Extracorporeal Membrane Oxygenation in the Treatment of Novel Influenza Virus Infection: A Multicentric Hospital-Based Health Technology Assessment in Lombardy Region

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Abstract—ECMO or Extracorporeal Membrane Oxygenation is a specialized heart-lung bypass machine used to take over the body’s heart and lung function while the body heals from injury or illness. One of the disturbing hallmarks of the novel A/H1N1 flu virus is that it produces severe lung damage resulting in ARDS (Acute Respiratory Distress Syndrome). Normally, patients with ARDS are placed on mechanical ventilation in Intensive Care Units (ICUs) and treated with a variety of pharmacological agents to reduce infection and lung inflammation. With A/H1N1 viral pneumonia, mechanical ventilation often does not result in adequate oxygenation so with ECMO the burden of pumping and oxygenating the blood is taken from the heart and lungs, and they are given time to heal. San Matteo Polyclinic Hospital was nominated by the Lombardy Region and the Ministry of Health as national reference for the installation of ECMO to deal severe heart failure and pulmonary caused by novel A/H1N1 flu virus. Clinical Engineering Department of the hospital had a fundamental coordination role in biomedical technology-related issues. It supported high-level management decisions (strategy, management, planning, procurement and maintenance) to answer to Lombardy’s guidelines about the organization of ECMO machines in the region. Moreover it had an important role in the assessment, by the use of HTA procedures, of ECMO alternative technologies.

Keywords—Hospital-Based Health Technology Assessment, Extracorporeal Membrane Oxygenation, influenza A/H1N1, Acute Respiratory Distress Syndrome.

I. INTRODUCTION

In April 2009, the Mexican Ministry of Health reported an increase in severe pneumonia cases in young adults [1]. The same month first two cases were reported in the United States of human infection with a novel influenza A/H1N1 virus [2]. This novel swine-origin pandemic began in the northern hemisphere during late spring and early summer and appeared to decrease in intensity within a few weeks [3-4]. In July 2009, a total of 122 countries had reported 94,512 cases of novel influenza A/H1N1 virus infection, 429 of which were fatal; in the United States, a total of 33,902 cases were reported, 170 of which were fatal [5].

Cases of novel influenza A/H1N1 virus infection have included rapidly progressive lower respiratory tract disease resulting in respiratory failure, development of acute respiratory distress syndrome (ARDS), and prolonged intensive care unit (ICU) admission. In some severe cases, extracorporeal membrane oxygenation (ECMO) was commenced for the treatment of refractory hypoxemia, hypercapnia, or both, which occurred despite mechanical ventilation and rescue ARDS therapies. ECMO is most commonly used in neonatal intensive-care units, for newborns in pulmonary distress, but it is also used for adults that, even with the use of a ventilator, need to be oxygenated until they are able to do the job without assistance. One of the new uses is in adults and children with the A/H1N1 flu. ECMO treatment provides oxygenation until their lung function has sufficiently recovered to maintain appropriate O₂ saturation.

In July 2009, Italy began to register same cases of novel influenza A/H1N1 virus infection. Epidemiological and virological influenza surveillance network (Influnet) is strengthened and the hospitals, above all those specialized in the treatment of infectious diseases, are alerted across the Regions to be ready to handle suspected cases of novel influenza, through appropriate containment and treatment measures.

II. MATERIALS AND METHODS

A. The Situation in Italy

In Italy, the estimated new cases of the flu syndrome in the third week of January 2010 are 96,000, for a total of 4,293,000 cases from the beginning of surveillance. The total value of the impact of the flu syndrome is equal to 1.61 cases per thousand assisted. The age group most affected is always the pediatric (0-14 years old), with an incidence equal to 3.23 cases per thousand assisted (4.76 ‰ in the range of younger children of 0-4 years old and 2.46 ‰ in the range 5-14 years old). There is a slight increase in incidence in the pediatric age groups (especially in children under 0-4) while among the people over 15 years old the incidence is almost stable [6].
Italian Regions have reported to Ministry 1038 hospitalizations for severe cases of influenza, of which 448 have required ventilatory support (0.010%). The percentage of victims related to influenza A has been updated compared to the total number of cases estimated by Influnet and is equal to 0.005% of patients [6].

Table 1 Deaths number from influenza A (H1N1) per Region at January 2010 in Italy [6]

| Region            | Deaths |
|-------------------|--------|
| Abruzzo           | 3      |
| Basilicata        | 3      |
| Calabria          | 15     |
| Campania          | 53     |
| Emilia Romagna    | 13     |
| Friuli Venezia Giulia | 5 |
| Lazio             | 14     |
| Liguria           | 3      |
| Lombardia         | 13     |
| Marche            | 4      |
| Molise            | 4      |
| Piemonte          | 21     |
| Puglia            | 35     |
| Sicilia           | 21     |
| Toscana           | 5      |
| Umbria            | 3      |
| Veneto            | 11     |
| P.A. Bolzano      | 1      |
| P.A. Trento       | 1      |
| Total deaths      | 228    |

The overall number of deaths is 228 [6] (Table 1). This value includes cases for which the regional health authorities have confirmed the finding of infection by new viruses A/H1N1. The Italian Government has faced the spread of new flu by providing a vaccine strategy and by promoting the Regions and Autonomous Provinces to identify the reference centers for patients suffering from acute respiratory failure. In particular, San Matteo Polyclinic Hospital was nominated by the Lombardy Region and the Ministry of Health as national reference for the installation of mobile ECMO to deal severe heart failure and pulmonary.

B. ECMO Technique

Extracorporeal Membrane Oxygenation (ECMO) is an adaptation of conventional cardiopulmonary bypass technique for providing life support used for long-term support of respiratory and cardiac function. In most cases patients with ARDS respond favourably to advanced methods of intensive care, which include various forms of mechanical ventilation and positional manoeuvres. For a small number of ARDS patients whose pulmonary gas exchange can not be improved sufficiently, ECMO can be an additional therapeutic option during the acute phase [7].

ECMO involves connecting the patient’s circulation to an external blood pump and artificial lung (oxygenator). A catheter placed in the right side of the heart carries blood to a pump, then to a membrane oxygenator, where exchange of oxygen and carbon dioxide takes place. The blood then passes through tubing back into either the venous or arterial circulation (Fig. 1). An anticoagulant is used to prevent blood clotting in the external system. An ECMO machine, in addition to remove CO₂ and add O₂ to blood, regulates the blood temperature with a heat exchanger, removes air bubbles via drip chambers and checks incoming and return pressures.

Moreover, the system is equipped with safety devices and monitors: Air bubble detectors can identify microscopic air bubbles in the arterialized blood; Arterial line filters between the heat exchanger and the arterial cannula are used to trap air and thrombi; Pressure monitors, which are placed, measure the pressure of the circulating blood and are used to monitor for a dangerous rise in circuit pressure.

ECMO technique, however, can cause mechanical complications as oxygenator failure, pump or heat exchanger malfunction, and problems associated with cannula placement or removal, but also patient-related medical complications as bleeding, neurological complications, additional organ failure, barotraumas and infection [8].
C. Hospital-Based HTA Methodology

In recent years, increasing attention has been placed on the adoption of HTA principles and tools to produce evidence for managerial decision making at an hospital level. Hospital based HTA has been recognized as a possible approach to foster HTA’s impact into practice and to sustain rational-based decision making processes regarding health technologies in health care organizations [9].

San Matteo is among the first hospitals that have organized a group of Health Technology Assessment (HTA), made by different professionals as doctors, clinical engineers, healthcare economists and, obviously, General Manager. This group is in charge of the assessment of the equipment to be introduced into the hospital, especially of the most innovative or most relevant from an organizational point of view. The group uses the procedures pointed out by The HTA Italian Network and guidelines of the Ministry of Health for the Hospital Based HTA.

First step has been the analysis of the characteristics, in terms of efficacy, efficiency and costs, of the existing alternative technology in order to point out the correct clinical needs. Second step has been the analysis of the existing literature and, more precisely, of HTA reports on each piece of equipment, both the most innovative and the most common, but not operating in the hospital yet. This has brought to a synthesis of evidences concerning efficacy and, where possible, to the analysis of costs. The evaluation of efficiency has been reached by the analysis of technologies and of existing organizing patterns, as well as of the information in existing guidelines.

D. Evaluated Technologies

Maquet technologies: The main components of the Emergency-MECC system (Fig. 2) include a centrifugal pump (Rotaflow™ MAQUET Cardiopulmonary AG, Hechingen, Germany) and a diffusion membrane oxygenator (Quadrox™ PLS — Permanent-Life-Support, MAQUET Cardiopulmonary AG, Hechingen, Germany), both mounted on a specially designed multifunctional holder (total weight 27 kg). A flow meter and a bubble sensor are integrated into the pump unit. The tubing circuit is a pre-connected, heparin-coated (Bioline™, MAQUET Cardiopulmonary AG, Hechingen, Germany), closed-loop extracorporeal circulation system for rapid setup and priming. It includes a shunt line to facilitate arterial blood gas monitoring and to simplify drug and volume administration. Total priming volume is 600 ml normal saline. The centrifugal pump provides non-pulsatile flow rates of up to 4.5 l/min and is connected to a steering unit by a driveline with an effective length of 150 cm.

In addition to wall connection points for 220 V and oxygen, the system is also provided with an oxygen bottle and battery pack, and thus can operate independently as a stand-alone device for approximately 90 min during patient transfer from intensive care to air or ground ambulances [10].

Decapsmart technology: The Decapsmart (Decapsmart®, Medica Srl, Medolla, Italy) is a venovenous, low-flow extracorporeal device to removal carbon dioxide (CO2) that does not need a specialized staff. This device, has low invasive properties and does not require surgical cannulation of large vessels. Its management does not require the presence of specialized personnel (perfusionist), and it requires minimum administration of heparin [11].

The bilume catheter inserted into the femoral vein aspires blood from the lateral openings. Blood, driven by a first pump, enters into the Decap device where the CO2 is removed. Subsequently, blood passes through an hemo-filter that separates plasma, which, thanks to a second pump, is re-placed upstream of Decap device. Filtered plasma in this way dilutes the blood by improving the efficiency of extraction of CO2 and by reducing the dose of anticoagulant, while the presence of hemo-filter prevents the formation of bubbles to the benefit of safety. Finally, the blood purified by hemo-filter is sent back to the patient through the opening located at the extremity of the catheter.

Novalung technology: The Novalung Interventional Lung Assist (iLA) device is a membrane ventilator that allows for oxygen and carbon dioxide gas exchange to occur by simple diffusion. It has been used in patients with severe acute lung failure due to ARDS, inhalation injury, severe pneumonia, chest injury, foreign body aspiration, and after thoracic surgical interventions [12]. Novalung system is a pump-less
extracorporeal system to remove carbon dioxide (iLA – Novalung® GmbH, Germany) during the secondary transfer for higher level of care of patients with severe hypoxemic-hypercarbic respiratory failure (ARDS, ALI, other interstitial disease but also in patients who require immediate and emergent management of CO2 levels (severe respiratory insufficiency, intracranial hypertension). This device is attached to the systemic circulation and receives only part of the cardiac output (1-2 L/min) for extracorporeal gas exchange. The iLA consists of a plastic gas exchange module with diffusion membranes made from polymethylpentene (PMP). Gas transfer takes place without the direct contact with blood and the PMP membrane surface in contact with blood is treated with a heparin coating to provide non-thrombogenic surface. Blood flows over the exterior surface of the device’s fibers so the ventilating gas (commonly O2) flows inside these fibers. In this way the Novalung iLA mimics the native lung. This allows for the normal amount of oxygen and carbon dioxide that exits the normal lung [13].

III. Conclusions

In the 1990s ECMO technique has been applied successfully in pneumonia and very severe chest trauma, but last year proved to be useful also in the treatment of pneumonia caused by swine influenza virus. These A/H1N1 pneumonia have proven resistant to many drugs and also nitric oxide: the effects on health of the patient become very serious so ECMO is used because it often is effective when other treatment options are not.

Since the alarm of swine flu and the serious lung complications it can cause, the Governor of the Lombardy Region, has announced the purchase of 20 ECMO machines and the activation in major hospitals of Lombardy against possible emergencies caused by influenza A. 10 ECMO machines were installed permanently in intensive care units of hospitals while 10 mobile ECMO machines were made available to be installed on ambulances or helicopters with special metal plates for mounting. All the machines have been bought by the Clinical Engineering Department and installed into the selected hospital of the region. This Department, using the Hospital-based Health Technology Assessment methodology, has performed an evaluation of commercially available alternative technologies (Maquet, Decapsmart and Novalung). The evaluation found that Decapsmart and Novalung systems are more similar respectively to a dialysis system and to a kind of artificial lung while the best results in terms of effectiveness of removal of CO2 are provided by the ECMO technique achieved by Maquet technology. Thanks to ECMO technology, in Pavia, in patients with A/H1N1 flu, the survival was 100% in 7 patients. During the pandemic peak, the A/H1N1 flu sufferers have occupied from 20% to 30% beds in ICU of San Matteo Polyclinic Hospital.

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