

# ECMO for Pulmonary Hemorrhage Secondary to Leptospirosis

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## KEY MESSAGE

- There is an increasing morbidity and mortality from leptospirosis in the Philippines. One of the most fatal sequelae of the disease is pulmonary hemorrhage<sup>1</sup>.
- There is limited evidence on the use of extracorporeal membrane oxygenation (ECMO) for leptospirosis. There are no randomized controlled trials that can provide evidence on the effectiveness of ECMO in these patients. The review found only 7 case reports which showed survival in 6 out of 7 cases<sup>18-24</sup>.
- Currently, there are no recommendations on the use of ECMO for pulmonary hemorrhage secondary to leptospirosis in local and international guidelines<sup>12</sup>.
- ECMO is a resource intensive therapy<sup>24</sup>; the high cost can be a major issue affecting feasibility and applicability.

## CONTEXT

### *Background of the disease*

- Leptospirosis is a spirochetal zoonosis that usually occurs in tropical countries such as the Philippines<sup>1</sup>.
- Humans are infected by direct contact with infected animal urine or tissues, or by indirect exposure with urine-contaminated soil or water<sup>2</sup>.
- It usually affects economically vulnerable populations such as people living in slums and rural farmers<sup>3</sup>, especially during heavy rainfall and flooding<sup>4</sup>.

### *Epidemiology of the Disease*

- A study by Costa et al.<sup>4</sup> showed that there are 55.54 (20.32 to 99.53) cases of leptospirosis per 100,000 population annually in South-East Asia, the highest in all the regions included.
- Philippine data shows an annual morbidity estimate of 1 to 10 cases per 100,000 population<sup>5,6</sup>. The Epidemiology Bureau of the Department of Health also reported that there was a total of 2,495 cases and 261 deaths from leptospirosis reported from January 1 to December 2, 2017. They are 49.1% and 65.9% higher, respectively, compared to the same period in 2016<sup>6</sup>. More recent data from January to June 2018 showed 1,467 cases and 153 deaths<sup>7</sup>.

### *Severity of the disease*

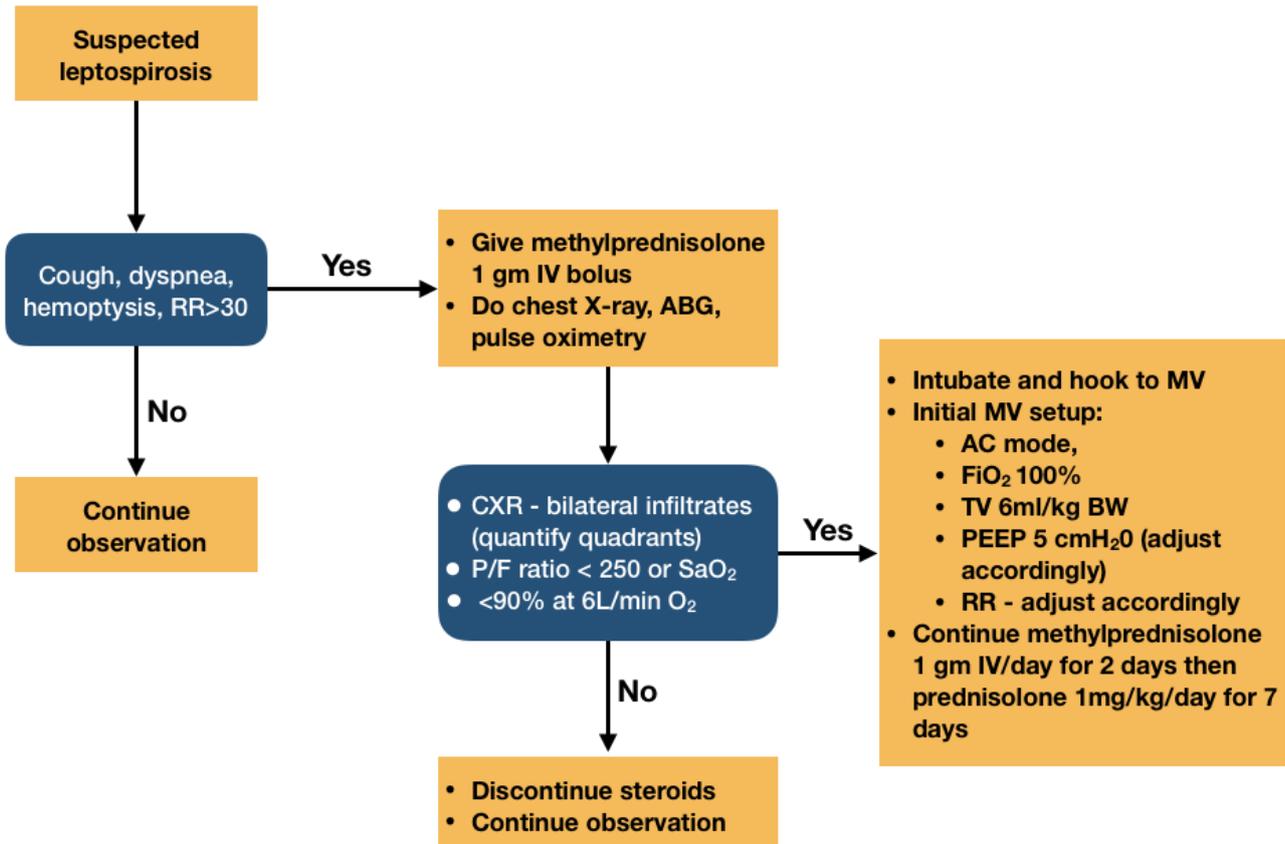
- The bacteria invade the internal organs by way of the bloodstream eventually causing damage<sup>2</sup>.
- Severe leptospirosis is highly fatal; it can lead to severe gastrointestinal bleeding, meningitis, acute renal, and pulmonary failure with multisystem disease<sup>3,4</sup>.
- Pulmonary involvement occurs in 20% to 70% of cases. While most cases are mild<sup>8</sup>, those that develop to severe pulmonary hemorrhage has a mortality rate of at least 50%<sup>4</sup>.

## *Extracorporeal membrane oxygenation*



- ECMO is a treatment used to provide temporary cardiopulmonary support in patients whose heart and lungs are damaged. It allows an external mechanism for gas exchange which will provide time for recovery and treatment of underlying problems<sup>9</sup>.
- Currently, the only consistent evidence of its effectivity is with its use in acute respiratory distress syndrome<sup>9,10</sup>.
- However, it is also being used in severe pulmonary hemorrhage from leptospirosis to help the lungs rest and recover<sup>11</sup>.

## CURRENT PRACTICE IN MANAGEMENT OF LEPTOSPIROSIS IN THE PHILIPPINES



**Figure 1.** Algorithm for the diagnosis and management of leptospirosis with pulmonary complications from the Philippine leptospirosis clinical practice guidelines 2010

RR=respiratory rate; IV=intravenous; ABG=arterial blood gas CXR=chest X-ray; P/F ratio=ratio of arterial oxygen partial pressure to fraction of inspired oxygen; SaO<sub>2</sub>=oxygen saturation; MV=mechanical ventilator; AC=assist control; FiO<sub>2</sub>=fraction of inspired oxygen; TV=tidal volume; PEEP=positive end expiratory pressure.

Source: Chua ML, Alehandria MM, Bergantin RG, Destura RP, Panaligan MM, et al. Leptospirosis Clinical Practice Guidelines 2010. Available from <http://philchest.org/v3/wp-content/uploads/2013/05/Leptospirosis-CPG-2010.pdf> [Accessed 22nd Aug 2018].



*Philippine Leptospirosis Clinical Practice Guidelines 2010<sup>12</sup>*

- Figure 1 shows the algorithm for diagnosis and management of leptospirosis in the Philippines. The initial management for patients with pulmonary symptoms is methylprednisolone.
- Intubation and use of mechanical ventilator are strongly suggested upon findings of bilateral infiltrates on chest X-ray, a ratio of arterial oxygen partial pressure to fraction of inspired oxygen less than 250 mmHg, or oxygen saturation less than 90% at 6 L/min oxygen.
- There is no recommendation for the use of ECMO in the current clinical practice guideline.

**INTERNATIONAL CLINICAL GUIDELINES FOR THE MANAGEMENT OF LEPTOSPIROSIS**

The review found 3 international guidelines for the management of severe pulmonary hemorrhage secondary to leptospirosis. Similar to the local guideline, they recommended the use of steroids and/or mechanical ventilation for management of pulmonary manifestations of leptospirosis. They also have no recommendation regarding the use of ECMO. Table 1 shows the summary of these guidelines<sup>13-15</sup>.

**Table 1.** Summary of recommendations from international clinical practice guidelines for the management of leptospirosis patients with pulmonary involvement.

Country	Date	Recommendation for Leptospirosis Patients with Pulmonary Involvement
Malaysia	2011	Mechanical ventilation is indicated as appropriate.
India	2013	Ventilatory support is indicated for patients with ARDS/ pneumonia
Sri Lanka	2016	<ul style="list-style-type: none"> <li>• Initial management for pulmonary complications includes methylprednisolone.</li> <li>• Mechanical ventilation is indicated for patients with the following:               <ul style="list-style-type: none"> <li>» ARDS with PaO<sub>2</sub>/FiO<sub>2</sub> ≤200 mmHg</li> <li>» Bilateral infiltrates on chest radiography</li> </ul> </li> </ul>

ARDS=acute respiratory distress syndrome; PAO<sub>2</sub>/FiO<sub>2</sub>= ratio of arterial oxygen partial pressure to fraction of inspired oxygen.

**CURRENT EVIDENCE**

There is limited literature on the efficacy of ECMO in the management of pulmonary hemorrhage secondary to leptospirosis. The literature search found 7 case reports published from 2005 to 2017. According to the grade approach, the evidence gathered have very low quality rating due to the design (i.e., case report)<sup>16</sup>. However, this design may provide evidence in novel cases and treatments as well in formulating hypothesis<sup>17</sup>. In these reports, 6 out of 7 patients survived following initiation of ecmo. Patients were hooked to ecmo from 2 to 10 days<sup>1,18-24</sup>.

**FEASIBILITY AND APPLICABILITY ISSUES**

- The use of ECMO is highly resource demanding; it involves a lot of additional hospital supplies, diagnostic tests, and manpower, thereby increasing the cost of its use<sup>24</sup>.
- Table 2 shows the cost of treatment in the National Kidney and Transplant Institute (NKTl). The average length of stay per treatment based on submitted data is 28 days. However, costing for 15 days of confinement was also included. The proposed PhilHealth package rates are PHP

465,750 and PHP 644,000 for 15 days and 28 days confinement, respectively, which will include a 10% mark-up for the institution and 15% professional fee<sup>11</sup>.

- Comparison of NKTl hospital package rate for 15-day treatment with 2 private hospitals is shown in Table 3<sup>11</sup>.

**Table 2.** Proposed package rate for the use of ECMO machine

Days of confinement	Cost Recovery (PHP)	10% Markup	Professional Fee (15%)	Total
28 days	503,949	560,000	84,000	644,000
15 days	362,010	405,000	60,750	465,750

ECMO=extracorporeal membrane oxygenation.

Source: Chico J, Jaro JM, Lagura D, Tribunalo EL, Canuto R. Project: Procurement of the ECMO equipment to provide cardiopulmonary life support for patients with severe respiratory failure in the immunocompromised patient and in patients with acute kidney injury requiring dialysis and pulmonary hemorrhage. National Kidney and Transplant Institute. ND.

**Table 3.** Comparison of NKTl package rate for a 15-day treatment with 2 private hospitals in Metro Manila

Hospitals	Rate for a 15-day treatment (PHP)
NKTl	465,750
Makati Medical Center	1,025,000
The Medical City	942,000

NKTl=National Kidney and Transplant Institute

Source: Chico J, Jaro JM, Lagura D, Tribunalo EL, Canuto R. Project: Procurement of the ECMO equipment to provide cardiopulmonary life support for patients with severe respiratory failure in the immunocompromised patient and in patients with acute kidney injury requiring dialysis and pulmonary hemorrhage. National Kidney and Transplant Institute. ND.

- Table 4 shows the budget impact analysis for ECMO treatment for both 15 and 28 days of confinement. It was calculated using the estimated number of leptospirosis patients needing ECMO per year and the cost of treatment provided by NKTl.
- The estimated number of leptospirosis patients needing ECMO per year was calculated using data from NKTl and the DOH Epidemiology Bureau. In 2016, the mortality rate for leptospirosis secondary to pulmonary hemorrhage despite maximal ventilator support was 18.41% (21 out of 114 patients); this subset of patients was argued to receive benefit from ECMO support<sup>11</sup>. Multiplying this figure to the 2017 leptospirosis morbidity data (2,495 patients)<sup>6</sup>, the estimated number of leptospirosis patients needing ECMO per year is 460 patients.
- The computed projected budget impact is PHP 214,245,000 and PHP 296,240,000 for 15 and 28 days of treatment, respectively. However, considering that ECMO is available in a limited number of institutions, computations for 50% and 30% utilization were also included.



**Table 4.** Budget impact analysis for ECMO treatment

Scenario	Estimated number of leptospirosis patients needing ECMO per year*	Cost of treatment (PHP)	Projected budget impact (PHP)		
			100% utilization	50% utilization	30% utilization
15-day treatment	460	465,750	214,245,000	107,122,500	64,273,500
28-day treatment		644,000	296,240,000	148,120,000	88,872,000

ECMO=Extracorporeal membrane oxygenation

Source: Chico J, Jaro JM, Lagura D, Tribunalo EL, Canuto R. Project: Procurement of the ECMO equipment to provide cardiopulmonary life support for patients with severe respiratory failure in the immunocompromised patient and in patients with acute kidney injury requiring dialysis and pulmonary hemorrhage. National Kidney and Transplant Institute. ND.

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## Appendix I. Review Protocol

### Research Question

Among patients with pulmonary hemorrhage secondary to severe leptospirosis, how effective is extracorporeal membrane oxygenation (ECMO) in preventing mortality?

### Objective

To determine the effectiveness and safety of ECMO in preventing mortality among patients with pulmonary hemorrhage secondary to severe leptospirosis.

### Search Strategy and Selection Criteria

Electronic databases such as PubMed/Medline, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and HERDIN were searched for articles on the efficacy/effectiveness of ECMO among patients with pulmonary hemorrhage secondary to severe leptospirosis. The search strategy was constructed by combining search terms with appropriate Boolean operators in order to describe records including key words referring to severe leptospirosis, pulmonary hemorrhage, and ECMO. The PICO and selection criteria are detailed in Appendix I.1. The search will be limited to English studies. The search criteria that was used in the database search are presented in Appendix I.2. The specific criteria for the population and intervention should be satisfied for the article to be included in the full-text review. Studies will be appraised critically/quantitatively before proceeding with analysis.

#### Appendix I.1. PICO and selection criteria for rapid review

Population	Patients with pulmonary hemorrhage secondary to leptospirosis
Intervention	ECMO
Comparator	No ECMO
Outcomes	Survival
Study Designs included in the Search	All
Study Design for Data Synthesis	Case reports, Observational studies, RCTs

ECMO=extracorporeal membrane oxygenation; PICO=population, intervention, comparator, and outcome; RCT=randomized clinical trial.

#### Appendix I.2. Keywords that will be used in the electronic search

Aspect	Search Terms/Keywords
Patients with pulmonary hemorrhage secondary to leptospirosis	Leptospirosis
ECMO	ECMO ELSO Extracorporeal Membrane Oxygenation



### Data Abstraction, Summarization, and Synthesis

An individual reviewer extracted the data from the studies following the selection criteria from Table 4. Extracted information from the final analysis of the included articles will be the article title, author/s, year of publication, outcomes measured, results, and conclusion.

### Appendix II. Characteristics and findings of studies

Study Design	Patient	Intervention	Outcomes
<b>Arokianathan D et al., 2005</b>			
Case report	30-year-old male pulmonary hemorrhage secondary to leptospirosis	ECMO for 48 hours	Survival
<b>Kahn JM et al., 2006</b>			
Case report	Patient with hemorrhagic pneumonitis	ECMO for 60 hours	Survival
<b>Héry G et al., 2015</b>			
Case report	38-year-old male pulmonary hemorrhage secondary to leptospirosis	ECMO for 9 days	Survival
<b>Liao CY et al., 2015</b>			
Case report	32-year-old male pulmonary hemorrhage secondary to leptospirosis	ECMO for 7 days	Survival
<b>Cantwell T et al., 2017</b>			
Case report	39-year-old male pulmonary hemorrhage secondary to leptospirosis	ECMO for 7 days	Survival
<b>Ludwig et al., 2017</b>			
Case report	34-year-old male pulmonary hemorrhage secondary to leptospirosis	ECMO	Mortality
<b>Umei N et al., 2017</b>			
Case report	50-year-old male pulmonary hemorrhage secondary to leptospirosis	ECMO for 10 days	Survival

Note: The patients received background therapy consisting of antibiotics, blood products, and/or vasopressors depending on the clinical picture. No standard therapy was given to all patients aside from the use of ECMO.