Standardized Postnatal Management of Infants with Congenital Diaphragmatic Hernia in Europe: The CDH EURO Consortium Consensus – 2015 Update

Kitty G. Snoek a, Irwin K.M. Reiss a, Anne Greenough c, Irma Capolupo e, Berndt Urlesberger f, Lucas Wessel g, Laurent Storme h, Jan Deprest d, i, Thomas Schaible g, Arno van Heijst b, Dick Tibboel a for the CDH EURO Consortium

a Erasmus MC – Sophia Children’s Hospital, University Medical Center Rotterdam, Rotterdam, and b Radboud University Medical Centre, Nijmegen, The Netherlands; c King’s College and d University College London Hospitals, London, UK; e Bambino Gesu Children’s Hospital, Rome, Italy; f Medical University Graz, Graz, Austria; g Universitätsklinikum Mannheim, Mannheim, Germany; h Hôpital Jeanne de Flandre, Lille, France; i University Hospital KU Leuven, Leuven, Belgium

Key Words
Congenital diaphragmatic hernia · Standardized treatment · Consensus

Abstract
In 2010, the congenital diaphragmatic hernia (CDH) EURO Consortium published a standardized neonatal treatment protocol. Five years later, the number of participating centers has been raised from 13 to 22. In this article the relevant literature is updated, and consensus has been reached between the members of the CDH EURO Consortium. Key updated recommendations are: (1) planned delivery after a gestational age of 39 weeks in a high-volume tertiary center; (2) neuromuscular blocking agents to be avoided during initial treatment in the delivery room; (3) adapt treatment to reach a preductal saturation of between 80 and 95% and postductal saturation >70%; (4) target PaCO 2 to be between 50 and 70 mm Hg; (5) conventional mechanical ventilation to be the optimal initial ventilation strategy, and (6) intravenous sildenafil to be considered in CDH patients with severe pulmonary hypertension. This article represents the current opinion of all consortium members in Europe for the optimal neonatal treatment of CDH.

Introduction

In 2008, the congenital diaphragmatic hernia (CDH) EURO Consortium was set up and during a consensus meeting drafted a standardized neonatal treatment protocol to improve outcome and permit comparison of outcome data [1]. Since then the number of participating centers has increased from 13 to 22 specialized CDH centers from all over Europe, and the guidelines from 2010 have been widely cited. Moreover, after the implementation of the protocol, the survival rate has increased from 67 to 88% in 2 centers. This indicates the impact of the original standardized protocol. After 5 years of additional research including a multicenter randomized clinical trial on initial ventilation strategy (VICI-trial; Netherlands Trial Register, NTR 1310), we aimed to update the standardized neonatal treatment protocol for...
CDH. All recommendations were summarized and compared with the protocol in 2010 (online suppl. file; see www.karger.com/doi/10.1159/000444210 for all online suppl. material).

Methods

The studies were graded according to the Scottish Intercollegiate Guidelines Network (SIGN) criteria [2]. Five experts individually primarily determined the levels of evidence on the guidance of the SIGN checklist. Differences in opinion were primarily discussed between the five experts until full consensus was reached, and thereafter consensus was reached between all participating centers. The final consensus statement, therefore, represents the opinion of all participating centers based on the interpretation of the results of the so-called VICI-trial [3]. A consensus meeting, in which neonatologists, pediatric intensivists, gynecologists, prenatal physicians, pediatric surgeons, pediatric cardiologists and general pediatricians from 22 centers participated, was organized to discuss the most controversial recommendations. If it was very hard to reach consensus on a specific issue, the consortium concurred to investigate those issues in future randomized trials. The levels of evidence and grades of recommendation according to the SIGN criteria are presented in online supplementary tables 1 and 2, respectively.

Results

Prenatal Management

With the increased use of second trimester 2D ultrasound and/or MRI, CDH has become a prenatal diagnosis. Subsequently, a more detailed expert evaluation should be performed to determine the location of the defect, the observed/expected lung-to-head ratio (O/E LHR) and the position of the liver (intra-abdominal or intrathoracic), in addition to ruling out additional congenital anomalies or syndromes [4, 5]. Associated congenital anomalies, such as chromosomal or genitourinary anomalies, are present in about 25% [6] and cardiac anomalies in about 20% of cases [7]. Comprehensive assessment will also include invasive sampling for high-resolution genetic testing. Only once a comprehensive assessment has been made can multidisciplinary prenatal counseling by clinicians in tertiary centers be offered to inform parents about the estimated prognosis after birth. Several other additional imaging methods, such as lung volumetry, 3D ultrasound and Doppler studies of the pulmonary vascularization, have been shown in individual series to be prognostic for pulmonary hypertension, the need for extracorporeal membrane oxygenation (ECMO) and survival [8]. All of these remain research tools, however, but may ultimately improve the predictive value of prenatal testing.

An experienced tertiary center with a high case volume (≥6 CDH patients per year) is the optimal environment for the delivery and neonatal treatment of prenatally diagnosed CDH fetuses [9, 10]. Prenatal intervention by fetal endoscopic tracheal occlusion (FETO) has been proposed to promote lung growth [11]. Therefore, FETO is being evaluated in two randomized clinical trials both in moderate (first interim analysis stage reached; >100 patients randomized) and severe cases (>25 patients randomized) in centers in Europe, Australia and Canada (TOTAL trial [12]; NCT01240057). Current reported survival rates are on average around 50%, yet there is a significant impact of gestational age at delivery. In the largest cohort study where 17.1% of all patients were born under 32 weeks, the survival rate was 49.4% for isolated left CDH and 37.9% for isolated right CDH [13]. This suggests that FETO introduces a significant risk for prematurity and all its consequences. It is recommended therefore that – while waiting for the results – FETO should not be performed outside the trial [11]. According to the consensus statement of the National Institutes of Health (NIH), CDH fetuses at risk for delivery before 34 weeks of gestation should be given prenatal steroid therapy.

Delivery

The timing and preferred mode of delivery in CDH pregnancies are still controversial. Hutcheon et al. [14] showed that neonatal and infant mortality significantly decreased with advancing gestation, from 25 and 36% at 37 weeks of gestation, respectively, to 17 and 20% at 40 weeks of gestation, respectively. Moreover, a study from Odibo et al. [15] among 107 CDH cases found that gestational age at delivery was inversely correlated to the need for ECMO. However, Safavi et al. [16] found no difference in mortality when dividing gestational age at delivery categorically as under 37 weeks, 37–38 weeks and 39 weeks or beyond. Neither did they find a difference in mortality between vaginal and cesarean delivery [16]. In the absence of true convincing data it seems intuitive to schedule delivery (induced delivery or cesarean section) carefully in the best possible conditions also dependent of maternal indications, i.e. at 39 weeks or beyond and in the presence of the relevant clinicians.

Recommendations (Prenatal Management and Delivery)

- Following prenatal diagnosis, disease severity should be assessed at an experienced center. This will involve
measurement of the O/E LHR and position of the liver (grade of recommendation = D).

- In case of an anticipated birth prior to 34 weeks of gestation, antenatal steroids should be given (grade of recommendation = D).

- Delivery after a gestational age of 39 weeks in a high-volume tertiary center should be planned (grade of recommendation = D).

**Delivery Room Management and Treatment in the Initial Postnatal Phase**

Initial treatment and procedures in the delivery room are based on the updated Guidelines of the International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations [17].

Monitoring and Goal of Treatment

Measurements of heart rate, pre- and postductal saturations and intra-arterial blood pressure are recommended. The key principles are the avoidance of high airway pressures and the establishment of adequate perfusion and oxygenation (based on preductal arterial saturation, SpO2 measurements). In a study from Dawson et al. [18] in term and preterm healthy neonates, the overall SpO2 values at 10 min after birth were median 94% (interquartile range 91–97%) in preterm infants and median 97% in term infants (interquartile range 92–98%). Based on expert opinion, the consortium agreed on preductal saturation and oxygenation (based on preductal arterial saturation, SpO2 measurements). In a study from Dawson et al. [18]

Vascular Access

The consortium recommends immediate placing of an arterial line because it reflects the postductal situation, but alternatively, an umbilical arterial line may be placed. This is less desirable, however, than a right radial artery line because it reflects the postductal situation, but on the other hand, it may give more secure longer-term arterial access. Each procedure should be performed as soon as possible. It is important, however, to prevent further agitation from recurrent insertion attempts as this may impair postnatal adaptation [25].

Blood Pressure Control

Measures to increase the systemic blood pressure may minimize the right-to-left shunting. However, there is no need to increase blood pressure levels to supranormal values if the preductal saturation remains above 80%. Therefore, the consortium recommends maintaining arterial blood pressure at normal levels for gestational age if pre-natal assessment (e.g. left-sided defect, O/E LHR >50%, and liver down), spontaneous breathing could be considered instead to prevent ventilator-induced lung injury. Low peak pressures, preferably <25 cm H2O, are recommended to avoid lung damage to the ipsilateral and contralateral lung.

**Sedation and Analgesia/Paralysis for Intubation**

Carabajal et al. [21] have studied physiological responses of neonates to awake intubation, and they reported significant rises in systemic arterial blood pressure and intracranial pressure, as well as significant decreases in heart rate and transcutaneous oxygen saturations. In 166 infants Caldwell and Watterberg [22] found that premedication for intubation significantly attenuated both the clinical pain score and the increase in blood glucose as markers of acute stress. Moreover, it seems that intubation success rates progressively improve with premedication, although in some cases this is not possible due to a lack of vascular access [23]. Murthy et al. [24] have shown no beneficial effects of administration of neuromuscular blocking agents immediately after intubation; in fact lung compliance deteriorated upon administration.

**Naso- or Orogastric Tube**

The consortium recommends immediate placing of an oro- or nasogastric tube with continuous or intermittent suctioning in order to prevent bowel distension and any additional ipsilateral lung compression.
ductal saturations remain between 80 and 95%. In the case of hypotension and/or poor tissue perfusion, a fluid bolus of 10–20 ml/kg NaCl 0.9% should be administered, although no more than 2 times. If tissue perfusion and blood pressure do not improve, inotropic and/or vasopressor medication should be considered according to local practice. Hydrocortisone may be used in the early phase for the treatment of hypotension after other treatment has failed [26].

Surfactant
There is no rationale for surfactant therapy because in CDH patients surfactant amounts are likely to be appropriate to lung size [27].

Recommendations
- After delivery, the infant should be intubated routinely without bag and mask ventilation (grade of recommendation = D).
- The goal of treatment in the delivery room is achieving acceptable preductal saturation targets, i.e. between 80 and 95% (grade of recommendation = D).
- Ventilation in the delivery room should be done with a peak pressure as low as possible, preferably with 25 cm H₂O, or below that (grade of recommendation = D).
- An oro- or nasogastric tube with continuous or intermittent suction should be placed (grade of recommendation = D).
- Arterial blood pressure has to be maintained at a normal level for gestation. In the case of hypotension and/or poor tissue perfusion, 10–20 ml/kg NaCl 0.9% should be administered 2 times (grade of recommendation = D).
- In cases of persistent hypotension after the administration of NaCl 0.9%, inotropic and vasopressor agents should be considered (grade of recommendation = D).
- In CDH infants who are predicted to have good lung development based on their prenatal assessment (e.g. left-sided defect, O/E LHR >50%, and liver down), spontaneous breathing could be considered (grade of recommendation = D).
- Premedication should be given before intubation if possible (grade of recommendation = D).
- Neuromuscular blocking agents should be avoided during initial treatment in the delivery room (grade of recommendation = D).
- No routine use of surfactant in either term or preterm infants with CDH (grade of recommendation = D).

Ventilation Management in the Intensive Care Unit
Permissive hypercapnia and ‘gentle ventilation’ have been reported to increase survival in neonates with CDH [28, 29]. A ventilation strategy aiming for preductal saturation between 80 and 95%, postductal saturation above 70% and arterial CO₂ levels between 50 and 70 mm Hg (6.9–9.3 kPa, permissive hypercapnia) is well accepted. In the first 2 h after birth, preductal SpO₂ levels as low as 70% are acceptable provided they are slowly improving and organ perfusion is satisfactory (indicated by a pH >7.2), and if ventilation is adequate (PaCO₂ <65 mm Hg, 8.6 kPa). Thereafter, preductal saturation levels are preferably kept between 85 and 95%. In individual cases, however, levels down to 80% may be accepted, providing organs are well perfused, as indicated by a pH >7.2, lactate levels <5 mmol/l and urinary output >1 ml/kg/h. Postductal saturations should remain above 70%. Oxygen toxicity can be avoided by decreasing FiO₂ on the guidance of the saturation levels described above. The optimal initial ventilation strategy was investigated in a collaborative initiative from the CDH EURO Consortium (VICI-trial, NTR 1310) [30]. Although the primary outcome (death/bronchopulmonary dysplasia at day 28) was not significantly different between the two groups, it was found that infants initially ventilated by conventional mechanical ventilation required a significantly shorter duration of ventilation, had less need for inhaled nitric oxide (iNO) or sildenafil, had a shorter duration of vasoactive medication and were less likely to require ECMO [3]. Therefore, the CDH EURO Consortium recommends conventional mechanical ventilation as the initial ventilation strategy. Recommendations for initial ventilation settings for pressure-controlled ventilation are summarized below. In the case of weaning, the peak pressure should primarily be reduced. Thereafter, frequency or PIP/PEEP may be reduced as long as pCO₂ <50 mmHg (6.7 kPa). In general, the consortium recommends aiming for a limitation of peak pressure to 25 cm H₂O or less, a PEEP of 3–5 cm H₂O and adjustment of the ventilator rate to obtain PaCO₂ between 50 and 70 mm Hg (6.9–9.3 kPa). If a PIP of >28 cm H₂O is necessary to achieve pCO₂ and saturation levels within the target range, other treatment modalities (such as high-frequency oscillatory ventilation or ECMO) should be considered.

Chest Radiograph
To assess the patient’s initial condition, a chest radiograph should be obtained as soon as possible.
Recommendations

- Conventional mechanical ventilation is the optimal initial ventilation strategy (grade of recommendation = C).

- High-frequency oscillatory ventilation can be used as rescue therapy if conventional mechanical ventilation fails (grade of recommendation = D).

- Adapt ventilation settings to reach a preductal saturation between 80 and 95% and a postductal saturation above 70% (grade of recommendation = D).

- The target PaCO₂ should be between 50 and 70 mm Hg (6.9–9.3 kPa; grade of recommendation = D).

- Pressure-controlled ventilation: initial settings are a PIP <25 cm H₂O and a PEEP of 3–5 cm H₂O; ventilator rate of 40–60/min (grade of recommendation = D).

- After stabilization, reduce FiO₂ if the preductal saturation is above 95% (grade of recommendation = D).

Further Management in the Intensive Care Unit

Sedation and Analgesia

A wide range of sedative and analgesic practices has been described [31, 32]. Most centers use opioids such as morphine sulfate or fentanyl. Although there is no specific evidence in infants with CDH, neuromuscular blockade is associated with side effects such as hypoxemia – and thus should be avoided. Infants should remain sedated during mechanical ventilation until weaning form mechanical ventilation is commenced.

Monitoring

Heart rate, invasive blood pressure, pO₂ and pCO₂, and pre- and postductal saturation should be monitored routinely. A head ultrasound scan should be performed at a time when there is little danger of arousing the newborn. Monitoring the regional cerebral oxygenation saturation with near infrared spectroscopy and transcutaneous saturation measurements may be indicated [33], although its additional value in CDH infants is not yet clear. Sedation and analgesia should be started as soon as venous access is established. Careful monitoring of the blood pressure is then warranted because more fluid volumes or vasoactive drugs may be needed in view of the potential adverse hemodynamic effect of sedatives, in particular midazolam. Supportive care such as cocooning and swaddling is recommended to prevent stress from too much noise, light and nociceptive stimulation. The infant’s condition should be regularly assessed using validated analgesia and sedation scoring systems, such as the COMFORT behavior score [34].

Hemodynamic Management

Hemodynamic management should be aimed at achieving appropriate end-organ perfusion determined by heart rate, urine output and lactate levels. If the heart rate is within the normal range [35], urine output is over 1.0 ml/kg/h, lactate concentration is <3 mmol/l and there are no other symptoms of poor tissue perfusion, inotropic or vasopressor support is not required. Echocardiography is indicated if there are signs of poor perfusion or if the blood pressure is below the normal level for gestation with a preductal saturation below 80%. This may show whether the poor perfusion is due to hypovolemia or myocardial dysfunction. If there is hypovolemia, saline fluid therapy should be given (10–20 ml/kg NaCl 0.9% or Ringer lactate up to 2 times during the first 2 h) [36]. If necessary, this should be followed by inotropic and/or vasopressor therapy. Hydrocortisone may be used for the treatment of hypotension after other treatment has failed.

Recommendations

- Infants should be sedated and be monitored using validated analgesia and sedation scoring systems (grade of recommendation = D).

- Neuromuscular blocking agents should be avoided if possible (grade of recommendation = D).

- If symptoms of poor perfusion and/or blood pressure below the normal level for gestation occur and are associated with preductal saturation below 80%, echocardiographic assessment should be performed (grade of recommendation = D).

- In case of hypovolemia, fluid therapy (10–20 ml/kg NaCl 0.9% or Ringer lactate) up to 2 times during the first two hours may be given and followed if necessary by administration of inotropic and/or vasopressor agents (grade of recommendation = D).

Pulmonary Hypertension

A 2D echocardiography performed within the first 24 h after birth remains the best modality to (1) rule out the presence of cardiac anomalies; (2) assess the right heart function, and (3) determine the amount of pulmonary hypertension classified accordingly (less or more than 2/3 systemic blood pressure) [37, 38]. Especially in severe cases of pulmonary hypertension, a cardiac ultrasound may help to evaluate right ventricular dysfunction and/or right ventricular overload, which condition can also lead to left ventricular dysfunction [39].

There is no evidence for the usefulness of increasing systemic vascular resistance to treat right-to-left shunting, but a number of centers from the consortium suggest us-
ing inotropic or vasopressor agents such as dopamine, dobutamine and (nor)epinephrine to maintain blood pressure at normal levels for gestation [40]. If preductal saturation falls below 85% and/or if there are signs of poor organ perfusion, treatment of pulmonary hypertention should be initiated. The first choice would be iNO, which is a pulmonary vasodilator. In neonates with pulmonary hypertension of the newborn (PHN) or severe hypoxic respiratory failure, iNO improves oxygenation and decreases the need for ECMO [41, 42]. At an oxygen saturation difference of 20% or higher and/or a pre- and postductal saturation index is above 20 and/or the saturation difference is more than 10% (grade of recommendation = D).

Recommendations

- Perform echocardiography within the first 24 h after birth to rule out structural cardiac anomalies (grade of recommendation = D).
- Blood pressure support should be given to maintain arterial blood pressure levels at normal levels for gestation (grade of recommendation = D).
- iNO administration for at least 1 h in a dose of 10–20 ppm should be considered if there is evidence of extra-pulmonary right-to-left shunting and the oxygenation index is above 20 and/or the saturation difference is more than 10% (grade of recommendation = D).
- In nonresponders iNO should be stopped. iNO responders are defined as follows: a decline of 10–20% in the pre-postductal saturation difference, or an increase of 10–20% of PaO₂, or improvement in hemodynamic parameters meaning a 10% increase in mean blood pressure, or a decrease in lactate levels (grade of recommendation = D).
- Intravenous sildenafil should be considered in CDH patients with severe pulmonary hypertension (grade of recommendation = D).
- In case of suprasystemic pulmonary artery pressure and right-to-left shunting through the foramen ovale, intravenous prostaglandin E1 should be considered (grade of recommendation = D).

Extracorporeal Membrane Oxygenation

The benefit of ECMO in the treatment of infants with CDH remains unclear. The ELSO registry showed a survival rate of 51% of patients with CDH who required ECMO [49]. The use of ECMO has decreased in recent years [50]; it is more used for preoperative stabilization, and the preferred method (venoarterial vs. venovenous) is still being debated. The VICI-trial showed no difference in survival between patients born in ECMO centers and patients born in non-ECMO centers [3].

Recommendations

- Criteria for ECMO (grade of recommendation = D):
  - Inability to maintain preductal saturations >85% or postductal saturations >70%.
  - Increased PaCO₂ and respiratory acidosis with pH <7.15 despite optimization of ventilator management.
  - Peak inspiratory pressure >28 cm H₂O or mean airway pressure >17 cm H₂O is required to achieve saturation >85%.
  - Inadequate oxygen delivery with metabolic acidosis as measured by elevated lactate ≥5 mmol/l and pH <7.15.
  - Systemic hypotension, resistant to fluid and inotropic therapy, resulting in urine output <0.5 ml/kg/h for at least 12–24 h.
  - Oxygenation index ≥40 present for at least 3 h.

Surgical Repair

Surgery should be performed electively. The effect of hospital volume on mortality is unclear. While a large study (2,203 infants) concluded that hospitals with a high volume of CDH repair have lower in-hospital mortality [51], a more recent study in 3,738 infants showed no difference in mortality between lower and higher surgical volume centers [52]. Controversies about the exact timing of the surgical repair in patients on ECMO remain [53]. A recent study from Partridge et al. [54] showed improved outcomes with surgical repair after ECMO, i.e. a higher likelihood of sur-
vival, less surgical bleeding and shorter duration of ECMO. A relative small study \( n = 46 \) from Fallon et al. [55] found that repair within the first 72 h of ECMO correlated with a shorter duration of ECMO, less circuit complications and a trend towards improved survival.

The routine use of a chest tube postoperatively to drain the effusion filling the pleural cavity has been abandoned. This does not preclude its use in individual cases to drain an effusion that is symptomatic, for example due to chylothorax existing before surgery.

The optimal surgical technique also remains under debate. Minimal access surgery has esthetic advantages and may be performed in patients with a left-sided defect and liver down, but carries a significantly higher risk of recurrence [56, 57]. There is also concern about absorption of CO\(_2\) used for insufflation in minimal access surgery [58], and CO\(_2\) insufflation pressures should therefore be minimized. A meta-analysis from Lansdale et al. [59] showed that thoracoscopic repair had greater recurrence rates and operative times but similar survival and patch usage compared with open surgery. Recently, Costerus et al. [60] concluded that thoracoscopic primary closure seems a safe and effective procedure, but efficacy of thoracoscopic patch repair has not been established. To allow for better comparison of patient groups between studies it is recommended to record the diaphragmatic defect size in all surgeries [37].

**Recommendations**

- Surgical repair of the diaphragmatic defect should be performed after clinical stabilization, defined as follows (grade of recommendation = D):
  - Mean arterial blood pressure normal for gestation.
  - Preductal saturation levels of 85–95% on FiO\(_2\) below 50%.
  - Lactate below 3 mmol/l.
  - Urine output more than 1 ml/kg/h.
- No routine chest tube placement postoperatively (grade of recommendation = D).
- Repair can be performed while the patient is on ECMO (grade of recommendation = D).

**Fluid Management, Parenteral Feeding, Entering Enteral Feeding and Gastroesophageal Reflux**

Restrictive fluid management in the first 24 h after birth consists of 40 ml/kg/day of fluids including medication, with additional saline volume top-up for intravascular filling in the case of inadequate tissue perfusion or hypotension. Parenteral nutrition only is allowed until surgical repair and until postoperative enteral feeding has been achieved. Gastroesophageal reflux may be treated both by antireflux medication and by surgical intervention [61]. Maier et al. [62] did not show evidence for prof-it beyond the first year of life after prophylactic Thal procedure at primary CDH repair. Diuretics should be given in the case of persisting positive fluid balance without hypovolemia, aiming for diuresis of >1 ml/kg/h [63].

**Recommendations**

- 40 ml/kg/day saline including medication for the first 24 h after birth; increase intake thereafter (grade of recommendation = D).
- Diuretics should be considered in the case of persisting positive fluid balance; aim for a diuresis >1 ml/kg/h (grade of recommendation = D).
- Preventive antireflux therapy should be started in combination with enteral feeding (grade of recommendation = D).
- Preoperatively, patients should only receive parenteral nutrition (grade of recommendation = D).

**Conclusion**

The European task force for CDH (CDH EURO Consortium) has agreed on an updated protocol for standardized postnatal treatment guidelines. Although it is emi-


**Appendix**

*Members of the CDH EURO Consortium Group:*

- Austria, Graz, Medical University Graz: B. Urlesberger
- Belgium, Leuven, University Hospital KU Leuven: K. Allegaert, A. Debeer, J. Deprest
- Canada, Manitoba, University of Manitoba: R. Keijzer
- France, Paris, Hôpital Antoine-Béclère: A. Benachi
- France, Lille, Hôpital Jeanne de Flandre: L. Storme
- France, Paris, South Paris University Hospitals: P. Tissieres
- Germany, Bonn, Universitätsklinikum Bonn: F. Kipfmueller; Germany, Mannheim, Universitätsklinikum Mannheim: T. Schaible, L. Wessel
- Ireland, Dublin, Our Lady’s Children’s Hospital: C. Breatnach
- Italy, Milan, Fondazione IRCCS Cà Granda, Ospedale maggiore polifunzionale: E. Leva, F. Ciralli
- Italy, Rome, Bambino Gesu Children’s Hospital: P.
References


Acknowledgment

We thank Ko Hagoort for editing.


