrence of a NI prior to ECMO connection; and 4) missing medical records. The following baseline patients' data and ECMO variables were collected: demographics (i.e., gender, age), smoke habits, comorbidities stratified according to Charlson Comorbidity Index (8), immunocompromised status (i.e., chronic immunosuppressive therapies, active hematological malignancies, autoimmune diseases), diagnosis at admission, infections at admission, RRT before ECMO cannulation, severity scores (i.e., Sequential Organ Failure Assessment score and Simplified Acute Physiology Score II [SAPS II] of the first 24 hours of ICU stay), Pao_2/Fio_2 at ECMO connection, ECMO configuration (i.e., veno-venous [VV], veno-arterial [VA], other), site of cannulation (i.e., femoro-femoral, femoro-jugular, jugulo-femoral), transfer from peripheral hospital by mobile ECMO team, length of IMV before ECMO connection, and antimicrobial therapy.

The following outcomes were recorded: survival at ICU discharge, ICU LOS, duration of IMV, and ECMO.

All positive microbial cultures obtained from the beginning of ECMO support until 48 hours after decannulation were independently evaluated based on available clinical, laboratory, and radiographic data by two specialized intensivists (V.S. and G.G.) and two infectious diseases specialists (S.D.B. and L.A.) following international guidelines (9–11). Accordingly, the following NIs were diagnosed: ventilator-associated pneumonia (VAP), catheter-associated urinary tract infection (UTI), bloodstream infection (BSI), catheter-related bloodstream infection (CRBSI), *Clostridium difficile* colitis, and pulmonary aspergillosis (**Table S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C779) (12). ECMO cannula insertion-site infection was diagnosed when all the following were present: 1) local erythema and purulent drainage; and 2) cultures of the purulent drainage positive for microorganism other than common skin contaminants. Only the first NI episode was included in the analysis.

The causative microorganisms were defined multidrug resistant (MDR) according to Center for Disease Control definition (13).

Statistical Analysis

The crude incidence rate (IR) for the first NI for 1,000 person-days of ECMO (IR/1,000 ECMO-pd) was calculated and presented as 95% CIs for all the factors analyzed. The Kruskal-Wallis test was utilized to compare nonparametric continuous variables between infected and noninfected patients.

Cox regression models were used to identify independent risk factors associated with the first NI through hazard ratios (HRs) estimates. All subjects were included in the models, and follow-up began at the time of ECMO initiation. The time variable used to determine ECMO-infection rate (i.e., the infection-free ECMO days) was calculated as the sum of the total number of days of ECMO for noninfected patients and as the total number of ECMO days before infection for infected ones.

A similar analysis was carried out to identify potential factors associated with death during ECMO. First NI event, type of infection, microorganisms resistance, and type of microorganism were entered in the model predicting ECMO death as a time-dependent variable.

In the multivariable models, variables found to be statistically significant in the univariable model (i.e., year of hospitalization, age, and first infectious event) were considered as covariates.

The distributions of microorganisms identified in the first NI, as well as the median and interquartile range of the total number of days of ICU, ECMO, and mechanical ventilation were showed in strata of type of infection for descriptive purpose.

Statistical significance was defined as p less than 0.05. Analyses were performed using SAS 9.4 (SAS Institute, Cary,

NC), JMP 11 statistical (SAS, Cary, NC), and Sigmaplot 12.0 (Systat Software, San Jose, CA) software.

RESULTS

From January 2010 to November 2015, 105 patients were treated with ECMO at the General ICU of San Gerardo Hospital (Monza, Italy). Ninety-two subjects (median age, 48.5 yr; 63% male) were included in the analysis. Thirteen patients were excluded for the following reasons: one died less than 24 hours from ICU admission; 10 had a documented NI prior to ECMO start; in two cases, medical records were not available.

The 92 included subjects underwent 2,223 ECMO-days (14 [8–27] d) and 3,319 days of IMV (25 [12–44] d) during a total of 3,458 ICU-days (26 [14–47] d). Patients' characteristics, comorbidities, and indications for ECMO support are summarized in **Table 1**. All but a single patient underwent IMV during ECMO. In all patients, percutaneous peripheral cannulation was performed. The most frequent indication for ECMO initiation was acute respiratory distress syndrome (ARDS), diagnosed in 72 patients (78%). In 52% of these patients, primary ARDS was caused by community-acquired pneumonia, which was due to viral causes in 48% of the cases (with influenza A/H1N1 being the most common pathogen) and of bacterial etiology in 38% of the cases. Overall, 71% of the patients had a primary infection at admission (**Table S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/C779). At the time of ECMO start, all patients were receiving antibiotics.

Fifty-two subjects (55%) developed an NI during their ECMO course. A total of 1,032 infection-free ECMO days were observed, corresponding to an IR of the first NI of 50.4 infections/1,000 ECMO-pd. Infections occurred at a median of 18.5 (11.2–29) days after hospital admission, 14 (8–22) days postintubation, and 9 (4–18.5) days after ECMO start. The cumulative probability of being infection-free was 49% (95% CI, 35–60%) after 14 days of ECMO (**Fig. 1**). Twenty-nine patients (56% of the infected patients) suffered a recurrent NI following the first episode (maximum 10 episodes in a single patient), for a total of 100 subsequent infections.

Age was the only variable independently associated with the risk of NI using the multivariate Cox regression analysis (for further details, see **Table S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/C779): the NI IR/ECMO-pd was significantly higher in younger patients. Patients in the first quartile of age (2–35 years old) developed 93 infections/1,000 ECMO-pd, compared with 35 and 41 infections/1,000 ECMO-pd observed in patients of the second (36–49) and third (50–56) quartiles of age, respectively. Among the other variables, longer IMV (> 3 d) prior to ECMO connection and non-VV ECMO setup were shown to have higher, but not significant, HR estimates: 1.72 (0.98–3.01) and 1.82 (0.70–4.74), respectively.

Microorganisms causing the first NI and the IR of each NI type are listed in **Table 2**. VAP due to G– bacteria (especially nonfermenting organisms) was the most common cause of infection. NIs due to MDR bacteria occurred in 24 cases (56%) of all bacterial infections. Infections due to G+ bacteria

TABLE 1. Patients' and Treatment Characteristics at the Extracorporeal Membrane Oxygenation Connection (*n* = 92)

Patients' and Treatment Characteristics	Median or Frequency
Age (yr)	48.5 (37–56)
Gender (male), *n* (%)	58 (63)
Weight (kg)	70 (65–85)
Charlson Comorbidity Index	1 (0–3)
Major comorbidities, *n* (%)	
Active smoke	26 (28)
Immunomodulating therapies[a]	22 (24)
Hematologic malignancies	13 (14)
COPD	10 (11)
Hepatopathy	10 (11)
Coronary artery disease	9 (10)
Diabetes	7 (8)
AIDS	3 (3)
Transferred from peripheral hospital, *n* (%)	76 (82)
Transferred while on ECMO support, *n* (%)	58 (63)
Diagnosis at admission, *n* (%)	
Acute respiratory distress syndrome	72 (78)
Cardiogenic shock	6 (7)
Asthma	4 (4)
COPD exacerbation	4 (4)
Septic shock	4 (4)
Other	2 (2)
Infection at admission, *n* (%)	65 (71)
Autoimmune disease, *n* (%)	8 (9)
Simplified Acute Physiology Score II	37 (32–47)
Sequential Organ Failure Assessment score	8 (6–11)
$Pao_2/Fio_2 < 100$ mm Hg, *n* (%)	70 (76)
ECMO duration (d)	14 (8–27)
Veno-venous ECMO, *n* (%)	80 (87)
Low flow extracorporeal carbon dioxide removal, *n* (%)	8 (9)
Femo-femoral cannulation, *n* (%)	76 (83)
ECMO circuits	2 (1–4)
IMV duration (d)	25 (12–44)
IMV duration prior to ECMO connection (d)	2 (1–6)
RRT during ECMO course, *n* (%)	33 (36)
RRT prior to ECMO connection, *n* (%)	15 (16)

COPD = chronic obstructive pulmonary disease, ECMO = extracorporeal membrane oxygenation, IMV = invasive mechanical ventilation, RRT = renal replacement therapy.

[a]Including high-dosage corticosteroids, immunosuppressants or both.

Data are presented as absolute frequency (% of the included patients) or as median and interquartile range.

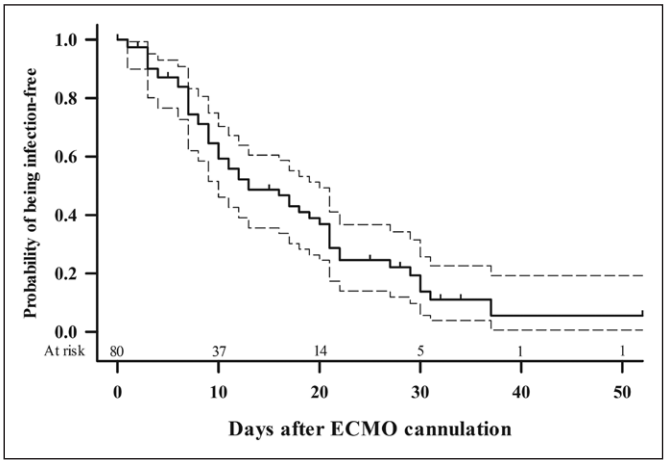

Figure 1. Probability of being infection-free. Kaplan-Meier estimates of the unadjusted cumulative probability of being infection-free (*bold line*). *Stacked bands* represent 95% CI of the cumulative probability, *tick marks* represent censored patients. ECMO = extracorporeal membrane oxygenation.

developed earlier than those due to G– (7.5 vs. 18 d postintubation, $p = 0.004$ and 4 vs. 13 d from ECMO connection, $p = 0.007$) (**Fig. S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C779). However, the onset of NI did not differ between VAP, UTI, BSI, and CRBSI (**Table S4**, Supplemental Digital Content 1, http://links.lww.com/CCM/C779) as well as between MDR and non-MDR infections. Among the patients' characteristics at admission, older age, infection at admission, and RRT prior to ECMO connection were associated to a higher incidence of MDR infections ($p = 0.03$, $p = 0.04$, and $p = 0.02$, respectively) (for further details, see **Table S5**, Supplemental Digital Content 1, http://links.lww.com/CCM/C779). Recurrent infections were mostly VAP due to G– bacteria or fungal pathogens (for further details, see **Table S6**, and **S7**, Supplemental Digital Content 1, http://links.lww.com/CCM/C779).

Forty-nine (92%) of the 52 patients who developed an NI were receiving an antibiotic therapy on the day positive cultures were collected. In 24 cases (46%), antimicrobial therapy

TABLE 2. Microorganisms of First Nosocomial Infections

Gram Staining	Microorganism	Ventilator-Associated Pneumonia	Urinary Tract Infection	Blood Stream Infection	Catheter-Related Blood Stream Infection	Overall	Multidrug Resistant
Number (% of the included patients)		32 (35)	8 (9)	5 (5)	3 (3)	52 (56)	24 (46)
Incidence (No. of infections/1,000 extracorporeal membrane oxygenation days)		31.0	7.8	4.8	2.9	50.4	23.2
G–, *n* (%)		20 (63)	1 (13)	1 (20)	1 (33)	25 (48)	15 (60)
	Acinetobacter baumannii	7 (22)	1 (13)	1 (20)		9 (17)	7 (77)
	Pseudomonas spp.	4 (13)				6[a] (12)	4 (67)
	Enterobacteriaceae[b]	4 (13)				4 (8)	1 (25)
	Klebsiella pneumoniae	3 (10)			1 (33)	4 (8)	3 (75)
	Other	2 (6)				2 (4)	
G+, *n* (%)		6 (19)	4 (50)	4 (80)	2 (67)	18[c] (35)	9 (50)
	Enterococcus spp.		4 (50)	3 (60)	1 (33)	8 (15)	4 (50)
	Staphylococcus aureus	5 (17)		1 (20)		6 (12)	3 (50)
	Coagulase-negative *Staphylococci*				1 (33)	1 (2)	1 (100)
	Other	1				3[c] (6)	1 (33)
Fungal[d], *n* (%)		6 (19)	3 (38)			9 (17)	NA
	Aspergillus spp.	6 (19)				6 (12)	NA
	Candida spp.		3 (38)			3 (6)	NA

NA = not applicable.

[a]Including one pulmonary catheter and one extracorporeal membrane oxygenation cannula insertion-site infections.

[b]All Enterobacteriaceae except for *Klebsiella pneumoniae*.

[c]Including two *Clostridium difficile* colitis.

[d]Antifungal resistance pattern were not performed uniformly.

Data are presented as absolute frequency (% of the subgroup).

was empirically changed immediately after collection of the specimen (i.e., without waiting for the results of the cultures), whereas in the remaining 28 cases (54%), the treatment was modified when the results of the cultures became available. Antimicrobial therapies for the first NIs are detailed in **Table S8** (Supplemental Digital Content 1, http://links.lww.com/CCM/C779).

Twenty-nine of the included patients (31.5%) died; overall death rate was of 13.0 deaths/1,000 ECMO-pd. Infected patients had a significantly higher mortality rate than noninfected ones (40.4% vs. 20.0%; $p = 0.037$). Similarly, infected patients had longer ICU LOS (32.5 [19.5–78] vs. 19 [10.5–27.5] d; $p = 0.003$), prolonged duration of IMV (36.5 d [20–80.5] vs. 16.5 [9–25.5]; $p < 0.001$), and ECMO (25.5 d [10.75–54] vs. 10 [5–13]; $p < 0.001$), see **Figure 2**. Seventeen (58%) of the patients with multiple infections died. Furthermore, each infection increased the odds of death by 1.50 (1.13–2.09) ($p = 0.003$). The multivariable Cox regression analysis was used to identify independent risk factors for death. Several clinical variables were independently associated with a higher mortality risk (**Table 3**). Specifically, older age (> 50 yr old) (HR up to 8), reason for ECMO initiation other than ARDS (HR = 3.54), higher SAPS II at admission, diagnosis of VAP (HR = 3.14), and infection due to MDR bacteria (HR = 2.99) were significantly associated with an increased risk of death. Interestingly, patients admitted in the years 2014 and 2015 had a lower death rate (HR, 0.35).

DISCUSSION

In this study, we retrospectively analyzed incidence, microbial etiology, risk factors, and impact on patients' outcome of NI in a large cohort of patients receiving ECMO for refractory respiratory and/or cardiac failure.

Our results confirm the high incidence of infections during ECMO: more than half of our patients (55%) had at least one NI episode. The IR of infections in our cohort (50.4 per 1,000 ECMO-pd) is within the range previously described in literature (from 11.9 to 75.5 cases/1,000 ECMO d) (4, 5). However, this comparison is affected by important differences with previous studies, concerning study design and statistical methods, diagnostic criteria, infection control policies, case-mix, ECMO management (i.e., VV-ECMO vs. VA-ECMO, cannulation site and technique). Importantly, our analysis was based on the first incidence of infection and thus we were able to calculate the infection rate and the infection-free ECMO days (i.e., the "actual" at-risk period). However, we also performed a descriptive analysis of reinfections: infected patients had a high risk of recurrent infections that were very frequently due to MDR germs and associated with high mortality. Indeed, each infection significantly increased the odds of death by 1.5. Our patient population was quite homogeneous: all patients had a medical disease, and no surgical (postcardiothomy) patients were included in the study. The vast majority of the patients (87%) received VV-ECMO for ARDS, and all patients had peripheral percutaneous cannulation. Of note, no patient underwent emergency cannulation and connection to ECMO for extracorporeal resuscitation following cardiac arrest. These are major differences with recent studies (4, 5, 14–16) that included a majority of patients on VA-ECMO and a significant proportion of surgical patients requiring central cannulation.

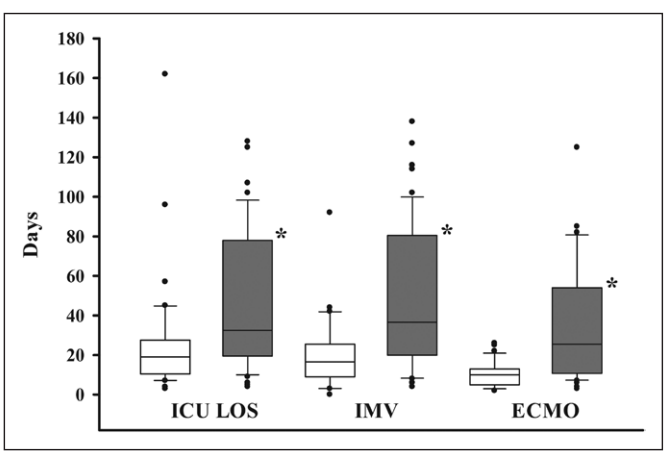

Figure 2. ICU length of stay (LOS), days of invasive mechanical ventilation (IMV), and extracorporeal membrane oxygenation (ECMO). Box and whisker plot of the ICU LOS, IMV, and ECMO of infected (*green boxes*) and noninfected (*white boxes*) patients. Data are presented as the median (*horizontal line in box*) with interquartile range (*top and bottom of box*), 10th and 90th percentiles (*whiskers*) and outliers (*black dots*). *$p < 0.05$ versus noninfected patients.

Many studies reported a clear association between the risk of NI and ECMO duration (5, 14, 17); however, the presence of an infectious complication may cause prolongation of ECMO support. In our study, patients developing an infection had more than double duration of ECMO and IMV and almost double ICU LOS. By means of the survival analysis, we confirmed that the probability of remaining NI-free decreased with the increase in time spent on ECMO: more than half of the patients on ECMO for 2 weeks developed NI. Among the patients' characteristics at admission, only younger age was significantly and independently associated with an increased risk of NI. These results may be skewed due to the inclusion of four young asthmatic patients, who received high doses of steroids and developed NI earlier than the other patients. This finding differ from previous reports (17), which described an increased risk of NI in older patients, but did not adjust the analysis for comorbidities or severity scores, possibly biasing the results against older (and sicker) patients. It is important to underline that in our patient population two other variables (duration of IMV before ECMO > 3 days and ECMO configuration other than VV) showed very high HR estimates for risk of NI but did not reach statistical significance probably due to the limited sample size. Of note, we chose a cutoff of 3 days of IMV prior to ECMO initiation (compared with 7 days as reported in previous literature), given that 3 days was the median duration of IMV prior to ECMO. Indeed, in our institution, we rarely cannulate a patient ventilated for more than 7 days.

The clinical diagnosis of infection in ECMO patients is challenging, since they invariably have signs of systemic inflammatory response, possibly triggered by ECMO itself and fever

TABLE 3. Cox Regression of the Independent Risk Factors Associated to Death

Characteristics	Ranges	Number of Patients	Dead Patients (%)	Death Rate of Infection (Death/1,000 ECMO Patient Days)	Adjusted Hazard Ratio (95 CIs)
Age (yr)	2–35	22	5 (23)	8 (5–19)	1
	36–49	26	7 (27)	16 (8–33)	3.69 (0.90–15.12)
	50–56	24	7 (29)	13 (6–27)	**5.24 (1.24–22.16)**
	58–76	20	10 (50)	23 (12–43)	**8.77 (2.15–35.77)**
Gender	Female	34	8 (23)	14 (7–28)	2.28 (0.89–5.87)
	Male	58	21 (37)	13 (8–19)	1
Years	2010–2011	27	12 (44)	21 (12–37)	1
	2012–2013	29	11 (38)	13 (7–24)	0.69 (0.27–1.77)
	2014–2015	36	6 (16)	7 (3–16)	**0.35 (0.12–0.99)**
Active smoke	Yes	26	5 (19)	10 (4–24)	0.55 (0.17–1.75)
	No	66	24 (36)	14 (9–21)	1
Charlson Comorbidity Index	0–1	49	12 (24)	10 (6–18)	1
	2–3	21	6 (28)	12 (5–27)	0.65 (0.21–2.00)
	4–10	22	11 (50)	20 (11–36)	1.39 (0.57–3.75)
Diagnosis at admission	Acute respiratory distress syndrome	72	24 (33)	12 (8–17)	1
	Other	20	5 (25)	35 (14–83)	**3.54 (1.09–11.56)**
Infection at admission	Yes	65	20 (30)	13 (8–19)	1.23 (0.49–3.08)
	No	27	9 (33)	14 (7–26)	1
Transferred from peripheral hospital	Yes	76	21 (28)	11 (7–53)	1.05 (0.37–2.98)
	No	16	8 (50)	27 (13–56)	1
Ventilation before ECMO connection	≤ 3 d	60	14 (23)	14 (08–24)	1
	> 3 d	32	15 (47)	12 (7–20)	1.01 (0.43–2.30)
ECMO setup	Veno-venous	80	24 (30)	12 (8–18)	1
	Other	12	5 (41)	23 (10–56)	1.38 (0.46–4.16)
Simplified Acute Physiology Score II	17–33	27	7 (27)	9 (4–18)	1
	34–40	30	10 (33)	14 (7–25)	2.58 (0.70–9.58)
	41–77	29	11 (38)	20 (11–36)	3.58 (0.82–15.50)
Sequential Organ Failure Assessment score	2–6	31	9 (29)	11 (6–21)	1
	7–9	28	7 (25)	10 (5–20)	0.87 (0.27–2.77)
	10–18	33	13 (39)	19 (11–32)	2.06 (0.81–5.24)
Pao_2/Fio_2 (mm Hg)	< 100	70	22 (31)	12 (8–18)	0.75 (0.29–1.95)
	> 100	22	7 (31)	17 (8–37)	1
Renal replacement therapy prior to ECMO connection	Yes	15	7 (46)	13 (6–28)	1.08 (0.40–2.93)
	No	77	22 (28)	13 (9–20)	1
Infected	Yes	52	21 (40)	18 (15–27)	2.40 (0.90–6.42)
	No	40	8 (20)	8 (4–15)	1

(*Continued*)

TABLE 3. (*Continued*). Cox Regression of the Independent Risk Factors Associated to Death

Characteristics	Ranges	Number of Patients	Dead Patients (%)	Death Rate of Infection (Death/1,000 ECMO Patient Days)	Adjusted Hazard Ratio (95 CIs)
Type of infection	VAP	32	13 (40)	19 (11–33)	**3.14 (1.09–9.00)**
	Other	20	8 (40)	16 (8–31)	1.82 (0.60–5.50)
	No infection	29	8 (27)	8 (4–15)	1
Microorganism	G–	25	9 (36)	17 (9–32)	2.76 (0.86–8.86)
	G+	18	6 (33)	20 (9–44)	2.44 (0.79–7.54)
	Fungal	9	6 (66)	17 (8–38)	1.88 (0.49–7.26)
	No infection	29	8 (27)	8 (4–15)	1
Resistance pattern	MDR	23	10 (43)	23 (12–42)	**2.99 (1.06–8.42)**
	Non-MDR	20	5 (24)	13 (5–30)	1.80 (0.49–6.69)
	Fungal	9	6 (66)	23 (12–42)	1.76 (0.46–6.81)
	No infection	29	8 (27)	8 (4–15)	1

ECMO = extracorporeal membrane oxygenation, MDR = multidrug resistance.

Data are presented as absolute frequency (of the subgroup), crude death rate, and hazard ratio with 95 CIs adjusted for age, year, and infected status. Boldface values indicate statistically significant results.

is often nonapparent since body temperature is controlled by ECMO heat exchanger. For this reason, we analyzed only microbiologically confirmed infections: all positive cultures have been reviewed by experienced intensivists and infectious disease specialists, and the diagnosis of infection was based on rigorous criteria described previously.

We found that G– infections occur significantly later than G+ infections. The shift from G+ to G– bacteria can be possibly due to increasing antimicrobial exposure, intestinal microbiota selection during the hospital stay (18), and gut mucosal barrier impairment (19, 20). To the best of our knowledge, this is the first study describing the pattern of antimicrobial resistance of microorganisms infecting ECMO patients. We observed a very high incidence of infections caused by MDR bacteria, especially G– nonfermenting germs causing VAP. This finding is not surprising, since ECMO patients are frequently exposed to broad-spectrum antibiotics, have an acquired or primary immunocompromise, and are hospitalized and mechanically ventilated for longer periods of time (21). Furthermore, our study included a large number of patients with influenza A-H1N1 pneumonia, in whom the incidence of MDR bacterial superinfections is known to be very high (6). The higher incidence of infections due to G– bacteria and the pattern of antibiotic resistance confirmed a trend already described in recent studies in ICU patients (22, 23). Interestingly, we did not observe CRBSI caused by *Candida spp.* This may be due to an appropriate management of catheters that prevented previously described yeast-associated CRBSI (24). As recently described (25), we observed a high incidence of invasive pulmonary aspergillosis even in subjects without classical risk factors for *Aspergillus spp.* infections, suggesting a possible causative role of ECMO per se in favoring mold infections. Larger studies are needed to investigate fungal infections during ECMO.

We observed a significant association between occurrence of NI and death rate: in our patient population, infected patients, in particular with VAP, had more than double chance of dying compared with noninfected ones. Other factors independently associated with death were older age, a diagnosis other than ARDS, and higher SAPS at admission. Importantly, our study is the first to report a significant association between infections (in particular VAP) caused by MDR organisms and mortality during ECMO: patients developing an MDR infection had three times higher odds of death than noninfected subjects. Of note, MDR infections were more frequent in older, infected, and dialyzed patients. The effect of MDR infections on mortality of critically ill patients is controversial; only a few studies showed a significant association with an increased risk of death (22, 25, 26). Our results confirm that MDR infections have an important clinical impact in this fragile population. We observed a reduction in mortality during the 2014–2015 time period that may be associated to the higher number of cases of ARDS due to H1N1 influenza, which is known to be have low mortality rates (27). Indeed, 12 patients with H1N1-ARDS (of whom nine survived) were treated during the period 2014–2015, whereas only nine cases were admitted during the previous four years. The main limitation of our study is its retrospective and single-center nature limited to medical patients only, which precludes the extrapolation of the results to the general population of medical ECMO patients. In addition, it does not allow to draw any definitive conclusions with regard to the cause-effect relationship between ECMO and the risk of infection due to the lack of a control group of ARDS patients who did not receive ECMO support. Prospective, multicenter studies are necessary to evaluate the epidemiology of NIs in ECMO patients and their impact on outcomes. Such trials could help in understanding whether patients in ECMO

have an increased risk of NI in comparison with general ICU patients in order to implement specific prevention strategies in this particular population (28).

CONCLUSIONS

Our study shows that, in a homogeneous population of medical patients requiring ECMO therapy mainly for respiratory support, the incidence of NI is very high. The most common NI observed was VAP, most frequently caused by G– bacteria. Patients developing an infection had a longer duration of ECMO and mechanical ventilation, a longer ICU stay, and lower survival rates. The rate of MDR bacterial isolates was very high, and a first NI episode caused by MDR organisms was an independent risk factor for death.

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