



## INTEGRATIVE REVIEW ARTICLE

### COMPLICATIONS RELATED TO EXTRACORPOREAL MEMBRANE OXYGENATION

COMPLICAÇÕES RELACIONADAS À OXIGENAÇÃO POR MEMBRANA EXTRACORPÓREA

COMPLICACIONES RELACIONADAS CON LA OXIGENACIÓN POR MEMBRANA EXTRACORPÓREA

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#### ABSTRACT

**Objective:** to identify the complications associated with extracorporeal membrane oxygenation (ECMO) in adults, as described in the literature. **Methods:** An integrative review including articles published from 2011 to 2016, in Portuguese, English or Spanish, using standardized terms (MeSH and CINAHL titles) in the Medline and CINAHL databases. The complete titles, abstracts and texts of the articles meeting eligibility criteria were read and classified, based on the level of evidence. The complications of ECMO were grouped into: hemorrhagic, infectious, renal, vascular, mechanical, neurological, and other. **Results:** Six hundred sixty-six studies were found, of which 45 were included. The main complications identified were: hemorrhagic, in 747 individuals (21.23%), followed by infectious (10.85%), renal (9.18%), vascular (5.99%), mechanical (15%), and neurological (3.8%). **Conclusion:** The main complications of ECMO in adult patients were identified. The knowledge about them supports planning of care, avoiding complications and, thus, reducing morbidity and mortality, costs, and length of hospitalization. **Descriptors:** Adult; Cardiology; Critical Care; Nursing care; Extracorporeal membrane oxygenation; Pneumology.

#### RESUMO

**Objetivo:** identificar na literatura as complicações associadas à oxigenação por membrana extracorpórea (ECMO) em adultos. **Método:** estudo bibliográfico, tipo revisão integrativa de artigos publicados de 2011 a 2016 em português, inglês ou espanhol, nas bases de dados Medline e CINAHL utilizando-se termos padronizados (MeSH e títulos CINAHL). Os títulos, resumos e textos na íntegra dos artigos encontrados foram lidos para aplicação dos critérios de elegibilidade e classificação do nível de evidência. As complicações da ECMO foram agrupadas em hemorrágicas, infecciosas, renais, vasculares, mecânicas, neurológicas e outras. **Resultados:** foram encontrados 666 estudos, dos quais 45 foram incluídos. As principais complicações identificadas foram: as hemorrágicas, encontradas em 747 indivíduos (21,23%), seguidas das infecciosas (10,85%), renais (9,18%), vasculares (5,99%), mecânicas (4,15%) e neurológicas (3,8%). **Conclusão:** identificaram-se as principais complicações da ECMO em pacientes adultos. Conhecê-las subsidia o planejamento do cuidado prestado, podendo evitá-las ou diagnosticá-las precocemente, diminuindo assim, a morbimortalidade, custos e tempo de internação. **Descriptores:** Adulto; Cardiología; Cuidados Críticos; Cuidados de Enfermagem; Oxigenación por Membrana Extracorpórea; Pneumología.

#### RESUMEN

**Objetivo:** identificar en la literatura las complicaciones de la oxigenación de membrana extracorpórea (ECMO) en adultos. **Método:** estudio bibliográfico de revisión integradora con artículos publicados desde 2011 hasta 2016 en portugués, inglés o español, en MEDLINE y CINAHL utilizando términos estandarizados (MeSH y CINAHL). Se leyeron Los títulos, resúmenes y textos en su totalidad de los artículos encontrados para aplicación de los criterios de elegibilidad y clasificación del nivel de evidencia. Se agruparon las complicaciones de la ECMO en hemorrágicas, infecciosas, renales, vasculares, mecánicas, neurológicas y otras. **Resultados:** se encontraron 666 estudios, de los cuales se incluyeron 45. Las principales complicaciones identificadas fueron: las hemorrágicas, encontradas en 747 individuos (21,23%), seguidas de las infecciosas (10,85%), renales (9,18%), vasculares (5,99%), mecánicas (4, 15%) y neurológicas (3,8%). **Conclusión:** se identificaron las principales complicaciones de la ECMO en pacientes adultos. Conocerlas subsidia la planificación del cuidado prestado, pudiendo evitarlas o diagnosticarlas precozmente, disminuyendo así, la morbimortalidad, costos y tiempo de internación. **Descriptores:** Adulto; Cardiología; Cuidados Críticos; Atención de Enfermería; Oxigenación por Membrana Extracorpórea; Neumología.

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## INTRODUCTION

Ischemic heart and cerebrovascular diseases are among the circulatory diseases, those with leading causes of death in developed and developing countries, respectively.<sup>1</sup>

According to Department of Informatics of the Unified Health System (DATASUS-Departamento de Informática do Sistema Único de Saúde), deaths caused by the diseases of the circulatory system (DCS), in 2011, occurred in approximately 335,000 people in Brazil, the majority of whom were male (52.25%), and increasing in proportion to age.<sup>2</sup> However, recent studies have shown that there has been a decrease in mortality from DCS in Brazil and in industrialized countries. This fact can be associated with improvements in the socioeconomic conditions of the population, as well as an advance in controlling risk factors with therapeutic interventions.<sup>3-4</sup>

Among these advances, extracorporeal life support (ECLS) has been progressively implemented in the adult population.<sup>5-6</sup> Extracorporeal Membrane Oxygenation (ECMO) is a form of cardiopulmonary support used to provide pulmonary and/or cardiac support, when one or both organs are affected, aiming to maintain tissue perfusion while awaiting recovery of the affected organ. Therefore, it can be used as an intermediary for recovery, as well as for transplantation, or for other types of longer-term devices.<sup>7</sup>

This type of device prevents the affected organ from suffering additional damage due to high doses of inotropes, vasopressors, and high ventilatory parameters. In addition, this treatment model can provide biventricular and pulmonary support, different from other types of ventricular care, and is easier and faster to set up, and has a lower cost.<sup>8</sup>

A randomized controlled trial in 2009, called the Conventional Ventilatory Support vs Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR trial), found eloquent results in relation to ECMO, demonstrating better survival compared to conventional treatment (63% vs 47%).<sup>6</sup> Recent data from the Extracorporeal Life Support Organization (ELSO - January 2017) show that approximately 11,000 patients with heart problems in the past year benefited from ECMO, with a 56% survival. This reflects how much this type of intervention has favored the treatment of these patients.<sup>9</sup>

ECMO is an invasive device with high complexity and specificity; however, although there are many advantages, it is not free of

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complications. Among the patients with indication for ECMO, specifically due to cardiogenic shock and cardiac arrest, the most frequent complications identified were vascular, neurological, renal, bleeding, and infection, with renal failure being the most prominent.<sup>10</sup> Thus, nurses must know the complications of ECMO in different populations, in order to promote a planning of care that prevents or treats them early.

## OBJECTIVE

- To identify the complications associated with ECMO in adults.

## METHOD

This was an integrative review based on the following steps: problem identification, literature search, data assessment, data analysis, and presentation of results.<sup>11</sup>

**Problem identification:** conducted using a research question formulated using the PICO strategy - P (patient): adults; I (interest factor): use of ECMO; C (comparison): not applicable; O (outcome): complications). Thus, the guiding question was "What are the complications related to ECMO in adult patients?"

**Literature search:** This was conducted in the Medline and CINAHL databases, in March of 2017, using the standardized term (MeSH/Title CINAHL) "Extracorporeal Membrane Oxygenation" and the non-standard terms "ECMO" and "complications". The search strategy used was (((Extracorporeal Membrane Oxygenation [MeSH Terms]) OR ECMO)) AND complications)).

The published articles included were from 2011 to 2016, published in Portuguese, English or Spanish, which studied adult patients who underwent ECMO for a cardiac and/or pulmonary indication. The articles that investigated complications associated with other types of devices in addition to ECMO, and narrative reviews of the literature, were excluded.

**Data assessment:** The selection of the articles first accomplished by reading the titles and abstracts. Those that met the eligibility criteria were read in full to determine inclusion or exclusion in the study. Among the selected studies, the following data were extracted: country/year of publication, type of study, population studied, sample size, and complications identified.

**Data analysis:** The articles were classified according to the level of evidence. The hierarchical pyramid of evidence was used for categorization and to classify the studies as

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follows: Level I - studies that group evidence of multiple systematic reviews, also known as Overviews of Systematic Reviews (OoRs);<sup>12</sup> Level II - systematic reviews with or without meta-analysis; Level III - randomized clinical trials or mega trials, in which the number of patients exceeds one thousand cases; Level IV - randomized clinical trials, in which patient numbers are less than one thousand; Level V - cohort studies; Level VI - case-control studies; Level VII - series of cases; VIII - case report; Level IX - expert opinion /animal experimentation/in vitro research.<sup>13</sup><sup>13</sup>

Presentation of results: ECMO complications are presented descriptively, and grouped into: hemorrhagic, infectious, renal, vascular, mechanical, neurological, and other.

## RESULTS

Six hundred sixty-six articles were found, 544 in Medline and 122 in CINAHL, with 45 articles selected for review (Figure 1); these included 3518 patients who presented some complications related to ECMO.

The studies were mostly cohort studies (n=26, 57.77%), conducted mainly in the United States (n=14, 31.1%), followed by France (n=6, 13.3%), Germany, and the United Kingdom (N=4/4, 8.8%). Only one article from

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Latin America was found. Regarding the level of evidence, most articles were classified as level V (n=26, 57.77%).

The majority of the patients had Acute Respiratory Distress Syndrome/respiratory failure (n=13, 28.8%) and, consequently, were treated with venovenous ECMO (VV-ECMO). The sample sizes ranged from one (case report) to 569 individuals.

The complications most frequently found were classified as hemorrhagic, identified in 35 studies (77.77%) and with 747 individuals (21.23%): bleeding/hemorrhage (28.91%), bleeding at the site of insertion (6.96%), excessive bleeding requiring thoracotomy or correction of hemostasis (6.42%), gastrointestinal bleeding (4.8%), hemorrhagic stroke (4.41%), bleeding at the surgical site (4.41%), cardiac tamponade (3.07%), and disseminated intravascular coagulation (DIC) (0.19%).

Infectious complications were found in 19 studies (42.22%), and in 382 (10.85%) individuals. Those classified as infectious were: infection (87.17%), pneumonia (6.80%), septicemia (2.87%), sepsis (2.61%), and septic shock (0.52%).

| Year               | Country           | Study/Sample                   | Complications                            | Population                        |
|--------------------|-------------------|--------------------------------|--|-----------------------------------|
| 2011 <sup>14</sup> | USA               | Descriptive/36                 | Vascular                                 | VA-ECMO, (femoral cannulation)    |
| 2012 <sup>15</sup> | USA               | Case report/5                  | Hemorrhagic                              | Patients with RF                  |
| 2012 <sup>16</sup> | UK                | Case report/1                  | Mechanic                                 | Patient with HF                   |
| 2012 <sup>17</sup> | USA               | Case report/1                  | Hemorrhagic                              | VV-ECMO with ARDS                 |
| 2012 <sup>18</sup> | Taiwan            | Prospective cohort/52          | Hemorrhagic                              | Refractory septic shock           |
| 2012 <sup>19</sup> | Republic of Korea | Retrospective cohort/27        | Infectious; Hemorrhagic; vascular; renal | ECMO after-AMI                    |
| 2012 <sup>20</sup> | China             | Descriptive /9                 | Hemorrhagic; infectious                  | ARDS by H1N1                      |
| 2012 <sup>21</sup> | Japan             | Retrospective cohort/98        | Hemorrhagic; vascular                    | Patients with ACS                 |
| 2013 <sup>22</sup> | France            | Descriptive/52                 | Hemorrhagic; infectious; renal           | Patients with Avalon Cannula      |
| 2013 <sup>23</sup> | UK                | Retrospective cohort/569       | Hemorrhagic                              | Patients with RF                  |
| 2013 <sup>24</sup> | France            | Cross-sectional descriptive/14 | Hemorrhagic; vascular; infectious        | Refractory septic shock           |
| 2013 <sup>25</sup> | Australia         | Retrospective cohort/139       | Infectious                               | VV and VA-ECMO more than 48 hours |
| 2013 <sup>26</sup> | Switzerland       | Retrospective cohort/15        | Hemorrhagic; infectious; renal           | Lung TX                           |
| 2013 <sup>27</sup> | Australia         | Prospective cohort/151         | Hemorrhagic; vascular; infectious        | VV and VA-ECMO                    |
| 2013 <sup>28</sup> | USA               | Retrospective cohort/101       | Vascular                                 | ECMO (femoral cannulation)        |
| 2013 <sup>29</sup> | USA               | Retrospective cohort/99        | Mechanic; renal; Hemorrhagic             | Seniors over 65 years old         |
| 2013 <sup>30</sup> | USA               | Retrospective cohort/12        | Hemorrhagic; Infectious                  | Patients with ARDS                |
| 2013 <sup>31</sup> | USA               | Descriptive /36                | Hemorrhagic; Mechanic                    | Patients with ARDS                |
| 2014 <sup>32</sup> | Germany           | Retrospective cohort/265       | Infectious; renal                        | Patients with RF in VV-ECMO       |
| 2014 <sup>33</sup> | Croatia           | Prospective                    | Mechanic                                 | ARDS by H1N1                      |
|                    |                   |                                | Hemorrhagic; Infectious;                 |                                   |

|                    |           |                                     |   |   |
|--------------------|-----------|-------------------------------------|---|---|
| 2014 <sup>34</sup> | France    | cohort/17<br>Prospective cohort/325 | Mechanic; renal<br>Hemorrhagic; Infectious  | VV and VA-ECMO                                  |
| 2014 <sup>35</sup> | USA       | Retrospective cohort/212            | Hemorrhagic; renal;<br>Vascular; Infectious | Patients with HF or RF                          |
| 2014 <sup>36</sup> | France    | Descriptive /16                     | Hemorrhagic                                 | Patients with HF                                |
| 2014 <sup>37</sup> | Hong Kong | Descriptive /31                     | Hemorrhagic; Mechanic                       | Patients with ARDS                              |
| 2014 <sup>38</sup> | USA       | Descriptive /26                     | Hemorrhagic; vascular                       | Patients in ECPR                                |
| 2014 <sup>39</sup> | UK        | Retrospective cohort/83             | Vascular                                    | VA-ECMO (femoral cannulation)                   |
| 2014 <sup>40</sup> | USA       | Interventional uncontrolled study/5 | Vascular                                    | Adults with femoral cannulation (VA-ECMO)       |
| 2014 <sup>41</sup> | UK        | Descriptive/72                      | Hemorrhagic; infectious;<br>Mechanic        | VV-ECMO (Avalon Cannula)<br>Lung TX             |
| 2015 <sup>42</sup> | Argentina | Retrospective cohort/15             | Mechanic; vascular;<br>Hemorrhagic          | Lung TX   |
| 2015 <sup>43</sup> | France    | Descriptive/36                      | Hemorrhagic; Infectious                     | VV and VA - ECMO                                |
| 2015 <sup>44</sup> | Australia | Retrospective cohort/45             | Infectious; renal; vascular;<br>Hemorrhagic | Seniors over 70 years old                       |
| 2015 <sup>45</sup> | China     | Retrospective cohort/24             | Infectious; Hemorrhagic;<br>renal; vascular | ECMO after-cardiotomy                           |
| 2015 <sup>46</sup> | USA       | Retrospective cohort/132            | Hemorrhagic                                 | VV and VA - ECMO                                |
| 2015 <sup>47</sup> | USA       | Case report/1                       | Hemorrhagic                                 | Patients with RF                                |
| 2015 <sup>48</sup> | USA       | Retrospective cohort/105            | Vascular                                    | Patients with peripheral cannulation            |
| 2015 <sup>49</sup> | Germany   | Retrospective cohort/262            | Hemorrhagic, Mechanic                       | Patients with ARDS                              |
| 2015 <sup>50</sup> | Germany   | Descriptive/10                      | Hemorrhagic; vascular                       | Patients with RF VVA-ECMO                       |
| 2015 <sup>51</sup> | Taiwan    | Retrospective cohort/6              | Hemorrhagic; Infectious;<br>renal           | VA-ECMO with PH after cardiogenic shock         |
| 2015 <sup>52</sup> | USA       | Retrospective cohort/85             | Hemorrhagic                                 | ECMO after chest trauma                         |
| 2016 <sup>53</sup> | Italy     | Retrospective cohort/57             | Renal; Hemorrhagic,<br>Infectious; vascular | Patient with myocarditis                        |
| 2016 <sup>54</sup> | China     | Case-control/29                     | Hemorrhagic; renal;<br>Infectious           | 29 - ECMO (case)                                |
| 2016 <sup>55</sup> | Italy     | Case report/6                       | Hemorrhagic                                 | Neurologic injury after ECMO                    |
| 2016 <sup>56</sup> | Italy     | Retrospective cohort/100            | Vascular                                    | ECMO with femoral cannulation                   |
| 2016 <sup>57</sup> | Germany   | Case report/1                       | Mechanic                                    | Adult without sedation after 20 days in VV-ECMO |
| 2016 <sup>58</sup> | France    | Prospective cohort/135              | Hemorrhagic                                 | VV-ECMO   |

CVA: Cerebrovascular accident; VA-ECMO: venoarterial extracorporeal membrane oxygenation; VV-ECMO: venovenous extracorporeal membrane oxygenation; VVA-ECMO: veno-veno-arterial extracorporeal membrane oxygenation; ECPR: extracorporeal cardiopulmonary resuscitation; PH: pulmonary hypertension; AML: acute myocardial infarction; HF: heart failure; RF: respiratory failure; CA: cardiac arrest; ARDS: acute respiratory distress syndrome; ACS: acute coronary syndrome.; Tx: transplantation.

**Figure 1.** Distribution of articles, according to year, country, type of study, complications, population, and sample. São Paulo (SP), Brazil, 2017.

Regarding renal complications, 323 individuals (9.18%) presented with some renal injury, and were identified in 12 articles (26.66%). The complications were: acute renal failure (23.21%), with or without the need for hemodialysis.

Vascular and mechanical complications were identified in 211 (5.99%) and 146 (4.15%) individuals, respectively. The vascular complications were: limb ischemia (30.80%), fasciotomy (2.84%), lower limb amputation (2.36%), compartment syndrome (0.94%), permanent peripheral neuropathy (0.47%), superior vena cava thrombosis (0.02%), and

jugular vein thrombosis (0.02%). The mechanical complications were specified as failure in the oxygenator, in the oxygenator membrane (OM) or in the pump (47.94%), exchange of OM or circuits (40.41%), cannula displacement (9.58%), and mechanical complications (2.05%).

Neurological complications were identified in 135 individuals (3.8%): ischemic stroke (8.8%), seizures (1.4%), hypoxic encephalopathy (1.4%), and brain death (2.2%).

Other complications identified in the studies were: multiple organ failure (4.06%),

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hepatic dysfunction (2.92%), cardiorespiratory arrest (2.75%), arrhythmias (0.96%), hemolysis (0.90%), and pneumothorax (0.31%).

## DISCUSSION

Extracorporeal membrane oxygenation contributes to the treatment of patients who no longer respond to the conventional therapeutic approach, however the complications must be quickly recognized by a specialized multiprofessional team.<sup>59</sup>

This review showed that most of the researches were cohort studies, with a high level of evidence, as this type of study is very relevant when the causes and risk factors must be evaluated, and associations of cause and effect are necessary.<sup>60</sup>

Among the complications identified, the most prevalent was bleeding, which was independent of the indication, cardiac and/or pulmonary (VV-ECMO or VA-ECMO). On average, 20% of hemorrhagic complications occur at the surgical site or cannula insertion, and are easier to control compared to other bleeding sites (gastrointestinal, intracranial and pulmonary), with less severe consequences that are reversible. This high prevalence is explained by the difficulty in determining the ideal level of anticoagulation, which can trigger both thrombosis and excessive bleeding.<sup>61</sup>

The nurse should pay attention to factors predictive of bleeding, such as the use of pre-ECMO antiplatelet and/or antithrombotic medications in the postoperative period; presence of renal and/or hepatic failure due to cardiogenic shock; and/or use of prohemostatic medications to reverse a bleeding that is difficult to control during the surgery. All these factors must be evaluated because the circuit of the device causes a generalized inflammatory and prothrombotic response, leading to activation and platelet aggregation on the circuit surface, inducing thrombocytopenia, and consequently increasing the chance of bleeding.<sup>61</sup>

The second most prevalent complication was infection, because of the multiple invasive devices to which the patient is subjected, such as central venous catheters, hemodialysis, and cannulation for ECMO.<sup>25</sup> Recent studies show a mortality rate of approximately 31% in patients who present any infection during ECMO treatment, and the risk can be related to the length of time in ECMO, its indication, and an elevated serum creatinine level.<sup>62-63</sup>

The main infections identified in these individuals were respiratory and bloodstream infections; the mortality rate increases with

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ARDS, the Simplified Acute Physiology Score II (SAPS II), multiresistant pathogen infection, and/or ventilator-associated infection.<sup>25,62-63</sup>

A recent study identified sepsis as the main cause of acute renal failure, and of the need for renal replacement therapy. Other causes include the use of nephrotoxic drugs/contrast, hepatorenal syndrome, major surgery, and cardiogenic shock:<sup>64</sup> conditions to which the patient treated with ECMO is submitted.

In addition, acute renal failure may be an independent risk factor for mortality in patients treated with ECMO, and the need for renal replacement therapy and its duration may increase mortality, showing a lower rate of survival in these patients.<sup>65</sup>

Treatment with ECMO may contribute to acute renal failure, because of several factors associated with the therapy. The continuous flow of the device, the systemic inflammatory response, and hormonal variables, such as the alteration in the renin-angiotensin-aldosterone system, do not allow for adequate renal tissue perfusion, resulting in renal injury.<sup>66</sup>

Retrospective studies analyzed the proportion of vascular complications in patients undergoing ECMO, and showed that lower limb ischemia, especially in those with cardiovascular indications, were highlighted. On average, 20% of these patients developed some peripheral vascular complication.<sup>28,39,67</sup> A variety of risk factors, such as hypertension, dyslipidemia and smoking, failed to influence mortality or development of these complications. However, among the diabetic patients, the mortality was 58% higher than in the non-diabetics.<sup>28,39,56</sup>

Hemodynamic aspects, such as vasoconstriction caused by high levels of catecholamines, low systolic blood pressure, and non-pulsatile flow, may also influence the progression of ischemia. Other reasons for this complication are the cannula diameter, coagulopathy, and even the injury caused by the cannulation procedure itself.<sup>28,39,56</sup>

Nurses should periodically assess body temperature, skin color, pain, pulses, and peripheral perfusion, to identify these complications early. Doppler ultrasound of the lower limbs should be performed every 4 hours, if possible.<sup>28,39</sup>

The main therapeutic intervention adopted to improve distal limb perfusion is retrograde cannulation, which improves the distal perfusion of the affected limb. It is the placement of a smaller caliber cannula, usually 6 to 9 Fr, in the femoral artery, but following the opposite flow of the arterial

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cannulation, with the aim of maintaining the distal perfusion of the affected limb.<sup>39,56</sup>

The complications identified less frequently in the articles were mechanical failures. The role of the ECMO specialist is to assist the patient, and he must know the device circuit in detail, checking it constantly in order to prevent potential complications.<sup>59</sup> The ECMO system must therefore be verified several times, according to the protocol of the institution. Mechanical complications are related to problems in the pump, the cannula, and the oxygenator membrane; for each component, an action must be taken.

Emergency equipment must be always available. A crank can replace the pump in the event of a failure, and must always be available and easily accessible. The nurse must be aware of the transmembrane pressure gradient, because when the pressure rises, this provides an early warning of oxygenator membrane failure due to the formation of thrombi. However, if this occurs acutely, bending can obstruct the tube, which can be easily solved.<sup>67</sup>

Considering the wide range of complications identified in this review, the nurse must have the expertise to enable early identification in order to provide adequate and safe care for the patient, in addition to preventive measures, which avoid possible complications.

The results of this review are limited by the period of publication, and the publication languages to which it was restricted, as well as the databases selected. However, the last five years of publication are considered the state of the art for the health sciences, and English-language publications, and Medline and CINAHL databases, include important studies for the scientific community.

## CONCLUSION

The main complications of ECMO in adult patients, regardless of the indication, were hemorrhagic, infections, vascular complications, and mechanical problems associated with the device.

A well-trained and specialized multidisciplinary team is needed, and the nurse is highlighted because she/he will be at the forefront of any identified problem, delivers alerts to the staff members, and therefore promotes better treatment results. Knowing the complications that contribute to planning the care provided, the nurse can aim to avoid or identify them early, and can reduce morbidity, mortality, costs, and length of stay.

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Submission: 2017/12/06

Accepted: 2018/04/19

Publishing: 2018/06/01

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