SIBEN’s First Clinical Consensus: Diagnostic and Therapeutic Approach to the Patent Ductus Arteriosus in Preterm Infants

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Objective
To report the process and results of the first neonatal clinical consensus of the Ibero-American region.

Design and methods
Two recognized experts in the field (Clyman and Van Overmeire) and 45 neonatologists from 23 countries were invited for active participation and collaboration. We developed 46 questions of clinical-physiological relevance in all aspects of patent ductus arteriosus (PDA). Guidelines for consensus process, literature search and future preparation of educational material and authorship were developed, reviewed and agreed by all. Participants from different countries were distributed in groups, and assigned to interact and work together to answer 3-5 questions, reviewing all global literature and local factors. Answers and summaries were received, collated and reviewed by 2 coordinators and the 2 experts. Participants and experts met in Granada, Spain for 4.5 h (lectures by experts, presentations by groups, discussion, all literature available).

Results
31 neonatologists from 16 countries agreed to participate. Presentations by each group and general discussion were used to develop a consensus regarding: general management, availability of drugs (indomethacin vs. ibuprofen), costs, indications for echo/surgery, etc. Many steps were learnt by all present in a collaborative forum.

Conclusions
This first consensus group of Ibero-American neonatologists SIBEN led to active and collaborative participation of neonatologists of 16 countries, improved education of all participants and ended with consensus development on clinical approaches to PDA. Furthermore, it provides recommendations for clinical care reached by consensus. Additionally, it will serve as a useful foundation for future SIBEN Consensus on other topics and it could become valuable as a model to decrease disparity in care and improve outcomes in this and other regions.

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PRIMER CONSENSO CLÍNICO DE SIBEN: ENFOQUE DIAGNÓSTICO Y TERAPÉUTICO DEL DUCTUS ARTERIOSO PERMEABLE EN RECIÉN NACIDOS PRETEMPERINO

Objetivo
Informar acerca del proceso y de los resultados del primer consenso clínico neonatal de la región iberoamericana.

Diseño y métodos
Dos expertos reconocidos en el área (los Dres. Clyman y Van Overmeire) y 45 neonatólogos de 23 países fueron invitados a participar y a colaborar. Se desarrollaron 46 preguntas de importancia clínico-fisiológica sobre la totalidad de los aspectos del ductus arterioso persistente (DAP). Las pautas para el proceso del consenso, la búsqueda de la bibliografía y la futura preparación de material educativo y autoría fueron descritas, revisadas y acordadas por todos los participantes. Los expertos de diferentes países fueron distribuidos en grupos, y asignados para interactuar y trabajar conjuntamente para responder a las 3-5 preguntas, revisando la totalidad de la bibliografía globalmente y los factores locales. Las respuestas y los resúmenes fueron recibidos, cotejados y revisados por 2 coordinadores y los 2 expertos. Los participantes y los expertos se reunieron en Granada, España, durante 4,5 h (con conferencias de expertos, presentaciones por grupos y discusión de toda la bibliografía de la que se disponía).

Resultados
Participaron 31 neonatólogos de 16 países. Las presentaciones de cada grupo y la discusión general se utilizaron para desarrollar un consenso en el que se consideraron: tratamiento general, disponibilidad de fármacos (indometacina frente a ibuprofeno), costes, indicaciones para eco/cirugía, etc. En este foro de cooperación, los participantes aprendieron numerosos aspectos del tratamiento de esta entidad.

Conclusiones
Este primer grupo de consenso de neonatólogos iberoamericanos de SIBEN llevó a la participación activa y cooperativa de neonatólogos de 16 países, mejoró la educación de todos los participantes y finalizó desarrollando un consenso sobre los enfoques clínicos del DAP. Además, indica recomendaciones para el cuidado clínico a las que se ha llegado mediante consenso. Asimismo, servirá como una base útil para futuros consensos de SIBEN en otros temas y podría llegar a ser un valioso modelo para disminuir la disparidad en el cuidado y mejorar los resultados en esta y en otras regiones.

Palabras clave:

INTRODUCTION
The education, training and advances in neonatology in Spanish and Portuguese speaking countries have been pretty dissimilar in the past 15 years. In 2004, the Iberoamerican Society of Neonatology (SIBEN) was created, with the principal objective of contributing to the improvement of quality of life for newborn infants and their families in the ibero-american population. SIBEN is a new society, with members from 25 different countries. The usefulness of a society that focuses in neonatology is to facilitate education, communication and advancement of professionals that contribute to the welfare/well-being of newborns and their families, in order to improve neonatal outcomes in the region, as it has been documented in its vision and mission.

In the past several years, it has been found that the process of medical consensus could be a way of increasing professional collaboration, as well as improving uniformity in the care given to patients.

The Patent Ductus Arteriosus (PDA) is a frequent and complex problem of preterm infants. It is the most common cardio-circulatory defect in neonates, and occurs in 60% of newborns less than 28 weeks gestation. PDA is associated with premature infants’ morbidity and mortality, and it is important from a public health perspective due to the development of Intensive Care Units in Iberoamerica, the controversies in the management of PDA, and it’s medical and surgical treatment.

Based on these three points, we proceeded to organize the First Clinical SIBEN Consensus on PDA. The Consensus Group, formed by a group of neonatologists from different countries from Iberoamerica (SIBEN Consensus Group), worked for several months with an intense and collaborative methodology, and met in Granada, Spain, during the XII National Congress of Perinatal Medicine (SEN), IV Iberoamerican Congress of Neonatology (SIBEN), and II Congress of the Spanish Society of Perinatal Medicine (SEMP), in October 2007.

The objective of this manuscript is to present the results of this first neonatal clinical consensus of the Iberoamerican region with regards to diagnostic, clinical and therapeutic aspects of PDA. We hope that the summary of available data as well as the recommendations of this SIBEN Consensus will contribute to unify criteria for infant care. The most important objective is to diminish the gap between knowledge and what every baby born in this region receives, thus decreasing the disparity in the care provided, and improving short and long term results.

METHODS
Starting at the beginning of 2007, Dr. Augusto Sola began to develop the idea of organizing “SIBEN Clinical
Consensus”. In March 2007, Drs. Sergio Golombek and Augusto Sola invited Drs Ronald Clyman (University of California at San Francisco) and Bart van Overmeire (Amberes, Belgium), world experts in the field of PDA, to be “key opinion leaders” for the First SIBEN Clinical Consensus. In the same month, they started to invite 71 neonatologists from 23 countries of the Iberoamerican region, to collaborate and participate in this consensus. Of all of the physicians invited, a total of 27 accepted to participate; together with the principal investigators, and the two experts a total of 31 physicians of 16 countries. The full list of participating physicians of this Consensus and authors of this paper is included at the end of the paper.

The methods of the Consensus included:

1. To elaborate in a consensus fashion a guide and recommendations for all of the relevant clinical topics related to the Patent Ducts Arteriosus in the Premature Infant.
2. During a period of 4 months, the following activities took place:
   a) Constituting a group of neonatologists from different countries in the Iberoamerican region.
   b) Assignment of sub-groups, with collaborative work in each subgroup.
   c) Conferences with both leading experts.
   d) Presentations of the conclusions of the work done by each subgroup.
   e) Discussion with all the participants of the SIBEN Consensus Group.
   f) Plan for the diffusion of the final document of the Consensus reached by an active, collaborative and participative method.

All of the participants of the SIBEN First Clinical Consensus signed a Confidentiality Agreement, of intellectual property, of authorship and conflict of interest, which will be also utilized in future SIBEN Consensus already being planned.

Sub-group work

The Directors of the Consensus formulated a list of multiple questions of clinical relevance and divided them between 10 sub-groups of 3-4 neonatologists from different countries. Each sub-group worked for 3 months on the assigned questions, and did not know the questions sent to the other sub-groups. The participants worked in a collaborative fashion, performing a complete search and an extensive analysis of the appropriate literature. Whenever necessary, the local and/or regional problems were investigated and known by each subgroup. The answers and all the literature used by each subgroup were sent in September 2007, approximately a month before the Clinical Consensus group met in Granada, Spain.

Meeting of the Consensus Group during the Conference in Granada, Spain (October 5th, 2007)

The participants of the Consensus attended three general conferences from Drs. Clyman and van Overmeire. Then representative of each sub-group presented the answers to each of the assigned questions and their recommendations, followed by a period of discussion with questions and answers, and dialogue between all the participants. Before the group’s meeting it was clear to all that it could be possible that in some of the themes the final document could include some concepts like “it is impossible to recommend based on “scientific knowledge”, but in light of the current knowledge and understanding, the recommendation of the SIBEN Consensus Group is…” or that for some items there could be a “main consensus” and a “second consensus alternative”.

This manuscript was subjected to 4 revisions made by all of the participants. In the paper we formulate the questions as posed originally and the pertinent comments and answers as per the Consensus Group. To complete the work, we end the manuscript with an abbreviated list of the consensus recommendations.

RESULTS

This section thoroughly describes the questions and answers obtained by consensus among all the participants according to the described methodology with the agreement of two experts and opinion leaders.

Initial definition

The theme that concerned this Consensus was the communication between the aorta and pulmonary arteries with left-to-right shunt in preterm newborn infants, although the shunt could either be minimal or bi-directional. This Consensus did not analyze the right-to-left shunt through the ductus, as this is not considered a “patent ductus arteriosus” (PDA). When the ductus remains open, and the shunt is right-to-left (with decreased pulmonary blood flow), the pathophysiology and clinical findings as well as the clinical management are totally different.

The connection between the aorta and pulmonary artery with left-to-right shunt is referred to with different terms in different Iberoamerican regions including: persistence of the duct, ductus arteriosus, permeable duct, patent ductus (or duct) arteriosus and patent ductus (o duct) arteriosus. There is general consensus that the term
patent ductus arteriosus (PDA) will be used here to unify terms. There is no uniform consensus on the exact period for PDA exposure for it to be considered as a persistent or prolonged PDA (PP-PDA). Some experts consider that PP-PDA remains open for more than 14 days whereas some other experts consider that it is open for more than 21 days.

1. High risk of PDA and persistently prolonged PDA (PP-PDA) development in newborns

The PDA is an alteration in the adaptation of the prematurely born neonate to the extraterine environment, the most common cardio-circulatory in preterm neonates. The preterm newborn < 1,500 grams, has a high incidence of PDA. The highest risk neonates to develop PDA are the preterm neonates with respiratory distress syndrome (RDS). The global incidence in preterm NB is 50-70% being more frequent at lower gestational ages. It has been estimated that PDA occurs in 53% of NB < 34 weeks and in more than 65% of NB < 26 weeks. Up to 80% of preterm NB with extremely low birth weight (< 1,000 g) and approximately 45% of NB with birth weight < 1,750 g show PDA and only 1 out of 5000 term newborns show PDA.

Several factors affect the incidence. For example, antenatal steroids reduce PDA incidence. In contrast, prenatal exposure to magnesium sulfate is associated with a high risk of PDA in preterm newborns (NB). Likewise, a high risk of PDA is associated with the administration of phototherapy, maternal diabetes, antepartum hemorrhages and multiple pregnancy.

Undoubtedly, in many preterm NB the PDA is non-significant that closes spontaneously without consequences. In healthy preterm NB, PDA closes in a period similar to that in full-term NB. In the rest of preterm NB, the frequency of spontaneous closure and the time in which it occurs can show great variability. Furthermore, in many unhealthy preterm NB, a symptomatic PDA is unable to close even with medical treatment. In preterm infants < 26 weeks, only 36% had spontaneous PDA closure, and this occurred in the more mature, with a higher prevalence of prenatal steroids, intrauterine growth retardation and maternal hypertension and less RDS. Early ductus diameter predicts the persistence of PDA and the lack of spontaneous closure. Ductal constriction has been predicted 5 hours after life when the diameter is < 1.6 mm. The newborns at risk to develop PP-PDA are those who show the aforementioned risks and also have: a) early, untreated PDA; b) early, treated PDA with no response to medical treatment, and without surgery or with late surgery; c) late PDA, untreated or treated with no response to medical treatment, and without surgery or with late surgery.

2. Diagnosis of ductus and hemodynamically significant ductus (HS-PDA)

The concept of hemodynamically significant PDA (HS-PDA) is rather wide. HS-PDA is generally symptomatic (Table 1) but it can also be asymptomatic. A Doppler echocardiogram can demonstrate the presence of a significant left-to-right shunt through the ductus. Clinical signs are not useful for early PDA diagnosis. The sensitivity and specificity of a heart murmur are more than 90% only after 6 days of PDA. Moreover, differential or pulse pressure is not statistically different in newborns with HS-PDA. These data show that PDA diagnosis can be made depending exclusively on physical signs, but it is only possible to make a late diagnosis. It is clear that when all the clinical signs shown in Table 1 are present, the clinical PDA diagnosis is easy to make. However, when the diagnosis is made, the PDA has already affected the newborn. Hence, echocardiography is considered important. It has been estimated that when the ductus diameter is > 1.5 mm, the pulmonary/systemic blood flow relation is > 1.5; and when the diameter is > 2.0 mm the relation is superior to 2 to 1. Table 2 shows the echocardiographic findings of HS-PDA; its severity can be assessed well by trained physicians.

3. Acute and long-term effects of HS-PDA.

The “natural” history of HS-PDA

Lack of respiratory improvements with no other clinical sign in preterm NB who undergo CPAP or intermittent artificial ventilation could be due to HS-PDA, visible through echocardiography (ECHO). A large PDA with left-to-right shunt is associated with serious compli-

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Manifestations of Patent Ductus Arteriosus (PDA) (the absence of many of them does not rule out PDA)</th>
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<tbody>
<tr>
<td>Tachycardia</td>
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<tr>
<td>Hyperactive precordium</td>
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<tr>
<td>Worsening of respiratory status</td>
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<td>Tachypnea</td>
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<td>Aprexia</td>
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<td>Cardiomegaly</td>
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<td>Decrease in mean arterial pressure (MAP)</td>
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<tr>
<td>Systolic murmur in crescendo</td>
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<tr>
<td>Bounding pulses</td>
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<tr>
<td>Inability of weaning O2 requirements</td>
</tr>
<tr>
<td>Dependency of CPAP or ventilator</td>
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<tr>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Hepatomegaly</td>
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<tr>
<td>Diastolic Hypotension</td>
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<tr>
<td>Increased pressure gradient (pulse pressure) &gt; 25-30 mmHg</td>
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AEP NOV INTERNET ingles 14/10/08 12:26 Página 458

Golombek SG et al. SIBEN’s First Clinical Consensus: Patent Ductus Arteriosus

4. Risks of a persistently prolonged PDA (PP-PDA). PP-PDA associated morbidities

Although some PDA cases are not hemodynamically significant, they can involve a risk of endovascular infections and thromboembolism. Those preterm newborns with a PDA that persists for more than two weeks gain less weight, take longer time to reach complete enteral feeds and require more days on mechanical ventilation. In a cohort study, newborns with PP-PDA required longer mechanical ventilatory support and $O_2$, and showed a higher incidence of severe bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), parenteral nutrition, cholestasis, osteopenia and malnutrition. Length of stay is also longer and more frequently these newborns require oxygen therapy upon discharge.

5. When should a HS-PDA BE TREATED? Avoiding a PP-PDA

PDA has been associated with acute decompensation and prolonged need for mechanical ventilation in several reports since 1972. Several studies also demonstrated a significant improvement in pulmonary function and ventilation parameters in NB with RDS after PDA closure. Cardiovascular abnormalities, and cerebral, mesenteric and renal flows also revert after closure. According to the reviewed literature by the Consensus, HS-PDA must always be treated in order to prevent other associated complications, like major neurodevelopment abnormalities that not only increase morbidity but also are potentially lethal.

Cases with clinically significant PDA treated with ciclo-oxygenase inhibitors (Indomethacin and Ibuprofen) have a clinical course with less $O_2$ requirements and artificial ventilation and, consequently, with less risk of BPD and even with less incidence of ROP.

The presence of PDA could cause no problems in some preterm newborns, similar as it happens in some full-term infants that have had a PDA for several months. However, the hemodynamic compromise that the PDA has on different organs (more evident the more premature and sicker the baby is), stresses the importance of trying to close it in order to avoid the associated morbidities. It is not easy to define a “healthy” preterm NB with PDA. When a preterm NB is on CPAP or CPAP support cannot be stopped, or the baby requires fluid or nutrient restriction or additional oxygen therapy, this is not a “healthy” baby. When the PDA is not treated in these or more affected preterm NB, there is a high risk of closure failure and development of PP-PDA. Of course, when the baby is on a ventilator and the settings cannot be weaned, or the status worsens, the cause could be a PDA. The available evidence, even if it is not definitive, indicates that in

these newborns with these clinical conditions, the ductus should not remain open due to a high risk of PP-PDA and associated morbidities.

Undoubtedly, a PDA that persists for more than three weeks increases such risks.5,12,27,34,35,53-57 All of the participants in this consensus, except for one, recommend that closure of a HS-PDA should be attempted before the first two weeks of life to prevent PP-PDA. The same is recommended for sick immature newborns with PDA.

6. Can a newborn with severe BPD that requires oxygen be discharged if he has a HS PP-PDA? Yes or no? Why?

A PP-PDA can be associated with serious complications as it has already been indicated above. When newborns with PP-PDA require oxygen, it is not possible to know how the left-to-right shunt contributes to this condition. Under these circumstances, a detailed Doppler echocardiographic evaluation is crucial. If PDA is larger than 1.5 mm and/or there is indication of HS-PDA, the newborn should not be discharged until the problem is solved (probably with the need for surgical ligation before discharge, even if it needs to be performed at a different institution). This consensus group does not recommend discharge before closure of a HS-PDA.

7. Infections, inflammation and PDA

The PDA has been associated with infections and inflammation. This can be clearly understood taking into account that circulating prostaglandins significantly increase during neonatal infection or sepsis. Therefore the ductus can re-open or not respond to the treatment with cyclo-oxigenase inhibitors.58 Moreover, in preterm NB with sepsis and HS-PDA there is a significant association with development of BPD with an odds ratio (OR) of 48.3 (95% CI: 6.3-100).59

In addition, low cortisol levels in the first week of life have been associated with pulmonary inflammation and PDA in very low birth weight infants.60 This suggests that early adrenal failure contributes to PDA and pulmonary inflammation associated with an adverse clinical respiratory course. However, the cause of this association has not been demonstrated. On the other hand, prenatal steroid administration and low postnatal doses affect the PDA response to treatment, with improved efficacy of postnatal pharmacologic treatment.60-62

These data demonstrate that the modulation of the inflammatory response could have a role in PDA treatment. However, at present, interfering with the neonatal inflammatory-anti-inflammatory balance cannot be recommended since it poses several risks.

8. Hydroelectrolytic balance, diuretics, nutrition and PDA

8A. Do volume infusions and total daily volume in ml/kg/day increase the prevalence of PDA in VLBW infants?

Preterm newborns require parenteral hydroelectrolytic and caloric support and must remain in a strict individual control to promote negative water balance and weight loss during the first days of life. These newborns tend to show an excess in insensible losses, and an immature kidney unable to control fluid excesses or deficits.63,64

At birth, the infant show an expanded fluid volume compared with the extrauterine requirements, more so with decreasing gestational ages.64 This volume excess must decrease to, among other reasons, allow good pulmonary function, although an excessive fluid loss can lead to dehydration, renal failure, hyperkalemia and death.65

In several studies it has been suggested that the fluid intake per kg and per day should be calculated according to tables depending on weight, gestational age and phototherapy use. This calculation can be inappropriate in many NB. Other aspects should be taken into account, for example, the fact that phototherapy use does not increase insensible losses. Therefore, individualized fluid intake is recommended, administering the required physiologic needs each and every day. Different guidelines on hydroelectrolytic intake have been recommended by different authors in different studies.66-68 like, for example, losing between 3 to 5 % of daily weight, up to 15 % of birth weight, stating with 50 ml/kg/day on the first day of life, and gradually increase depending on the urine output, weight loss and insensible water loss, or else providing 60-80 ml/kg/day in the first 3 days of life.66-68

In a study published three decades ago,69 an association between PDA and a higher fluid intake was found in NB < 2,000 g on mechanical ventilatory support due to RDS. After that,70 a retrospective study was published that described an association between excess fluid and PDA, with greater risk for BPD. In a randomized study in 1980, 170 NB with 501-2,000 g71 birth weight were studied comparing “high” vs. “low” fluid intake. The risk of PDA, congestive heart failure and NEC was higher in the “high” volume group.

The main result of a Cochrane meta-analysis72-73 was that the strategy of water restriction in preterm NB significantly reduces their weight compared to birth weight and hence reduces the risk of PDA, NEC and death. The lower relative risk of PDA was 0.40 (CI: 0.26-0.63) in the groups with water restriction. A tendency to reduce BPD was also reported. To summarize, the current recommendations are to prevent fluid boluses of normal saline solution, to start maintenance fluids around...
60-80 ml/kg/day, and to perform a frequent and individual evaluation of urine output, weight and serum sodium, estimate insensible water loss every 8-12-24 hours (based on the level of immaturity and sickness), to decide what the needs are. The objective is to achieve a negative water balance with a weight loss between 2-3%/day (12-15% in the first 5-7 days), adjusting fluid intake according to the scientific evidence and the basal metabolic needs.

Because of what was previously described, this Consensus group recommends a careful fluid restriction in preterm NB based on a strict fluid balance (evaluating fluid inputs and outputs, weight variation, frequently assessing insensible losses) in order to administer the required physiologic needs but nothing else. This implies that during the first hours it could be started at 60-75 ml/kg/d and that volume infusions (“water and salt”) must be used exceptionally and only when there is clear evidence of hypovolemia, which is an infrequent condition during the first days of life. Fluid intake should be individualized, based on each case’s insensible water loss and serum sodium levels. With this technique, a reduction in mortality, and a reduction in the incidence of PDA, BPD, NEC should be expected.

8B. Fluid volume (ml/kg/day) when PDA occurs during the first days or weeks of life

No studies report fluid management for HS-PDA cases. It is probable that the aim of a negative fluid balance in NB may show more benefits than it has been reported in the studies referred to in 8A. As was described, PDA as well as Indomethacin can cause oligo-anuria. For many years it has been recommended that fluid intake should be reduced at least 20 ml/kg/day because of PDA and the use of Indomethacin. Therefore, in newborns with a confirmed PDA a strict balance should be obtained (inputs, urinary outputs, insensible losses) generally reducing fluid input to provide fluids and to avoid fluid excess and weight gain. Fluid excess can be caused by a volume of 130 ml/kg/d, but also with 70 ml/kg/d if there are no insensible losses and there is a urinary volume of <24 ml/kg/d (1 mL/kg/h), for example. This is crucial to reduce possible complications due to edema or excess body water.

8C. Diuretics use for PDA. Does furosemide increase the prevalence of PDA?

The use of furosemide could increase the prevalence of PDA due to its effects as a prostaglandin inhibitor.

Diuretics are not necessarily part of PDA treatment, although some studies suggest their use if there is radiological evidence of pulmonary edema. Some other studies have recommended the use of furosemide after each indomethacin dose in order to avoid indomethacin adverse effects at the renal level. However, furosemide increases prostaglandin production at the renal level. Therefore, the ductus response to the pharmacologic closure treatment with prostaglandin inhibitors (indomethacin and ibuprofen) could be minimized according to randomized studies. Moreover, there are no studies that report significant benefits of furosemide, none documented at long-term. In a systematic review it was reported that there was not enough evidence to justify the use of furosemide in preterm infants treated with indomethacin.

Furthermore, furosemide not only increases the prevalence of ductal patency and can inhibit indomethacin efficacy for closure, but also leads to metabolic, electrolytic, renal risks and hypoacusia. Therefore, based on the available literature, this Consensus group does not recommend the use diuretics and even less of furosemide at this gestational and postnatal age.

9. Enteral nutrition

Several issues were reviewed when enteral nutrition was discussed, for example, whether to feed infants with PDA and HS-PDA, the appropriate fluid intake, or whether or not to feed when pharmacological closure is attempted.

This SIBEN Consensus Group considered the following points as relevant:

1. The studies that evaluate the effects of feeding neonates with ductus arteriosus and/or medical treatment for PDA do not provide enough evidence to reach appropriate conclusions.

2. The randomized studies that have investigated the use and response to indomethacin or ibuprofen do not provide a feeding protocol. Therefore, it is not possible to know whether the infants included in the studies were orally fed or not.

3. Even when there is evidence that ibuprofen, unlike Indomethacin, would not alter mesenteric vascular flow, the comparison between pharmacological treatment with Indomethacin and Ibuprofen showed no differences in the incidence of gastrointestinal complications. PDA pharmacological treatment with Indomethacin reduces mesenteric flow, which leads to risks of gastrointestinal complications; Ibuprofen does not have these effects.

Although differences in gastrointestinal complications such as NEC have not been demonstrated, more studies should be done to evaluate other effects and complications (other then NEC) more appropriately.

Despite this uncertainty and lack of strong evidence in the reviewed literature, this Consensus group considers that the following strategies could be recommended for NB with low birth weight focusing on potential risks and benefits:
1. Trophic enteral stimulation (with breast milk). There is evidence of cytologic changes in gastrointestinal cells with apoptosis which could lead to NEC in preterm NB with PDA, particularly when sepsis occurs. Hence it would be cautious not to perform enteric stimulation previously. Therefore, it is recommended that trophic stimulation is initiated after birth (before 24-48 hours) with a volume of 10-15 ml/kg/day at a maximum of q 4-6 h, without advancing volume any further. To decide how to continue advancing enteric nutrition, our recommendations are based on the early diagnosis of PDA, of its size and on hemodynamic relevance.

2. If a small PDA with no hemodynamic compromise or significant shunt is diagnosed with Doppler echocardiogram, trophic enteral stimulation could proceed or volumes could be cautiously increased (by 10-15 ml/kg/day) until the problem is solved.

3. In cases where there is doubt, or when there is a definitive diagnosis of HS-PDA, the recommendation of this Consensus is not to feed enterally during 48-72 hours before the problem is solved. It is still undecided whether it is convenient to maintain or to stop trophic gastrointestinal stimulation. It seems prudent to stop trophic stimulation if on top of the HS-PDA there is sepsis or significant intrauterine growth retardation.

4. Due to mesenteric blood flow changes, enteral nutrition is not recommended during 48-72 h until the problem is solved when NB are treated with intravenous indomethacin. If infants are previously fed, interruption of feeds is recommended at least 4 hours before therapy administration. As mentioned, it has not been determined whether it is convenient to continue or interrupt trophic enteral stimulation.

5. Ibuprofen could have advantages due to less negative effects on mesenteric blood flow, but there is still no evidence of clinical advantages in the GI tract compared with Indomethacin use. Therefore, feeding is not recommended since the risks seem to be more dependent on the presence of HS-PDA.

6. Once PDA is controlled or closed, feeding could be reinitiated, preferably with breast milk within 24-48 hours after treatment, strictly monitoring tolerance. Volume increase should be gradual and cautious (< 20 ml/kg/day).

7. Total volume provided would be the one required by the infant to compensate insensible losses according to a strict water balance.

10. Oxygen consumption and HS-PDA

Oxygen consumption is in general elevated when a HS-PDA occurs. This is due to worsening of the pulmonary function by increased pulmonary permeability, ensuing pulmonary edema and increased hydrostatic pressure. Consequently, pulmonary compliance is diminished. Moreover, congestive heart failure secondary to left-to-right shunt should be taken into account. This produces an increased metabolic rate and oxygen consumption which can cause metabolic or mixed acidosis with cellular harm and also reduced surfactant production. If catabolism and oxygen consumption are elevated when HS-PDA occurs, it can be predicted that caloric requirements would be elevated and/or that it will be difficult to adequately satisfy nutritional requirements.

11. Growth and head circumference with prolonged exposure to HS-PDA

At present there are not definite answers. Treatment for HS-PDA closure improves heart failure, decreases mechanical ventilation, oxygen consumption, reduces mortality and improves growth and neurodevelopment in preterm NB. In a recent study carried out in two centers located in two different countries, it was found that HS-PDA persisting for more than 3 weeks was associated with negative effects on growth and cephalic perimeter with poor nutritional status, which can have long-term negative consequences.

12. Volume of enteral nutrition of at least 150 ml/kg/d is reached at a later stage in newborns with prolonged persistent exposure to HS-PDA

The PDA, especially when it co-exists with sepsis, is a risk factor for feeding intolerance. In a study of newborns ≥ 28 weeks of gestational age, the time interval between the start of feeds and establishing “full feeds” was greater in the newborns with sepsis and in the newborns with PDA. Feeding volume is usually restricted in clinical practice when a PDA is present, due to the increased risk of heart failure, necrotizing enterocolitis and four times greater risk of death in premature infants with HS-PDA. If this is done for a prolonged period, it may lead to insufficient caloric supply and nutritional deficit, often associated to long term adverse effects, though these have not been fully studied. Overall, this Consensus group recommends that when there are nutritional limitations due a persistent HS-PDA which may affect the growth of the newborn, neither enteral nor parenteral volumes should be used in excess, and the PDA should be closed soon. This would for earlier establishment of adequate enteral nutrition without having repercussions on the development of these newborns.
13. Intravenous support, parenteral nutrition and HS-PDA

HS-PDA is associated with an increased metabolic rate and risk of NEC. Long term PDA exposure can lead to insufficient nutrition by enteral means and/or slow advance of enteral volume. The protein and caloric support is therefore provided via parenteral nutrition. As mentioned before, there are more IV infusion and parenteral nutrition days the longer the PDA persists.

14. Metabolic and nutritional problems due to longterm exposure to HS-PDA

Available randomized studies indicate that this has not been studied in detail. However, in the previously mentioned studies, a significant difference of clinical importance in these variables can be observed. In addition to poor nourishment and inadequate growth of the head circumference, osteopenia is 8 times more likely and direct hyperbilirubinemia is 10 times more likely in newborns with PP-PDA.

15. Pharmacologic treatment of the patent ductus arteriosus

The clinical decision of treating PDA should be carried out on an individual basis, according to the gestational age, respiratory condition and the size of the newborn. That is, we need to know “who” the newborn is, what the hemodynamic relevance of the PDA is, and the potential consequences and the risks of developing a PP-PDA.

15A. Which drug should be used?

Preference for indomethacin or ibuprofen?

The “preference” should be established after having evaluated all the aspects studied in the Consensus, including costs and local or regional availability. There are groups currently evaluating the effects in terms of cerebral hemodynamics and planning clinical studies to evaluate the gastro-intestinal and/or renal advantages. In this section the effectiveness of both drugs will be analysed in order to achieve PDA closure and some of its repercussions based on up-to-date published material (Table 4).

As a reference point for this comparison, two meta-analyses have been used. One of them includes 9 randomized clinical studies with a total of 566 patients and the other is based on 11 randomized clinical studies (the previous nine plus 2 new ones), with a total of 648 patients. The 11 trials that were carried out between 1995 and 2005, and referred to in the meta-analyses, are listed in the bibliography.

In all cases, the diagnosis of PDA was done by echocardiography. The main objective of the vast majority of studies was to evaluate the rate of ductal closure following pharmacological treatment received (either Indomethacin or Ibuprofen), except for 4 studies that primarily evaluated the hemodynamic effects of the two interventions and reported secondarily on PDA closure. Other effects recorded were death, need of surgical ligation, possibility of reopening following pharmacological treatment, complications and clinical progress. The rates of PDA closure were reported after one to three doses of Ibuprofen or Indomethacin were administered. The following are the main results.

Failure of PDA closure after Ibuprofen or Indomethacin treatment. The failure of closure depends on various factors: among these is postnatal age at the start of medical treatment. In general, with early treatment PDA closure is achieved at 9 days of life for up to 90% of the cases, whereas with late treatment it is only effective in 50-66%. According to the underlying pathology and gestational age, the rate of failure can be around 30% with gestational age < 28 weeks and 10% with 29 or more weeks of gestation. When treatment is begun at 3.1 ± 0.5 days the success rate is much greater than when it starts between 7 and 14 days or later, where failure rate can be as high as 66%.

All meta analysis studies confirmed these results. No individual study has found statistically significant differences in the rate of failure of PDA closure if INDO or IBU were used; neither have the meta-analysis (RR 0.96 [95% CI: 0.74-1.26]).

The secondary results comparing Indomethacin and Ibuprofen are summarized in Table 4. This table is based on a recent article and extensive bibliography. In brief, the only difference found is that IBU produced oliguria much less frequently than INDO. Regarding prophylactic use of INDO, it reduces IVH, and this is described later in the manuscript. This result has not been documented with IBU.

The failure rate and/or reopening rate varies around 25-30% and it increases with both gestational age < 28 weeks and birthweight < 1,000 g. On the other hand, the success rate of a second series or course is only 30-40%. The number of surgical ligations varied between 2% and 12% in this meta-analysis.

15B. Efficacy of ibuprofen and indomethacin based on gestational age, birthweight and postnatal age

As previously mentioned, the lower the birthweight and the gestational age, the higher the incidence of PDA. Therefore, most of the prospective randomized studies of cyclooxygenase inhibitors for the treatment of PDA include newborns < 35 weeks of gestation. In general, the more immature the newborn, the more difficult it is to achieve ductal closure with pharmacologic treatment.
logical treatment’. Between 27 and 29 weeks gestation, up to an 80% success rate has been recorded, with a greater failure rate noted with a lower gestational age. At the same time, with a gestational age > 33-34 weeks, the efficacy of the cyclooxygenase inhibitors is greatly reduced, since the capacity of the PDA to respond to PGE2 decreases as gestational and postnatal age increase. The data shows that if the treatment is begun at an early stage of postnatal life (days 2 and 4 of life), there is increased efficacy as far as achieving ductal closure, and preventing heart failure and clinical deterioration. The pharmacokinetic variability and the maximum serum concentrations of Ibuprofen suggest that it is more beneficial to start the treatment within 2-5 first days of life.

There is a study which aims to establish the efficacy of Indomethacin with short and long courses of treatment at different gestational ages. This study has not been conclusive and therefore we are unable to make recommendations based on it, since most of the required data is missing.

16. Preparations of indomethacin and ibuprofen and other cyclo-oxygenase inhibitors

In Iberoamerica it is of utmost importance to know the cost and availability of INDO and IBU, the potential problems associates with oral dosing, and the risks of using “similar” drugs, and non-approved preparations or those that have not been fully researched.

**Indomethacin**

**Dosage and speed of infusion of INDO.** The dosage is found in Table 5. Even though the manufacturer recommends its administration over 30 minutes, this and bolus administration produce a decrease in cerebral blood flow which was sustained for at least 90 minutes. The consensus has been reached that administration should not be by “bolus”. The majority of our group agreed with a recommended minimum administration period of 30 minutes and a maximum of 1 hour. Two members disagreed, one maintains that 30 minutes is sufficient, and another one that Indomethacin should be administered over one hour.

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**TABLE 4. Comparison between Indomethacin (INDO) and Ibuprofen (IBU)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>INDO</th>
<th>IBU</th>
<th>Relative Risk of IBU [95% CI]</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Mortality</td>
<td>325</td>
<td>2-7%</td>
<td>2-11%</td>
<td>0.86 [0.44-1.69]</td>
<td>No</td>
</tr>
<tr>
<td>Neonatal Mortality</td>
<td>148</td>
<td></td>
<td></td>
<td>1.17 [0.41-3.31]</td>
<td>No</td>
</tr>
<tr>
<td>Ductal reopening</td>
<td>84</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1.17 [0.51-2.70]</td>
<td>No</td>
</tr>
<tr>
<td>Surgical ligation</td>
<td>563</td>
<td>2-11%</td>
<td></td>
<td>1.06 [0.67-1.68]</td>
<td>No</td>
</tr>
<tr>
<td>Peri &amp; Intraventricular Hemorrhage III-IV</td>
<td>285</td>
<td>1-7%</td>
<td>2-10%</td>
<td>1.10 [0.53-2.57]</td>
<td>No</td>
</tr>
<tr>
<td>Periventricular Leukomalacia</td>
<td>386</td>
<td>6%</td>
<td>11%</td>
<td>1.15 [0.53-2.47]</td>
<td>No</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>473</td>
<td>1-2%</td>
<td>0-2%</td>
<td>0.60 [0.27-1.31]</td>
<td>No</td>
</tr>
<tr>
<td>Days to reach enteral feeding</td>
<td>386</td>
<td>21</td>
<td>22</td>
<td>1.14 [-1.50 to -3.77]</td>
<td>No</td>
</tr>
<tr>
<td>Oliguria</td>
<td>334</td>
<td></td>
<td></td>
<td>0.23 [0.10-0.51]</td>
<td>Yes (NNT: 8)</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>103</td>
<td></td>
<td></td>
<td>0.72 [0.39-1.32]</td>
<td>No</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia (28 days &amp; 36 weeks)</td>
<td>238</td>
<td>13%</td>
<td>23%</td>
<td>1.28 [0.77-2.10]</td>
<td>No</td>
</tr>
<tr>
<td>Duration of ventilation (days)</td>
<td>325</td>
<td>14-22</td>
<td>12-17</td>
<td>DMP 1.30 days [-4.31 to -1.72]</td>
<td>No</td>
</tr>
<tr>
<td>Duration supplemental O₂ (days)</td>
<td>238</td>
<td>25-31</td>
<td>17-35</td>
<td>DMP 3.14 days [-5.14 to -1.43]</td>
<td>No</td>
</tr>
<tr>
<td>Duration of hospitalization (days)</td>
<td>238</td>
<td>73</td>
<td>65</td>
<td>DM –3.52 days [-9.87 to -2.83]</td>
<td>No</td>
</tr>
<tr>
<td>Treatment Indomethacin Failure (3 doses)</td>
<td>492</td>
<td></td>
<td></td>
<td>0.90 [0.67-1.22]</td>
<td>No</td>
</tr>
</tbody>
</table>

See the text for references.

NNT: Number Needed to Treat.

Based in 4 Meta-analyses (references 37, 78, 91, 138), and 12 Clinical trials (references 7, 31, 81, 82, 84, 99, 100, 102-104, 287).
Indomethacin preparation. If 1 ml of diluent is used (sterile normal saline solution 0.9% or distilled water), the final result will be a concentration of 1mg/1ml (0.1 mg in 0.1 ml). If 2 ml is used to dilute, the final concentration is of 1 mg/2 ml (0.05 mg in 0.1 ml). The diluted preparation should be administered immediately after its preparation and the extra solution subsequently discarded. INDO can increase the half life of digoxin, amikacin and gentamicin, and is incompatible with amino acid solutions (parenteral nutrition), calcium gluconate, dobutamine, dopamine and gentamicin. The drug is compatible with furosemide, insulin, potassium chloride and sodium bicarbonate.

A study in Argentina with adult preparation of INDO reported that the concentration of INDO following 2 standard dilutions did not correlate to the actual prescribed dose. This indicated the uncertainty and risks of adapting adult pharmaceutical preparations for neonatal use. In Brazil, Indocid® is imported from the USA and Belgium. In El Salvador there are only 50 mg Indocid® capsules from Merck.

Indomethacin – Oral preparations. Studies on the effectiveness and pharmacokinetics of the oral form of INDO were carried out in countries where availability of the intravenous form is inexistent or inconstant.

Ibuprofen

IV ibuprofen (not PO) has the same efficacy for PDA closure as INDO (Table 4). The dose is presented in Table 6. Ibuprofen displaces the binding of bilirubin and albumin. With metromalol, a few cases of pulmonary hypertension have been described. The L-lysine form could prolong the half-life of amikacin.

In the USA it is called Neoprofen® (10 mg/ml in a 2 ml vial). In Europe it is called Pedea® (5 mg/ml in 2 ml vial). It is not available in Canada. In Argentina, the drug is available under the commercial name of intravenous Supragesic® (Beta laboratories), mixed with dextropropoxifen. It requires dilutions in normal saline solution to reach concentration of 10 mg/ml. Three cases of severe pulmonary hypertension have been reported after prophylactic administration of IBU (within the first 6 hours of life) with the trometamol preparation, and in a premature newborn infant that had received the L-lysine formulation. It seems that the lysine formulation is the safest.

Oral preparations of ibuprofen. In Brazil, there is no IV ibuprofen available, but there are more than 20 oral formulations varying from 20 to 200 mg/ml. In this country, oral ibuprofen is not used for the treatment of PDA. In El Salvador, there is only oral IBU available. Various small studies have shown that PO IBU has similar efficacy than INDO. Nonetheless, studies of oral IBU have been inconclusive, with only few patients included. There are 8 studies (5 of which are not randomized) and all reported similar efficacy between oral and IV IBU. One study reported intestinal perforation with oral IBU in 2 premature newborns less than 30 weeks gestation and less than 1,250 g.

Contraindications for the use of INDO or IBU

The presence of renal insufficiency, severe oliguria, creatinine > 2.5 mg/dl are all contraindications. Perhaps if the renal repercussion of the PDA has been significant, IBU might be a lower-risk option. Thrombocytopenia < 25,000 is also a contraindication, since these drugs inhibit platelet function. Depending on the clinical situation, one can opt to transfuse platelets as treatment is being given. Active bleeding is also a contraindication for the administration of these two drugs. Nevertheless, there is no evidence to suggest that these drugs increase the severity of pre-existing IVH. In cases of NEC, the majority of clinicians do not use these drugs.

Other similar drugs

Oral sulindac seems to be efficient in ductal closure, with fewer renal effects (16 patients, all with a birthweight greater than 1,750 g). It is metabolized in the liver where it is transformed into an active sulphite metabolite. Another non-steroidal anti-inflammatory is naproxen. There are three reported cases of prenatal use associated with premature ductal closure with severe pulmonary hypertension in the newborns. We do not know of its use in the neonatal period.

### TABLE 5. Intravenous indomethacin dose: every 12 hours (h), for a total of three doses

<table>
<thead>
<tr>
<th>Dose Type</th>
<th>&lt; 48 h postnatal age</th>
<th>&gt; 48 h postnatal age</th>
<th>&gt; 7 days postnatal age</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose</td>
<td>0.2 mg/Kg</td>
<td>0.2 mg/Kg</td>
<td>0.2 mg/Kg</td>
</tr>
<tr>
<td>Second dose</td>
<td>0.1 mg/Kg</td>
<td>0.2 mg/Kg</td>
<td>0.25 mg/Kg</td>
</tr>
<tr>
<td>Third dose</td>
<td>0.1 mg/Kg</td>
<td>0.2 mg/Kg</td>
<td>0.25 mg/Kg</td>
</tr>
</tbody>
</table>

References in the text.

### TABLE 6. Intravenous ibuprofen dose: every 24 hours (h), for a total of three doses for a complete IBU course

<table>
<thead>
<tr>
<th>Dose Type</th>
<th>IBU</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose</td>
<td>10 mg/Kg</td>
</tr>
<tr>
<td>Second dose</td>
<td>5 mg/Kg</td>
</tr>
<tr>
<td>Third dose</td>
<td>5 mg/Kg</td>
</tr>
</tbody>
</table>

References in the text.
**Recommendations from the Consensus**

The recommendation is that in each region of each country the physicians should know in detail the drug to be utilized by IV route, and use the most effective medication, the better prepared, and the one with the least possibility of errors during its preparation, i.e., administer IV drugs that have been studied and approved specifically for the treatment of PDA in premature infants. With the disagreement of only one member of the Consensus, we do not recommend the use of oral INDO, as the evidence is scarce or non-existent. The use of oral IBU cannot be recommended at this time by this Consensus group (except for one member that abstained). Furthermore, this Consensus cannot recommend the use of known drugs that have salts or excipients that have not been studied. The drugs that have not been studied or the salts and excipients that are added to the studied drugs can cause more adverse effects than benefits. Finally, we all agreed that this Consensus cannot recommend the use of sulindac nor naproxen.

**17. Treatment: age at initiation of therapy and repeating therapeutic courses**

The most frequently reported dosage and intervals for INDO are shown in Table 5, although there is research reporting 24 hour intervals. Only one study with one dose of 0.1 mg/kg and one study with a dose of 0.2-0.25 mg/kg have been published.

Each dose should be given as a slow infusion. Given over 30-60 minutes seems to reduce some of the negative effects in blood flow to the organs. Immediate constriction effect of Indomethacin varies but can be measured for two hours after the first dose. The ductus is often closed during the period when the second dose is being given. Echocardiographic observation has been used to limit the length of INDO treatment with no adverse effects on closure. With extensive echocardiographic vigilance, it is possible to give shorter treatments or smaller doses, depending on the individual response shown on the echocardiogram. Nevertheless, this requires new technologies and depends on the availability of experts, which is not always possible. Therefore, this Consensus group cannot recommend giving smaller dosages of INDO than those mentioned in Table 5. The IBU dosage is found on Table 6. Prophylactic INDO. Prophylactic administration of indomethacin (<6-24 h of life) is useful to diminish the severity of ICH and to reduce the incidence of PDA but has no effect on the incidence of BPD. A Cochrane review of 19 studies with 2,872 newborns treated with INDO at < 24 h demonstrates that this approach significantly reduces the incidence of PDA and the need for surgical ligation, besides reducing by 35% the occurrence of severe pulmonary hemorrhage. Although PDA is implied in the pathogenesis of and it is associated to BPD, the use of prophylactic Indomethacin appears to increase 1.5 times (95% CI: 1.05-2.15) the risk for BPD. In addition, the analysis of the authors of these studies revealed that prophylactic Indomethacin increases the need for supplemental oxygen from day 3 up until at least day 7 of postnatal age, and decreases urinary output in the first 4 days of life, making difficult to achieve the expected weight loss in the first week of life.

**Early treatment.** Pre-symptomatic treatment initiated when the PDA "begins to be symptomatic or is still clinically asymptomatic". Evans suggests performing an ECHO in the first 6 h of life to all newborns < 28 week gestation and 28-30 weeks with risk factors (such as absence of prenatal corticosteroids, RDS and perinatal asphyxia) and to initiate treatment when the diameter of the PDA is > 2.0 mm. As mentioned in this article, the results of more than 7 clinical trials show that to look for the PDA by ECHO < 3 days of life or to initiate treatment immediately after the first signs, without waiting for obvious symptoms, results in less PDA, less surgery, less PP-PDA and no differences in BPD and NEC.

**Therapeutic approach.** When clinical signs are clearly present. If treatment is started between days 2-5 there is a higher rate of therapeutic success, with prevention of cardiac failure and clinical deterioration associated with it.

**Delayed treatment.** Several studies show that there is more persistence of the PDA (56-60%) the longer the initiation of medical treatment is delayed.

This Consensus group leans towards early treatment of the PDA and it cannot recommend the uniform prophylactic use of cyclo-oxygenase inhibitors in order to decrease the incidence of PDA, since this would unnecessarily expose many newborns to the drug. Perhaps, in those units that do not have access to surgery and cannot refer the children who require it, it could be advisable to consider the prophylactic use in a limited group of patients with high incidence of PDA and PP-PDA. (We are not including in this consideration the potential advantages of prophylactic INDO for IVH, which is discussed later.)
When should other course of treatment be given if the first course fails? When should the first dose of the second course be given? Should a third course be used or not?

Unfortunately there is no evidence-based information to answer these questions. A suitable approach could be to repeat a second course of three doses of INDO or IBU in the case of failure of the first course (failure to close the PDA) or when the PDA “reopens” days after having documented its closing. A second therapeutic cycle should only be given if the ductus remains open and is symptomatic and there are no contraindications. If there is clinical contraindication for a second course and the ductus remains open and symptomatic with hemodynamic effects, surgical ligation is indicated. A third course of treatment does not seem indicated given the low probability of success, but it is used as a “last resource” before surgery in few cases in some centers when there is no contraindication to its use.

In whom can a “prolonged course” be recommended? What is the dosing for the so called “prolonged course”? What are the advantages and disadvantages?

There has been no detected difference regarding effectiveness (closure, “re-opening” or the need for re-treatment or surgery) between habitual short courses and the prolonged course of Indomethacin154. On the other hand, several years ago it was reported that somewhat lower doses than usual used for a longer period of time (0.1 mg/kg every 24 h during 5-7 days) could be effective in neonates that had not responded to a habitual cycle (course) of Indomethacin107,108,156. Nevertheless, it seems that the prolonged course is associated with a greater incidence of enterocolitis and changes in renal function (oliguria and increase in creatinine levels)156.

There is no definite evidence in the literature to recommend a therapeutic scheme for the use of a “prolonged” INDO treatment102,156.

Regarding Ibuprofen, there is no data on a more prolonged treatment. One concern is the metabolism of IBU in children and the risk for severe hepatic damage associated with elevated plasma levels of this medication. Thus, this drug should not be used in any other regime than as previously described.

18. Rate of “non-response to medical treatment”

The rate of non-response to the medical treatment is very variable in the literature, close to 30%. The published data vary between 10% and 56%157,158, depending on the medication used, postnatal age at the initiation of treatment, dose, interval and number of courses given (1, 2 or more courses)102,112,159,160. The individual data of each report show rates of failure in the closing of the PDA with medical treatment that varies from low rates (10-13%) in very few reports, to the frequently reported rates of failure between 21% and 34%. The higher rates are reported to be 43%-55% and up to 50% in infants transferred to referral centers12,20,35,59,88,90,102,112,138,157,160-174. Three studies are of interest. One with a failure rate of only 1.5% with high doses of INDO161, a second study where 56% of the infants less than 28 weeks of gestational age did not respond to a second therapeutic course with INDO and required surgical ligation2 and a third study where the rate of failure to respond to the first course of INDO in newborns < 1,000 g was 30%, and 21% failed to respond to 2 courses of INDO175.

19. Surgery for HS-PDA.

When is surgery indicated?

A variable percentage of newborns does not respond and requires surgery to close the PDA. The need for surgery varies, according to all issues previously discussed (8-14%). Surgery is indicated after failure of the medical treatment to close a HS-PDA. Surgery is also indicated when there are contraindications for medical treatment of a HS-PDA. However, some authors have considered surgery in very low birth weight infants with a large PDA, with very significant left to right shunt and severe hemodynamic and respiratory derangement by clinical evaluation and echocardiogram12,20,35,59,90,102,112,157,159-161,163,164,169,171,176.

In a retrospective study of 931 infants < 1,500 g, 156 were treated with INDO or primary surgical ligation165. Mortality was 13% in the group with INDO and 24% in the surgical group. The literature demonstrates that the group that required surgical ligation after failure of medical treatment had greater need for prolonged ventilation, greater concentrations of O2, and greater incidence of BPD when compared with the group of medical treatment that did not require surgery12,51,177. In addition, there is increased risk for severe ROP and neurosensory problems in very low birth weight infants51. It is not easy to differentiate if this is caused by the surgery itself or the time of occurrence of the HS-PDA or to a PP-PDA. In addition we do not know what would have happened to those newborns if the PDA had not been surgically closed. In premature primates the surgical closure of the PDA produces detrimental effects on pulmonary function and pulmonary growth51.

Obviously, it would be ideal not to have to perform surgery and there are no advantages in performing surgical ligation without having tried medical treatment, except in cases of NEC or absolute contraindications to the drug12. The recommendation of this Consensus, with two members in disagreement, is to perform surgical ligation without great delays in cases of contraindi-
of universal use in the future with a lower cost.

Complications of PDA surgery

An ample range of complications of PDA ligation has been described in the literature (Table 7). To mention some examples, one study has reported a 26% of intraoperative complications and 57% postoperative complications, in contrast to another study with 5% intraoperative and 6% postoperative complications. For the majority of the authors the complications are rare and surgical mortality is associated in general with other complications of prematurity.

Morbidity associated with PDA surgery

The morbidity or complications associated with the surgery of the PDA is described in Table 7, after extensive review of the literature.

Some studies show that video-assisted thoracic surgery for closing the PDA with “clips or clamps” is as effective and as safer as conventional thoracotomy. This technique can be used in ductus of size smaller to 9 mm, but the experience in VLBW infants is limited. Either by thoracoscopy or thoracotomy, “clips” have been used for several years successfully. This technique requires less operating time and less morbidity, compared with the classic ligation. The incidence of intra-operative hemorrhage is smaller compared with the classic tie. For that reason, this Consensus group, except for two members, recommends that the surgeons should be experts in the use of “clips” and use these to close the PDA surgically. Thoracoscopy can be a good technique.

20. NEC and intestinal perforations with PDA and its treatment

It has been debated whether there is an association of PDA with NEC, or if PDA tends to increase the risk for NEC. Epidemiological studies suggest that this association does indeed exist. This could be due to low mesenteric blood flow secondary to low diastolic pressure and vasoconstriction. Around 70% of premature infants < 28 weeks of gestational age need treatment of the PDA (clinical or surgical). If the PDA is not treated the risk for NEC increases. There is also controversy on whether NEC is related to the administration of cyclooxygenase inhibitors that diminish mesenteric blood flow. However, the current literature does not demonstrate that the use of Indomethacin as recommended increases the risk of NEC. Epidemiological studies of thousands of premature newborns have not found this association, but they have found that NEC is associated with the presence of PDA and not with INDO. More important yet, the prospective randomized placebo controlled trial of TIPP (Trial of Indomethacin Prophylaxis in Premature infants) demonstrated that NEC incidence is not greater in the treated group.
On the other hand, the prolonged treatment with INDO does increase the risk of NEC\(^{112}\) and the use of INDO associated with hydrocortisone also increases the risk of NEC\(^{303}\). As it was mentioned previously, there is no evidence that supports the use of furosemide in conjunction with Indomethacin\(^{210,219}\), and this practice results in greater risks (see above).

In regard to “isolated intestinal perforations” (without NEC), it is estimated that there is no significant increase in its incidence in relation to the PDA\(^{98}\). Cases of “isolated perforation” during INDO use have been described, but none of the placebo controlled trials have shown an increase in the frequency of this event in the INDO group. Many investigators think that there is a need for more placebo controlled randomized trials to confirm the association between INDO and isolated perforation\(^{210,212}\).

(Nota: The use of steroids could be associated with isolated perforation).

IBU, on the other hand, not being a selective COX inhibitor, causes less vascular effect and does not reduce mesenteric blood flow. In addition, IBU can have a cytoprotector effect in the intestinal tract\(^{210}\). However, as it was mentioned before, there is no evidence that it is different from INDO in regards to NEC (see Table 4). It is possible that it could be better, but this has not yet been clearly demonstrated\(^{215}\). What has been demonstrated is that IBU does not increase NEC nor the incidence of isolated perforation\(^{5,89,91}\). In some studies, even in the Cochrane database, there was no increase in the incidence of “isolated perforation” with the prophylactic use of IBU\(^{300}\). Finally, there is no description of greater incidence of NEC or isolated perforation when other drugs are used in association to IBU, unlike with INDO.

### TABLE 7. Complications of PDA surgery

<table>
<thead>
<tr>
<th>Complication</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative bleeding or hemorrhage</td>
<td>1.4 to 10%</td>
</tr>
<tr>
<td>Air leaks</td>
<td>&lt; 5 to 6%</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1% and up to 13% (4-6%)</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>1.4-5%</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>1%</td>
</tr>
<tr>
<td>Infection</td>
<td>7.8%</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1-1.7%</td>
</tr>
<tr>
<td>Ductal tearing</td>
<td>2-2.5%</td>
</tr>
<tr>
<td>Mortality</td>
<td>0-10%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2%</td>
</tr>
<tr>
<td>Neural damage with vocal cord palsy</td>
<td>0.8, up to 8.8% (3-5%)</td>
</tr>
<tr>
<td>Transient hypotension by anesthesia;</td>
<td></td>
</tr>
<tr>
<td>transient hypoxia, left lung retraction or</td>
<td></td>
</tr>
<tr>
<td>atelectasis</td>
<td></td>
</tr>
<tr>
<td>Vasopressor requirement secondary to hypotension</td>
<td>32%</td>
</tr>
<tr>
<td>Ligature of left pulmonary artery</td>
<td>Case reports</td>
</tr>
<tr>
<td>Recanalization of ductus or failure</td>
<td></td>
</tr>
<tr>
<td>of conventional ligation</td>
<td>Case reports</td>
</tr>
</tbody>
</table>

Based on references cited in the text (12, 202-207, 298, 299).

21. PDA, medical treatment and the central nervous system

The severity of complications such as intraventricular hemorrhage and cerebral hypoxia has a positive correlation with mental retardation\(^{214}\). The cerebral circulation in the preterm newborn is a system of low resistance, in which the diastolic blood flow is an important component. This, combined to the deficient self-regulation of the cerebral blood flow in the premature infant, explains the high incidence of intraventricular hemorrhage (57.5%) in newborns with HS-PDA\(^{215-217}\). Other problems described in the presence of PDA with hemodynamic repercussion include the development of cerebellar hemorrhage, with OR: 6.95 (95% CI: 2.34 to 20.64)\(^{218}\) and 4 times more risk of death (95% CI: 1.12 to 14.51)\(^{158}\).

These and other aspects are analyzed in detail below.

**Effect of HS-PDA and/or PP-PDA on the brain**

Different studies, both clinical and observational, have evaluated the repercussion on the brain of the “clinically quiet” HS-PDA in the development or extension of structural injury of the CNS in premature infants (ICH or PVL-ischemic injury)\(^{158,160,216,217,219-222}\). The PDA was associated statistically to the presence or extension of the ICH in some studies\(^{216,221}\) but not in others\(^{217,219,222}\). In a study\(^{221}\) where the systemic perfusion to the upper body was evaluated by measurement of the superior vena cava (SVC) flow, an indirect indicator of the cerebral blood flow (CBF), the normalization of the flow correlated with the delayed appearance of ICH, supporting therefore the theory of ischemia-reperfusion in the pathogenesis of the ICH. Observational studies also have supported the association between the presence of PDA and the ischemic injury\(^{217,219,222}\).

There is a significant correlation between low blood flow and adverse results like death, ICH, NEC and neurodevelopment abnormalities at 3 years of life\(^{32,216,217,222}\). After adjusting for potential confounding factors, there is an association between low SVC flow and neurodevelopment. The average value of this flow in the first 24 h of life is associated to disabilities, so that by each increase of the flow of 10 ml/kg/min the probability of death or disability is reduced by 28%\(^{225}\).

In randomized clinical trials of prophylactic use of INDO there has been a decrease in the incidence of PDA (symptomatic or asymptomatic) and of IVH\(^{158,160,220}\). This beneficial effect of prophylactic INDO, described later in
this paper has not been demonstrated in the meta-analysis on the early use (pre-symptomatic) of INDO or with prophylactic IBU, which very possibly is due to an effect of INDO on the cerebral perfusion, independent of its effect on the PDA.

**Effect of left to right shunt on the cerebral circulation by Doppler ultrasound**

In general, the presence of a left to right shunt at the ductal level is associated with changes in CBF velocity, mainly during diastole and to an increase of the pulsatility index or resistance. In addition, these findings correlate with changes in blood flow observed in the descending aorta (retrograde flow) and changes in the diastolic component of the systemic arterial pressure (direct correlation) and with the size of the PDA. A study has shown an inverse correlation between SVC flow and PDA diameter. These facts are likely due to the stealing of blood from the systemic circulation towards the pulmonary circulation. Although these are small studies and the evaluation of the cerebral perfusion is semi quantitative, the findings are consistent in all of the studies. In spite of the decrease of the CBF velocity due to the PDA, a decrease of the cortical electrical activity was not observed.

**Different effects from INDO and IBU in the brain? Prevention of ICH?**

**Effects of INDO in cerebral hemodynamics.** INDO administration produces substantial changes in cerebral hemodynamics immediately after its administration. This has been evaluated in clinical studies in premature infants by noninvasive techniques such as Doppler ultrasound, NIRS (Near Infra Red Spectroscopy) or combined modalities and also in animal models.

Essentially, INDO administration produces changes in cerebral oxygenation and hemodynamics consistent with the decrease in cerebral perfusion and these changes persist over time. Nevertheless, the findings are controversial, as far as the differential effect of the administration by bolus versus slow infusion. It seems that the effect of INDO decreasing cerebral perfusion occurs earlier when administered by bolus compared to a slow infusion, although there are no differences in the global effect or its duration if the period of observation is more prolonged. In fact, the period of observation was short (30 and 60 min) in the studies that report differences in Doppler findings according to the rate of infusion. Administering each dose in an slow infusion over 30-60 minutes seems to limit some of the negative effects in the blood flow to organs. There is no significant difference between infusion of the drug over 30 minutes or over 60 minutes.

The effect of INDO on the cerebral vessels seems to be a direct one, independent of potential changes in the metabolism of prostanoids. Early administration (<12 h) of INDO for the treatment of a large PDA (>1.6 mm) does not produce changes in the ductal diameter nor in SVC flow at the time of administration. In addition, INDO administration attenuates the physiological vascular response to CO2. Animal studies have shown that the decrease of the CBF occurs concomitantly with an increase of the fractionated oxygen extraction, while the metabolic rate of O2 in the brain remains unchanged.

The administration of INDO as a tocolytic does not seem to have effects on the cerebral circulation of the fetus. In other age groups and in animal models INDO has been beneficial in the control of the intracranial pressure in head trauma, as well as in the control of cerebral edema of hepatic encephalopathy.

**Effects of IBU on cerebral hemodynamics.** In neonatal experimental models IBU increases the capacity to autoregulate CBF, it protects neuronal function against oxidative stress and does not affect the cerebral vascular response to CO2.

In a randomized, masked clinical study on the prophylaxis of PDA in premature infants, IBU did not show effects on cerebral perfusion and oxygenation. The administration of IBU for the closure of PDA has not shown effects in the cerebral circulation in either animal or clinical studies when compared with INDO.

**Prophylactic administration of IBU and IVH.** A meta-analysis on the randomized clinical trials on the prophylactic treatment of the PDA with IBU included four trials. Only one of them has as the main outcome variable the evaluation of the severity of ICH. Six hundred and seventy two premature infants were included and all of them received the same treatment protocol. There were no observed positive effects of the prophylactic use of IBU for PDA on early mortality, severe IVH or PVL. There are no data reported on neurodevelopmental outcome in any of these studies. In a later multicenter trial by Dani et al the prophylactic use of IBU for the prevention of ICH did not demonstrate to be effective.

**Prophylactic and early administration of INDO.** We discuss here some specific aspects related to the brain. In a neonatal experimental model of hemorrhagic hypotension, the prophylaxis with INDO decreases basal CBF and prevents the increase of CBF after intravascular volume replacement, with significant reduction in the incidence of ICH in the group treated with INDO.

The meta-analysis on the studies published on the prophylactic use of INDO to reduce morbidity/mortality associated to PDA and IVH in premature infants includes 16 RCT that have been published in peer-reviewed jour-
nels6,140-152,173,250-256. There were a total of 2,872 infants randomized. Prophylactic INDO reduces significantly the incidence of severe IVH (grades 3 and 4), with a cumulative RR = 0.66 [0.53 to 0.82]. There is no evidence of differences in mortality or that the use of prophylactic INDO is associated with a decrease in the risk of neurodevelopmental abnormalities (cognitive delay, cerebral palsy, blindness or deafness) at 18 months of postconceptional age. Secondary analyses seem to suggest an improvement in the long term results in male newborns and recent information on even longer term suggests beneficial effects in both genders266-269.

The findings could have different interpretations. One would be that severe IVH is not a marker for later neurodevelopmental outcome. Another interpretation points towards a direct damaging effect of INDO, as it decreases IVH but does not improve results. On the other hand, it could mean that prophylactic INDO is safe, since no increase in the incidence of neurodevelopmental abnormalities was found on long term follow-up. In addition, as mentioned, there is a difference in response according to gender and it seems that prophylactic INDO produces an improvement in follow-up and evaluation at school age or adolescence266-268. This issue is not fully solved and the question remains on whether, with a better selection of the population to treat, we could decrease the number of patients exposed unnecessarily to the collateral effects of INDO, limiting it to those infants who could potentially receive benefit.

The meta-analysis on the clinical trials on early treatment (pre-symptomatic) of the PDA with INDO220 includes 3 studies270-272 with a total of 97 patients recruited. There is no evident effect on mortality or IVH. Long term neurodevelopmental follow-up has not been reported.

Other aspects on the INDO-IBU effects (experimental animal models)

There are a lot of animal experiments273-279 but such analysis is beyond the scope of this paper. In summary, IBU reduces the size of the infarct in a manner comparable to hypothermia; the effect of INDO over cerebral hemodynamics is not related to the prostanoïd system, is independent of the parasympathetic system and seems to be mediated by vasopressin and opioids. INDO also protects the neurons attenuating oxidative stress and the reperfusion.

22. Aspects of echocardiography in PDA

22A. When should the first echocardiogram (ECHO) be performed? In whom?

Some aspects related to this issue have been mentioned before in this report. Based on current evidence, the present Consensus Group (with some doubts and reservations on the part of three members) recommends performing an early ECHO (within 24-72 hours of birth) in symptomatic newborns (NB) ≤ 1,500 g, in NB < 28 weeks of age, and in high risk NB of 28-30 weeks of age, in order to evaluate the size and the degree of defect. It is advisable to always perform ECHO before medical therapy.

Most of the studies on PDA have demonstrated that when PDA closes “spontaneously” it happens relatively early and even within 48-72 hours of life. In 30-50% or over of NB < 1,500g, PDA remains open, triggering clinical symptoms20,23,24,280.

22B. When should echo be repeated?

The approach is variable. For the NB that has received medical therapy it would be advisable to confirm the closure of PDA or treatment failure by means of a detailed ECHO, especially in the case of small and symptomatic NB in which the symptoms may not be clear but can be attributed to PDA, like the need for CPAP, oxygen, mechanical ventilation or when these respiratory treatments cannot be removed. ECHO should certainly be performed in every case where clear clinical symptoms persist and/or there is a radiological suspicion after pharmacological treatment.

This approach is rather empirical, based on clinical assessment and, indirectly, on published studies that report the incidence of error or failure of pharmacological treatment.

22C. Medical treatment without echocardiogram? In which cases?

In no case should echocardiogram be omitted, except in the presence of clinical and radiological symptoms when there is no echo equipment or pediatric cardiologist available.

The sensitivity of clinical symptoms barely reaches 30 to 50% in the first five days of life5,5-17. In addition, although it is extremely infrequent, INDO/IBU pose a risk of ductal closure in the presence of a ductus-dependent congenital cardiopathy that has not been clinically detected. On the other hand, if this rare complication does occur in a NB weighing 500-800 g or even 1,000 g, it is rather unlikely that the problem can be nowadays solved with cardiothoracic surgery in most neonatal units.

A recent report has shown good results with “conservative treatment”, although the sample size was too small to make definitive recommendations. This report, on the other hand, raises more doubts as to whether to proceed with treatment without ECHO confirmation280. The present Consensus Group acknowledges that in the Latin-American reality many neonatal units are faced with difficulties to reach diagnostic confirmation with echocardiography at certain times of the day (or night), since, regrettably, they cannot perform an accurate ECHO. In these cases, and when there is clear clinical evidence of hemodynamically...
significant PDA, it is agreed that efforts should be made to achieve PDA occlusion.

In situations like this, however, the problem is that the NB may already be affected and/or the response to prostaglandin inhibitors may be less effective. Thus, the debate lies on what to do when there is no ECHO. The Consensus Group, except for two abstentions, believes it could be important to start treatment as soon as possible in the presence of some clinical features without waiting for more visible clinical signs.

22D. Echocardiography: Who should be in charge: the neonatologist or the pediatric cardiologist?

The tendency towards the training of neonatologists in echocardiography is gaining momentum. There are several arguments in favor of ECHO being performed by well-trained neonatologists. These are: immediate and frequent access to neonatal hemodynamic evaluation, the assessment of circulatory transition in sick children, and the evaluation of myocardial dysfunction, PDA, pulmonary hypertension and detection of cardiac obstruction. Furthermore, in this way, unnecessary delays in cardiac evaluation are avoided and there is a better cost-benefit ratio. The reasons against this view are: erroneous interpretation by omission or mistake, the legal implications of erroneous interpretations, and the potential abuse of the technique.

23. Cost-effectiveness of the treatment:

Estimating the cost of not treating a hemodynamically significant PDA

There is no pharmacoeconomic study on this issue that can provide an accurate answer to what could be the cost of not treating a hemodynamically significant PDA in relation to days of oxygen therapy, IMV, parenteral fluids and hospitalization, in comparison to a PDA medically or surgically treated. The following Consensus’ arguments are based on the reviewed literature and, especially, on some articles from which some ideas may be inferred.

According to what has been analyzed by the SIBEN Consensus Group, the early treatment of hemodynamically significant PDA (when the first clinical signs appear or when it is documented by ECHO) by means of general measures and the use of cyclo-oxygenase inhibitors or with surgical occlusion (when therapy fails) decreases the frequency of chronic pulmonary disease and NEC, the duration of mechanical ventilation and perhaps the days of oxygen therapy and hospital stay. Moreover, it seems that when preventing the appearance of persistently prolonged PDA for over 2-3 weeks, the differences are even greater. If this is really the case, the economic benefit of treatment would be highly significant.

Nevertheless, there is a retrospective study which included only 65 NB with significant PDA that closed with medical therapy, and 33 NB in which the PDA remained open due to the impossibility of surgery because of geographical location. In the latter group, the rate of mortality was higher, but morbidity was not worse. After adjusting the groups for gestational age and score of clinical risk, there were no significant differences in the duration of ventilation, the days of hospital stay and incidence of NEC and severe ICH in the NB that were not surgically treated due to lack of resources. This issue requires further careful evaluation. It is necessary to bear in mind that, although there was no increase in morbidity rates, the mortality rate was higher in the untreated group. It would be interesting to carry out a randomized controlled study with careful design, with an adequate sample size in NICU’s of medium and small size that have little or no possibility of providing surgical closure, where mortality and morbidity rates can be compared with or without surgical ligation in patients that have been unsuccessfully treated with prophylactic or medical therapy.

CONCLUSIONS

This first SIBEN consensus, integrated by neonatologists of 16 Ibero-American nations, led to active participation and collaboration of the members and improved their education.

The Consensus task ends with the publication of this manuscript that includes all the clinical aspects related to PDA. The participants consider that this process will serve as the basis for future SIBEN Clinical Consensus and may have a value as a model to decrease the disparity of clinical care and the gap between knowledge and delivery of clinical measures. Accordingly, improved outcomes could be obtained in this and other regions of the world.

Based on the literature review, presentation and discussion generated, the following is a summary of recommendations for the clinical aspects of PDA, made by the participants in the SIBEN Consensus Group.

A. Fluid intake and use of Furosemide when PDA is present in premature newborn infants

1. A fluid restriction strategy is necessary in the ELBW/ VLBW infant, leading to a negative fluid balance and weight loss in the first 5 to 7 days of postnatal life. The absence of this strategy will lead to increase morbidity.

2. Volume infusion (crystalloid solutions) could lead to excess water, sodium, and positive fluid balance worsening outcomes and morbidity and mortality.

3. A positive fluid balance and excessive volume (ml/Kg/day) increases PDA prevalence in the premature infant.
4. Fluid restriction in premature infants significantly decreases the risk of PDA, NEC and death. This restriction should be done carefully, avoiding dehydration.

5. Fluid balance should be strictly monitored evaluating intake, diuresis, insensible losses, weight and electrolytes, especially Na+.

6. A premature infant should loose a minimum of 10% to 12% of BW during the first 5 to 7 days of life, but not more than 15%.

7. A reasonable volume to start on the first day of life is 60 to 80 ml/Kg/day with modifications in several hours according to fluid balance.

8. Currently, the literature shows that the recommendation of increasing 10 to 20 ml/Kg/day because of phototherapy is not necessary.

9. During the first 5 to 7 days of life, fluids should be not more than 140 to 150 ml/Kg/day, in newborns at high risk of developing PDA. However, if fluid balance is negative (increase insensible loose, high urinary output, excessive weight lost), higher fluid intake may be necessary.

10. When a PDA is diagnosed, do not give excessive volume (fluids calculations as per water balance, keeping below 110-120 ml/Kg/day). When indomethacin is given, oliguria could occur. One should be attentive to reducing fluid intake when necessary, considering the fluid balance.

11. Furosemide should not be given to premature infants within the first 7 to 10 days of life. It is not only unnecessary, and does not benefit the patient, but could lead to metabolic, fluid and electrolyte imbalance, and greater risk of PDA. Furthermore, furosemide is not indicated when treating the PDA

B. Diagnosis

1. See tables 1 & 2.
2. Clinical signs are of not great value.
3. Early echocardiogram.

C. Enteral feedings while HS- PDA is present and/or with treatment

1. One could continue or not trophic gastro-intestinal stimulation (no clear evidence).
2. While more conclusive studies appear, it is best not to feed orally while the infant is hemodynamically unstable due to HS-PDA and during medical treatment.
3. Maintain parenteral nutrition to avoid catabolism.
4. Once PDA is closed or the patient is stable, feedings can be restarted, 24-48 hours after completion of therapy, preferably with breast milk and evaluating tolerance carefully.

D. Treatment

1. Three doses of IV INDO or IBU, at intervals and doses as indicated in the tables. Recommended infusion speed is no less than 30-60 minutes, and never by bolus.
2. Early treatment once diagnosis is made (within 1-4 days).290
3. We cannot recommend routine use of prophylactic INDO/IBU for PDA (with exception of some cases, as seen in the text).
4. Avoid presence of excessively prolonged HS-PDA. All the consensus participants but one recommend closing of HS-PDA within the first 2 weeks of life (or maximum 3 weeks), to avoid PP-PDA.
5. Medical treatment courses; if PDA persists after first course give a second or third course, if clinically appropriate and considering surgical possibilities.
6. Surgical indications (clip surgery technique is preferable): Medical treatment contraindication and medical treatment failure, avoiding hemodynamically significant PP-PDA for longer than 3 weeks.

7. The consensus group does not recommend discharging patients without closing a HS-PDA.

This clinical consensus document was done through an extensive process with the participation of more than 30 neonatologists of 16 Ibero-American countries, following established clear scientific guidelines. It is evident that some clinical aspects of PDA are not yet clearly defined. Those may be solved in the future and we should be attentive to this. Although, we could not establish what the “perfect practice” is in all cases, this document will be useful to avoid some erroneous or detrimental practices throughout the region. SIBEN’s final objective is the large practices, reducing unnecessary diversity in neonatal care and increasing uniformity of care. This would benefit many newborn infants in this region and hopefully elsewhere.

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