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Lung transplantation in neonates and infants: ESPNIC survey of European neonatologists and pediatric intensivists

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Abstract

Lung and heart & lung transplantations in neonates and infants are extreme treatments offered for some life-threatening conditions especially in some North-American centers with promising results. These transplantations are rarely performed in Europe, and we set up a continent-based survey to describe the attitude of European neonatologists and pediatric intensivists on the subject and identify the main indications for this transplantation and the obstacles for the realization of a European lung transplantation program.

Conclusion: The main indications for lung transplantation program for neonates and infants are represented by congenital disorders, and physicians indicate as main obstacles the donors' availability. European neonatologists and pediatric intensivists are interested to create a European network to overcome this problem and realize a lung transplantation program for neonates and infants.

What is Known:

- Lung transplantation in neonates and infants seems to slowly increase, and some North-American centers accumulated a relevant experience.

What is New:

- European neonatologists and pediatric intensivists are interested in creating a European network for a lung transplantation program for neonates and infants.
- The main indications for lung transplantation program for neonates and infants are represented by congenital disorders and main obstacle to lung transplantation is the donors' availability

Keywords Lung · Transplantation · Neonate · Infant

Abbreviations

ACD Alveolar capillary dysplasia and related disorders
CASP Congenital anomalies of surfactant proteins

PPHN Persistent pulmonary hypertension of the neonate
CHD Congenital heart defects
CDH Congenital diaphragmatic hernias

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BPD	Bronchopulmonary dysplasia
ESICM	European Society for Intensive Care Medicine
ESPNIC	European Society for Pediatric and Neonatal Intensive Care
NICU	Neonatal intensive care units
PICU	Pediatric intensive care units

Introduction

Lung and heart & lung transplantations in neonates and small infants are extreme treatments offered for some end-stage respiratory disease that do not have any therapeutic alternative. Surgical difficulties and medical issues, such as managing immunosuppression and follow-up in rapidly growing patients, make these transplants difficult to accomplish. Logistic problems add to the complexity of these interventions, as a critical number of patients might be needed to gain enough technical expertise, while gathering patients and finding donors require a dedicated network and program.

Despite these problems, the number of lung and heart & lung transplantations in these small patients seems to slowly increase, and some North-American centers accumulated a relevant experience [1]. Notably, results seem promising especially for congenital anomalies of surfactant proteins which are incompatible with a normal lung function (i.e., surfactant protein-B, ATP-binding cassette subfamily A3, or for thyroid-transcription factor-1 mutations [2]) and, to a lesser measure, pulmonary vascular diseases and developmental lung disorders (i.e., alveolar capillary dysplasia and similar conditions) [3].

Lung and heart & lung transplantations in infants have been performed in a few US centers since the early 1990s [4], but they are still almost never performed in European countries, and no center has accumulated a significant experience so far. We aimed to describe the attitude of European physicians working in neonatal (NICU) or pediatric intensive care units (PICU) about lung and lung & heart transplantations for neonates and infants aged 12 months or less. Secondly, we aimed to identify the main indications for this transplantation and the obstacles for the realization of a European lung transplantation program. Our hypothesis was that physicians are interested in such a program and willing to collaborate to overcome the obstacles to its realization.

Methods

The European Society for Pediatric and Neonatal Intensive Care (ESPNIC) started a continent-wide project with the purposes described above; the European Society for Intensive

Care Medicine (ESICM) also endorsed the project. These are the two main European scientific societies with a significant number of pediatric intensivists among their members.

A web-based survey was created following a systematic approach. The survey questionnaire was originally prepared by a neonatologist (DDL) and a pediatric intensivist (MCK) and tested among the members of their intensive care units in order to ensure its clarity. Based on their suggestions, the questionnaire draft was modified. Moreover, in a second step, two colleagues answered the survey twice with 1-week interval to test intra-rater reproducibility (that turned out to be 99%). The project and the questionnaire were given ESPNIC and ESICM endorsements after internal review, following dedicated procedures.

The web-based survey was finally distributed using ESPNIC SurveyMonkey® account to all members of ESPNIC or ESICM and to other colleagues using authors' personal contact list. For the survey to be completed, recipients had to declare to practice in European Union and work in a NICU or in a PICU. Recipient working in other pediatric units or in adult intensive care units were not allowed to the survey. The survey dissemination was performed during the congress of these societies and during a European Academy of Pediatric Society congress. Burns' recommendations for this type of survey were followed [5]. Two reminder mails were sent 6 and 12 months after the original distribution, and data were analyzed with descriptive statistics. The participation to the survey was completely anonymous and voluntary; no ethical approval was needed, and no honorarium was offered.

Results

We had 75 respondents all from different neonatal or pediatric intensive care units, and the majority (73.3%) declared to have never taken care of a neonate or infant who received a lung or heart & lung transplantations. For the few transplantations actually performed, 70% were done in a referral center different from that of the respondent; thus, the patient was transferred solely for the transplantation. Interestingly, 72% of respondents admitted to have no or poor knowledge of any clinical programs and clinical outcomes for this type of transplantation in Europe or abroad. Regarding technical difficulties for this type of transplants, donors' availability (85.7%) was considered the most important one. Figure 1 depicts indications for these transplantations as supposed by the responders: the vast majority of indications are congenital disorders. Responders indicated bronchopulmonary dysplasia and cystic fibrosis as the only chronic disorders developing overtime potentially needing transplantation, albeit they only

Fig. 1 Clinical conditions that could ideally have a maximum benefit from lung or heart & lung transplantations in neonates and infants aged less than 12 months, according to the opinion of European neonatologist and pediatric intensivists. Recipients were able to freely indicate several conditions

represent a minority. Despite the lack of knowledge on this transplantation, respondents would consider referring a patient for this type of surgery (78.1%); although, in a minority of cases (17.8%), this was acceptable only if the referral center was located in their country of origin. However, if a specific European network dedicated to lung or lung & heart transplantations for infants less than 12 months of age is started, 92% of respondents would refer a patient to this network.

Discussion

Lung or heart/lung transplantation are challenging procedures, and their introduction in the early pediatric age has been probably delayed by their technical difficulty. However, the availability of good results where a dedicated program has been established pushes to create similar programs and networks elsewhere. Although the European Union has more inhabitants than the USA and Canada, it is divided in several healthcare systems, which are also regionalized in some areas. These are connected and, when a therapeutic intervention is not available in a given country or region, it could theoretically be performed in another European Union country and covered by the patient's healthcare system. This background, if a European project is launched, makes possible the movement of patients across the Union and the offer of the best available treatment, notably for the less common conditions or for those needing unusual therapeutics. Our findings clearly demonstrate that this opportunity should be exploited for lung or

heart & lung transplantations in children aged 12 months or less. In fact, from one side, there is a lack of knowledge on the topic, while, from the other side, the few transplantations performed so far demonstrate that some centers tried to offer this intervention, without having reached a critical threshold of case mix and significant experience. The rarity of patients and donors' availability justifies the creation of a supra-national, continent-wide network to gather patients to dedicated centers. At a more local level, sharing care of pediatric cardiac transplantation between two close European countries has achieved good outcomes [6]. Moreover, the fact that most critical care physicians identified congenital disorders as the main transplant indications increases the need for the creation of such a network, since these disorders typically evolve towards intractable respiratory failure within a relatively short course. Thus, there is commonly not much time available before the transplantation. For all these reasons, critical care physicians feel that a dedicated continent-wide network should be created, and in fact, they opt to refer patients to this network. The importance of such transplantation program is even more important since, for the majority of congenital lung disorders needing transplantation, there is currently no other therapeutic option. Other treatments (for example, genetic therapies) that might reduce the need for such invasive intervention are being studied only for cystic fibrosis while not even under investigation for other conditions as they are multifactorial and not totally linked to a single gene dysfunction.

The European Union healthcare is well developed, but to organize complex and uncommon interventions, such as lung

or heart & lung transplantations in neonates and infants, a dedicated, appropriately funded continental network is necessary and highly needed. These will be able to fill the gap of knowledge, to offer this therapy to more patients and potentially improve their outcomes by facilitating surgical experience and clinical research on a relevant number of patients.

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Authors' contributions DDL conceived the project, prepared the survey questionnaire, wrote the manuscript draft and managed contacts with scientific societies.

PT helped in the contacts with scientific societies and helped in data analysis and interpretation.

MCK prepared the survey questionnaire and the online platform and helped in the contacts with scientific societies.

MH helped in the project conception and in data analysis and interpretation.

OM conceived the survey, helped in data analysis and interpretation and supervised the whole project.

All authors critically reviewed the manuscript for important intellectual content.

Compliance with ethical statements

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not needed (anonymous survey without patients' data)

Informed consent Not needed (anonymous survey without patients' data)

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