ECMO : EFFICACY AND POTENTIAL NEED IN QUEBEC

1) REPORT
2) RESOURCE DOCUMENT

Prepared at the request of the
Ministère de la Santé et des Services sociaux du Québec

by

The Conseil d'évaluation des technologies de la santé

(version française disponible)

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Introduction

In mid-September the Conseil d'évaluation des technologies de la santé received a request from the Ministre de la Santé et des Services sociaux for an evaluation of the efficacy of ECMO and the need for such a program in Québec. ["Pour évaluer l'opportunité de développer un programme d'ECMO pour nouveau-nés au Québec, ... et un avis sur l'efficacité de la technique et la viabilité d'un tel programme dans notre système de santé"]. The Conseil first requested the preparation of a resource document [RD] from Dr. Barry Smith, Professor of Pediatrics at the University of Toronto, Head of the Division of Neonatology at the University of Toronto and Physician in Chief at the Mount Sinaï Hospital. His report is attached. The report which follows was prepared on the basis of Dr. Smith's document, in the light of 3 reviews of this document and of discussions within the Conseil and with experts in the field.

ECMO [Extracorporeal Membrane Oxygenation] is a procedure by which the normal gas exchange function of the lungs is temporarily assumed by an artificial heart-lung machine, similar to those used in routine open-heart surgery. By this means the lung, and to some extent the heart as well, are put at rest and the body is supplied with normal oxygenated blood. ECMO is used when the infant's survival is considered to be unlikely and when it is also believed that the 5 to 10 days of life gained by its use may provide an opportunity for natural recovery to take place.

Since the first report of successful use of ECMO in 1975, its use has expanded steadily. As of December 1989, over 3,000 infants had received ECMO therapy in the U.S.A. alone [RD]. In Canada, there is one centre in Edmonton which has functioned for several years and a second, in Toronto, is in the process of starting up.

Efficacy

Proof of efficacy of ECMO leaves much to be desired. Two randomized trials, involving a total of 12 and 19 patients respectively, have concluded that ECMO produced "statistically significant" reductions in mortality [1, 2]. Both studies have been criticized on the basis of the small numbers of patients involved and one on the basis of design as well. There are numerous reports of the success of ECMO based on comparison of the survival of infants treated with ECMO compared to historical controls. [see RD]. The validity of this approach is highly questionable in view of the steady improvement that has taken place in the outcome of patients treated by means other than ECMO over this time. Thus, whenever a survival rate is reported in a series of ECMO patients, it is not really known what percentage would have survived without ECMO had they received contemporary treatment. It is therefore not surprising that opinion on the efficacy of ECMO is divided.

In spite of this, there is a fairly widespread agreement, with some notable exceptions, that ECMO is capable of saving the lives of some babies. There is more disagreement, however, as to how many babies may be saved and whether the number is sufficient to justify the use of the necessary resources.

Complications of ECMO

ECMO requires the use of anticoagulants and may cause gastric hemorrhage or intracranial hemorrhage in 5 and 17% respectively [8]. Cannulation and eventual ligation of the infant's carotid artery and jugular vein are necessary and there have been fears that this may result in some degree of brain damage [3-7]. Seventeen percent sustained intracranial hemorrhage and 32% had some evidence of neurological involvement (3% severe) in the 1987 summary of the National Registry [8]. However, neurologic damage is not uncommon in individuals who have survived without receiving ECMO [9,10] and the question of whether, and how many instances of neurologic damage are due to the treatment remains uncertain.

It is reported that 5 to 10% of ECMO survivors may have persistent lung disease [8]. Long-standing and sometimes permanent lung damage is also reported in survivors who have not received ECMO though the frequency may be lower [8,9,11]. Thus, persistent lung disease requiring respiratory assistance for at least 4 weeks is to be expected in a small number of these infants. There is no convincing evidence that more are to be expected following ECMO than in its absence.

Cost of ECMO

The cost of treating such infants in the ICU is already high without the use of ECMO. The additional cost of operating an ECMO program in Toronto has been estimated at between $250,000. and $300,000. per year [RD]. Any hospital which opens an ECMO centre must, however, attract patients from other hospitals. Thus, in addition to the increased cost of operating the ECMO centre, there will be increased admissions of resource demanding neonatal ICU patients in that hospital. As is usual when patients are concentrated because of some expensive high technology, the referring hospitals will be relieved of the costs of caring for those patients which are transferred. This factor should be recognised by appropriate financial adjustment.

The need for ECMO

In the absence of agreement as to the efficacy of ECMO and of agreement on the pathological conditions for which it is indicated, it is impossible to evaluate with any precision how many Quebec infants might require ECMO in a year. Smith estimates, using only the frequency of pulmonary hypertension resulting from meconium aspiration as an indicator diagnosis, that between 10 and 20 cases per year might result from each 100,000 deliveries [RD]. This means that if all appropriate cases with this diagnosis were referred to an ECMO centre, the 80,000 deliveries per year in Quebec might furnish 8 to 16 infants suitable for ECMO treatment. Some reviewers of Smith's report believe, however, that this is a very conservative estimate, and that there may be at least an equal number of candidates who might profit from ECMO, with the diagnoses of hyaline membrane, persistent fetal circulation, severe sepsis, and diaphramatic hernia,

The use of ECMO in each of these conditions is contentious. Hyaline membrane is the commonest cause of respiratory insufficiency in the newborn. It can be the source of some successful treatments. However, it is a disease of premature infants, the vast majority of whom are smaller than the 2.5 kg generally considered to be the lower limit of size for the application of ECMO [12]. In addition, these premature infants are at increased risk of hemorrhage associated with the use of anticoagulants, also an essential component of ECMO. In spite of this, in the 715 ECMO treatments summarized in the U.S. ECMO Registry, there were 96 such patients compared to 310 treated for meconium aspiration. Some infants with persistent fetal circulation due to other causes than Meconium Inhalation, and some with severe lung infections, are also ECMO candidates. Together, they made up 164 of the Registry series [8].

Though doubt has been expressed that these diagnoses are found with equal frequency in the Canadian experience, almost all would agree that the lives of some infants with these diagnoses may be saved by ECMO. For the purpose of estimating the number of potential patients for this therapy in Quebec, we will assume that the frequency of patients with the diagnoses of hyaline membrane, persistent fetal circulation and lung sepsis relative to meconium aspiration might be half that in the Registry report. Using this approach, the relative frequency of potential subjects with these diagnoses compared to meconium aspiration is approximately 1:3. Based on the previous estimate of 8 to 16 potential meconium aspiration patients per year, the total potential treatment population would thus be approximately 11 to 21. (Projection of the U.K. estimate of one ECMO candidate with meconium aspiration per 5,000 deliveries, would give 16 newborn candidates for ECMO based on this diagnosis alone).

Diaphragmatic hernia is an even more contentious use for ECMO. In the same Registry, 121 of the patients treated had this diagnosis. While some believe that ECMO can be life-saving in this situation, others believe that approximately 45% of patients with this diagnosis will succumb whether ECMO is used or not and less invasive therapy can achieve at least as much for these infants as can ECMO [13]. Treatment of this condition by ECMO must therefore be considered experimental until this question is solved. Extrapolation from the ratio of this diagnosis to meconium aspiration (1:3), would result in the addition of 3 to 5 potential subjects (7 newborn infants with this diagnosis died in Quebec in 1989 [16]).

Thus, bearing in mind the uncertainty of these estimates, if all ECMO candidates in

Quebec could be referred to one centre, it is possible that between 11 and 21 infants [14 and 26 if diaphragmatic hernia were included], would be treated per year. In any event, it is clear that these estimates are too small to justify more than one centre in Quebec and that this centre might well serve New Brunswick and Northern New England as well.

The status of ECMO

The present, predominent, contemporary opinion is that ECMO ***can*** save lives and is accordingly no longer an "experimental" procedure. There is, however, uncertainty as to the amount of benefit which it may bring and the ***precise circumstances*** which should determine its use. Thus, its general application as a standard treatment cannot yet be recommended.

According to Lantos and Frader [14], the view that ECMO and conventional therapy are two mutually exclusive alternatives for infants with respiratory failure and that one can be proved to be better than the other over-simplifies the situation [14]. The real problem, according to these authors, remains a more complex set of questions about how ECMO and various other therapies should be combined or used sequentially to maximize benefit for particular infants.

At the present time, with the exception of its use for diaphragmatic hernia which must be considered experimental, the status of ECMO can be considered to lie between that of an accepted standard treatment and that of an experimental procedure. It should, therefore, be considered as a ***restricted*** or ***innovative procedure*** requiring carefully controlled conditions of use and further observation of outcome. Its use should, therefore, as expressed by the American Academy of Pediatrics [15], be limited to centres with "adequate strength in the necessary sub-specialties and a good track record in research".

With this status, ECMO would be considered an intervention which would justify reimbursement through the RAMQ, only when carried out in a designated centre. Although no longer an experimental procedure, consent for its use should be obtained.

Should Quebec develop an ECMO centre?

The following points must be considered by those who must make this decision.

1º The number of cases who might profit from ECMO therapy in Quebec cannot be estimated with precision. It is possible that it might be between 10 and 20 per year. This would constitute a sufficient number to maintain a programme of adequate quality if all cases were referred to a single center.

2º If it were assumed that ECMO raised the average survival rate (with the exclusion of diaphragmatic hernia), from 30% to 80%, the procedure might save 5 to 10 lives per year, **IF** all potential candidates resulting from 80,000 deliveries were transferred for treatment.

3 º The quality of most, but not all, of the lives saved would be normal, that is to say full health could be expected in at least 60% of those saved. Long term follow up is not yet available. However, within the first year persistent lung disease might be expected in 5 to 10% and some evidence of neurological deficit in 30% of survivors.

4 º The cost of such a centre might be $275,000. per year [± $25,000]. Thus, the additional cost per life saved over and above all other expenses incurred, might range from $27,500. to $55,000 if the above estimate of effectiveness were realized. Assuming an average 75 year life-expectancy, estimates of the cost per life-year would thus range from $367. to $733. While even the higher figure is not excessive compared to some other therapeutic interventions, such as chronic renal dialysis, the validity of comparing the cost per life-year of a newborn to that of an adult will be considered by many with some scepticism.

5 º In evaluating the costs to the Quebec Health Care System it must be recalled that ECMO is, if the American Academy of Pediatrics is correct, "here to stay", [15]. Even in the absence of strong quantitative evidence, its use elsewhere than in Quebec has increased and will probably continue to increase. As a result, the demand for such services by Quebec residents may also increase. If this demand should result in the transfer of as few as 3 patients per year for treatment outside the province this would be a significant financial outlay (the cost of each transfer is estimated to be $125,000).

6 º In addition to possible clinical benefits, there is an incentive for Quebec to establish data on the relative merits and costs of ECMO versus alternative management strategies, for each of the different clinical conditions for which ECMO may be used. Thus, any centre applying to open an ECMO unit should be required to submit, and carry through, an acceptable research protocol designed to provide some significant portion of this needed information.

Conclusion

On the basis of present opinion it is possible that an ECMO centre might save the lives of 5 to 10 newborn infants in Quebec at an additional direct cost to the Health Care System of $275,000 (± $25,000).

If it is decided to proceed, no more than one centre should be considered.

Such a centre should be situated in a University Teaching Hospital with a proven research capacity.

The opening of such a centre should be conditional on the submission of a full and satisfactory research proposal designed to provide some substantial portion of the data necessary for the establishment of health policy.

If it were decided to open a centre, its status should be considered provisional and dependant on, not only its satisfactory functioning, but on the regular provision of the needed research data.

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Neonatal Extracorporeal Membrane Oxygenation:

What is its Role in 1990?

RESOURCE DOCUMENT

Prepared at the request of the
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Neonatal Extracorporeal Membrane Oxygenation: What is its Role in 1990?

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Neonatal Extracorporeal Membrane Oxygenation: What is its Role in 1990?

I. Introduction

This document reflects a review of the literature and consideration of the need (if any) for introduction of extracorporeal membrane oxygenation (ECMO) in the neonate at the request of The ***Conseil d'évaluation des technologies de la santé du Québec***. It is germane to point out that the author works in another Canadian centre where the same question is actively being asked and where a pilot ECMO program is just under way (within the past two months): that program, however, is not carried out in the author's unit, so he has no vested interest in ECMO per se. The literature cited reflects a literature review carried out covering the period ending on September 30th, 1990.

II. Historical Background

ECMO is essentially the temporal extension of cardiopulmonary bypass, a technique which was originally developed for open heart surgery, to long term use (days vs hours). It is used for the support of patients with cardiac or pulmonary conditions (usually the latter) which are incompatible with life but which, if the patient survives sufficiently long, may resolve spontaneously or as a result of some intervention such as transplantation. Thus, ECMO provides a wider temporal window in which to institute the alternative therapy.

ECMO was predicted in the 1950's (1) when cardiac bypass was first developed, but first attempted in the 1960's, as a therapy for respiratory distress syndrome (2-4). These early attempts uniformly failed due to uncontrolled hemorrhage in these premature infants since anticoagulation was, and remains, a necessary component of the procedure. This, in addition to the technical problems of high volume vascular access in the premature infant, mean that ECMO remains limited to infants greater than 2.0 to 2.5 kg in weight and 34 to 36 weeks gestation. The larger number in both instances is the limit most often used. Thus, ***ECMO is not available to the largest category of newborns with respiratory failure, namely premature infants with respiratory distress syndrome.***

In the 1970's, ECMO was "successfully" applied in ***adults*** with shock lung, also called respiratory distress syndrome (5). (The quotes around "successfully" indicate that the definition of survival used here means survival where such was unexpected, rather than increased survival meeting the usual standards of statistical significance). The physicians then did the right thing: a large multicentre trial of ECMO in adults was carried out under the auspices of the United States National Institutes of Health (6). No difference between patients receiving ECMO and patients receiving conventional therapy was seen, and, in fact, few patients survived in either group (6).

Thus, while ECMO has convincingly been demonstrated to be of no use in the adult, at least in the condition for which it was tested, it was quite correct not to extrapolate this result to pediatric patients, particularly neonates. The pioneers of neonatal ECMO, particularly Bartlett, reasoned that since the lung continues to grow and develop new alveoli for many years (7), a temporary period of replacement of function by ECMO could allow the generative (and perhaps regenerative) properties of the infant lung to reverse otherwise fatal lung injury. Bartlett first reported ECMO treatment of 13 infants who were felt to be destined to die of respiratory failure with 4 survivors, in 1976 (8). By 1980, some groups reported survival rates exceeding 70% (9) in infants who met criteria which predicted an 80% mortality (10). Was this enough to treat ECMO as standard therapy? The following sections will point out that this question is still not answered a decade later, and that practice has diverged on a geographical (more properly, geopolitical) basis.

III. Neonatal ECMO, the Modern Era

The first successful studies in neonates (8,9) and most that have followed (11,12) used retrospective controls: that is criteria would be developed from a past cohort of patients which would predict a sufficiently high risk of death (generally 70 to 90%, see for example reference 10) to justify use of an experimental and highly invasive therapy. If the survival rate subsequently exceeded that predicted, this was assumed to indicate that ECMO was an effective therapy. The problem, of course, is that this assumption is predicated on the expectation that outcomes would not have changed due to other factors in the time period under consideration. This assumption has been specifically disproved in the population of infants under consideration (13-15). For example, Dworet et al (15) developed "ECMO criteria" which would predict 90% mortality. Then, rather than using ECMO, they pursued conservative therapy, and their survival rate was 90%. These, however, are small studies and are not randomized.

Thus, the need for the randomized, prospective trial is again revealed. Fortunately, two such trials are now available (16,17). In the first, Bartlett used a relatively new statistical technique called "play the winner" (16). This technique is advocated for new therapies which either carry very high risk or which are thought to potentially provide major advantage: i.e. the concept of equipoise, essential for the justification of randomization, may not be correct. Given that Bartlett's group previously had published positive (albeit retrospectively controlled) studies of ECMO (11), it is certainly understandable that they would choose this strategy. The study design is as follows. The first patient is randomized, and if the random therapy succeeds each successive patient is treated in the same way. When a randomly assigned therapy fails, the next patient is assigned to the alternative therapy. The investigators continue to "play the winner" and analyze the difference between the two therapies in an ongoing manner using appropriate non-parametric statistical techniques and correcting for the repeated analyses until a statistical winner is determined. In this study (16), the first patient was assigned to conventional therapy and died. The next 11 patients were treated with ECMO and survived, at which point statistical significance was achieved (16). This study has been criticized (18,19) because this strategy forces one to use a very small ***n*** (indeed it is designed to do so for the reasons noted above), and the individual patients in such a small study may or may not be representative of the population.

More recently, a larger randomized study was carried out by the Boston group (17) with crossover criteria which were not based on single patients, but on shifting therapy when more than 4 deaths had occurred in either arm. In the initial randomized phase, 9 of 9 ECMO treated babies survived, while only 6 of 10 conventionally treated infants survived. In the subsequent phase (the crossover point of 4 deaths having been reached in the conventional arm), 19 of 20 babies treated with ECMO survived. This is also a small study, reflecting only a single centre, but at least the results are consistent with another prospective study (16) and also with numerous retrospective studies (8-14). ***While it could be argued that further large prospective studies should be done before ECMO is made the "standard" therapy, it is clear that most but not all (19,20) would conclude that equipoise no longer exists and further controlled studies would thus be unethical.***

IV. Experimental, Innovative, or Standard?

The above discussion makes it clear that there remains disagreement as to whether ECMO should now be widely adopted. This disagreement is also reflected in regional and national differences. Whatever the academic disagreement in the United States, in practice ECMO is rapidly becoming the routine therapy. As of December 1989, over 3,000 infants had received ECMO therapy (19). On the other hand, a consensus has been reached in Australia (in November 1989 and published in August 1990) that only 2 centres will offer this therapy and then only as "optional" (i.e. innovative) therapy (21). In the United Kingdom, a strong opinion was expressed in September of 1990 that ECMO is not needed. This opinion was based on the very low number of infants who might benefit (1:5,000 births) based on analysis of outcomes in a region with 55,000 deliveries (22) (see also section VI, following). In Canada, only one centre (Edmonton) has an ongoing program and a second (Toronto) is just undertaking a pilot program. Clearly, there is no Canadian consensus as yet.

A good argument that ECMO is acceptable and should be used as at least innovative therapy is made by Lantos and Frader (20). The following table summarizes the suggested categories under which new therapies may be introduced, based on the above literature:

	Standard	Innovative	Experimental
Use	required	optional	restricted
Insured?	yes	possibly	no

Lantos an Frader are somewhat apologetic about the lack of randomized trials of ECMO and point out that no consistent alternative therapy exists against which ECMO could be tested (20). However, this situation which also applied to the adult application of ECMO (5), did not prevent a definitive trial (6).

Secondly, while ethical issues facing clinical trials in children are more difficult (23), it would be nihilistic in terms of children's health care to accept Lantos and Frader's implication (20) that since the ethics are more difficult, the introduction of new therapies should be held to less stringent rules of acceptable proof of efficacy. Despite that above criticisms, this reviewer is in basic agreement with the position taken by Lantos and Fradeer (20), namely that equipoise no longer exists to allow controlled studies; but that ECMO should not yet be viewed as satandard therapy. Thus, consistent with the Australian consensus (21), ECMO should at present be restricted to specific centres and then only be used as in innovative technique.

V. Persistent Pulmonary Hypertension due to Meconium Aspiration and Congenital Diaphragmatic Hernia

While neonatal ECMO has been used for a variety of conditions, the two most common indications have been, and likely will remain, persistent pulmonary hypertension due to meconium aspiration (hereafter called pulmonary hypertension) and congenital diaphragmatic hernia (19,20). The reported survival with ECMO in current US experience (19) is 92% in pulmonary hypertension in infants selected on the basis they would be expected to only have a 20% survival. This result is clearly superior to current therapy. On the other hand, survival where ECMO is applied in cases of diaphragmatic hernia is currently 65%, a survival rate which is not far superior to rates achieved with convential therapy. A recent paper to the contrary (24), in which a survival of 64% was reported in diaphragmatic hernia and the authors recommended early (even prenatal) referral to an ECMO centre, ***the new Toronto centre will not be using ECMO for this indication except for possible randomized trials. Thus, it is our belief : that current planning for ECMO as an innovatiave therapy should be based upon pulmonary hypertension as the primary planning indicator.*** Other disease processes might also be treated, but they should be approached as experimental uses.

VI. Crystal Ball: Projections

Congenital diaphragmatic hernia may soon be treated by prenatal surgery (27) but it seems likely this will be even more expensive than ECMO. Pulmonary hypertension due to meconium aspiration is largely preventable by good obstetric care and this may be a cause of the the lower incidence in Canada calculated in section VII, above. It is probable, however, that we have about maximized prevention in this country and that no major further reductions in the number of these cases is to be expected. Other new therapies, such as surfactant replacement have no physiological basis for use in this disease process.

Sufficient data are not yet available to suggest that ECMO provides acceptable long term outcomes, but limited data are reassuring (19). Any decision to apply ECMO must include plans for long term follow up to settle this point.

VII. Estimates of Predicted Need

Two estimates of predicted need are available in the literature: one from the UK of 1:5,000 births (22) (from which the authors concluded ECMO should not be used) and a second from the state of Georgia (25) which concludes that it could be used in 1:3,717 births. Thus, based on current US outcome data, ECMO could possibly lower the neonatal mortality rate by 0.13/1,000 births or by 1.4%. Preliminary calculations for Central East Ontario presented in Appendix I, indicate that: ***ECMO might be used in 1:15,000 deliveries to save 3 lives per year in a region serving 100,000 annual***

deliveries. The lower Canadian estimate reflects use of exclusion criteria such as CNS lesions not made in the USA and UK studies and the possibility that obstetric management may be better in this country. Therefore, based on the British, USA and Canadian estimates cited, the need for ECMO would be predicted to lie somewhere between 1:5,000 and 1:15,000 deliveries. This very clearly indicates that, based on considerations of maintenance of skills alone, ***ECMO centres should be severely limited in number and should serve a population base which produces at least 100,000 deliveries per annum,*** i.e. such a centre might be expected to treat at least 10 to 20 cases per year.

VIII. Costs

Only one study has reported on costs (26). This US study suggested that using ECMO was, overall, 2% less costly than not using ECMO, with cost reduction being related to reduced length of stay. In the Canadian system, however, reduced lengths of stay in NICUs do not convert to real dollars since occupancy already approaches 100%. Thus, mounting an ECMO program requires real, new dollars. These are needed partly for equipment, but mainly for personnel as the caregiver to patient ratio increases from 1:1 to 2:1 due to the need for a dedicated perfusionist around the clock in addition to the 1:1 nursing required for this type of patient. At The Hospital for Sick Children the estimated add on costs for a pilot one year program for 10 patients are between $250,000 and $300,000 with the resultant saving of perhaps three infants (Appendix 1). Thus, based on these numerous assumptions the ***expenditure may be between $80,000 and $100,000 per life saved.*** Applied to a projected life expectancy of 75 years (Quebec average, Statistics Canada) one might therefore project ***an expenditure of $1,066 to $1,333 per life year.*** It is for society to decide whether this is a justifiable expenditure and if so what other priorities will not be met?

IX. Summary of Key Points

a. *ECMO is not available to the largest number of newborns with respiratory failure, premature infants with respiratory distress syndrome.*

b. *While it could be argued that further large prospective studies should be done to make this "standard" therapy, it is clear that most but not all (19,20) would conclude that equipoise no longer exists and further controlled studies would be unethical.*

c. *This reviewer believes that the evidence to date indicates that (a few) children's lives can be saved by ECMO, that equipoise no longer exists to allow controlled studies, but that this should not yet be viewed as standard therapy.*

d. *I believe that current planning for ECMO as an innovative therapy should be based upon meconium aspiration/persistent pulmonary hypertension as the primary use and planning tool.*

e. *ECMO centres should be severely limited in number and should serve a population base which produces at least 100,000 deliveries per annum*

f. *It will be up to society to determine whether $25,000 to $30,000 is worth spending to save the few additional lives (70 productive years) and, if so, what other priorities will have to be lowered.*

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XI. Annexe I

Central East Ontario
Data from July 1, 1987 - December 31, 1989

1.	60 000 deliveries per year (Ontario total) :	120,000
2.	Births in study period (2,5 x 60 000) :	**150,000**
3.	Deaths from pulmonary hypertension caused by meconium aspiration :	**14**
4.	Not ECMO candidates (CNS lesions) :	**6**
5.	ECMO candidates who dies :	**8**
6.	Total candidates with an 80% mortality predictor and (8 x 0,8) :	**10**
7.	Need for ECMO (150 000 / 10) :	**1:15 000**
8.	Actual death rate despite 80% prediction might be 50% (réf. 13-15) :	**5**
9.	With ECMO death rate 10% (réf. 19) :	**1**
10.	Lifes saved with ECMO in 30 months :	**4**
11.	Lives saved per 100 000 deliveries (4 / 150 000) :	**approx. 3**