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Hepatopulmonary syndrome in pediatric patients with portal hypertension – an integrative review

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HIGHLIGHTS

- Hepatopulmonary syndrome (HPS) is not an uncommon complication of cirrhosis in children and adolescents, particularly when biliary atresia is the underlying condition.
- Screening with pulse oximetry (O2 saturation <96%), unlike in adults, has low sensitivity in the pediatric age group.
- No differences were found in post-liver transplantation mortality between children of different hypoxemia ranges, contrary to findings from adults.
- There are still many gaps to be filled regarding the condition and not all data obtained in studies with adults reflects the disease's behavior in pediatrics, especially concerning prognosis.

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ABSTRACT – Background – Hepatopulmonary syndrome (HPS) is characterized by the triad of abnormal arterial oxygenation caused by intrapulmonary vascular dilatations (IPVD) in the setting of advanced liver disease or portal hypertension, impacting the patient's quality of life and survival. There are still many gaps in the literature on this topic, especially in pediatrics, with practices frequently based on extrapolation of data obtained from adults. **Objective –** Provide a synthesis of the current knowledge about HPS in children. **Methods –** The research was carried out through narrative review. The databases used for the search include Medline, Embase, Elsevier, Lilacs and Scielo. The keywords used were "hepatopulmonary syndrome" AND child, children, infant, preschool, pediatric. **Results –** In cirrhotic children, the prevalence of HPS can reach up to 42.5%, and it is even more common in those whose underlying condition is biliary atresia, reaching up to 63%. Screening with pulse oximetry (O_2 saturation <96%), unlike in adults, has low sensitivity in the pediatric age group. Management involves supportive care with oxygen therapy; liver transplantation is the only definitive treatment to reverse the condition and HPS is considered an exceptional criterion for waitlist. The waitlist mortality is similar among children listed by HPS as a special criterion when compared to those listed for other reasons. The reported rates of complete resolution of hypoxemia after liver transplantation are close to 100% in children. The post-liver transplantation survival is similar or slightly lower in children with HPS when compared to those without HPS. Contrary to findings from adults, no differences were found in post- liver transplantation mortality between children of different hypoxemia ranges, although longer mechanical ventilation time and hospital stay were observed in children with PaO_2 <50 mmHg. **Conclusion –** HPS is not an uncommon complication of cirrhosis in children and adolescents, particularly when biliary atresia is the underlying condition. There are still many gaps to be filled regarding the condition, and this article demonstrates that not all data obtained in studies with adults reflects the disease's behavior in pediatrics, especially concerning prognosis.

Keywords – Hepatopulmonary syndrome; portal hypertension; liver cirrhosis; hypoxemia; liver transplantation; pediatrics.

INTRODUCTION

Hepatopulmonary syndrome (HPS) is a complication of portal hypertension (PH) described in patients with cirrhotic and non-cirrhotic liver diseases, as well as in patients with vascular abnormalities that limit hepatic venous outflow to the lungs, such as congenital portosystemic shunts[1].

The triad that characterizes the disease is abnormal arterial oxygenation caused by intrapulmonary vascular dilations (IPVD) in a patient with preexisting liver disease, PH, or congenital portosystemic shunts. The diagnostic criteria were defined in 2004 by the European Respiratory Society (ERS) and reaffirmed in 2016 by the International Liver Transplant Society (ILTS) in the Guidelines for Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Hypertension. Such criteria are based on the confirmation of the presence of each of the components of the triad (TABLE 1)[2,3].

TABLE 1. Diagnostic criteria for hepatopulmonary syndrome.

All of the criteria below must be present:
1 - Liver disease, portal hypertension or congenital portosystemic shunts.
2 - Abnormal arterial oxygenation defined as alveolar-arterial oxygen gradient (A-aO_2) ≥15 mmHg (or ≥20 mmHg if age >64 years) in arterial blood gas analysis collected in room air with the patient seated at rest at sea level.
3 - Intrapulmonary vascular dilations (IPVD) diagnosed using contrast enhanced transthoracic echocardiography (CE-TTE) or ^{99m}technetium-macroaggregated albumin perfusion lung scan (^{99m}Tc-MAA).

It's known that pulmonary capillaries of patients with HPS have increased diameters of around 15–100 µm, measuring up to 500 µm, while a normal capillary vessel measures 8–15 µm. This vascular dilation alters the ventilation/perfusion (V/Q) ratio and limits the diffusion of oxygen into the lungs, with the return of partially deoxygenated blood to the systemic circulation. In some cases, there are also anatomical shunts that further worsen the condition[4,5].

Animal models for HPS have showed that these pulmonary vascular changes develop because of higher circulating levels of vasodilatory and angiogenic mediators[4-6]. In humans, these mechanisms were demonstrated by studies that showed genetic polymorphisms related to angiogenesis and higher levels of exhaled nitric oxide (NO) and circulating endothelin in cirrhotic patients with HPS, as well as the normalization of NO levels following liver transplantation[7-10].

The disease is classified according to the severity of hypoxemia as mild if arterial oxygen pressure (PaO_2) ≥80 mmHg, moderate if PaO_2 ≤79 and ≥60 mmHg, severe if PaO_2 ≤59 and ≥50 mmHg and very severe if PaO_2 <50 mmHg in room air[3].

The natural history of HPS is better understood in the setting of chronic liver disease (CLD), with the majority of patients experiencing progressively worsening gas exchange over time, with a negative impact on quality of life and increased mortality[11,12]. Management is supportive with oxygen therapy and treatment of the underlying liver disease, however liver transplantation (LT) is the only definitive treatment that reverses hypoxemia and improves survival. Given the higher mortality risk among patients with HPS when compared to cirrhotic patients with similar severity, in some countries, allocation systems in waiting transplant lists grant special criteria for individuals with severe and very severe HPS, aiming to prioritize their transplantation[3].

In children and adolescents, a smaller number of studies is available on this topic, and many concepts derive from extrapolation of data from studies conducted with adults. This integrative review aims to present a synthesis of current knowledge about HPS in pediatric patients in the context of CLD and PH. Studies investigating HPS in patients with congenital portosystemic shunts were not in the scope of this work.

METHODS

Medline, Embase, Elsevier, Lilacs and Scielo databases were searched to identify articles that addressed HPS in the pediatric age group, without any date or language restrictions. The keywords used for the systematic search were "hepatopulmonary syndrome" AND child, children, infant, preschool, pediatric. Case reports were excluded, and relevant articles cited in the references of the selected studies were considered. After the review, 26 original articles were included.

RESULTS AND DISCUSSION

Prevalence / incidence

The prevalence of HPS varies widely in published studies. In reports from different LT centers, the prevalence in cirrhotic adults ranged from 4 to 47%[5].

In children and adolescents, prevalence rates ranged from 0.66% to 42.5% (TABLE 2). The great variability is due to the different diagnostic criteria applied and the specific subgroups of studied populations.

In the pediatric series included in this review, authors who found lower prevalence rates used diagnostic criteria that excluded patients with HPS in its initial stages, in which PaO_2 is still normal or mildly reduced. On the other hand, higher prevalences were observed in studies which applied the criteria suggested by the ERS/ILTS (TABLE 1), due to its greater sensitivity.

To date, it is not clear in available literature why some patients with liver disease develop HPS and others don't. In all age groups, there is a lack of consistent studies to identify predictive factors for this progression. In general, a higher prevalence of HPS was identified in cirrhotic children when compared to non-cirrhotic children with PH. Among the etiologies of cirrhosis, samples with a high proportion of biliary atresia (BA) observed even higher prevalences.

The prospective study conducted in India by Pandey et al. explored the relationship between BA and HPS evaluating a group of 104 children with CLD, 40% of whom diagnosed with BA. The analysis showed a higher prevalence of HPS in the group with BA when compared to those with other CLD (OR 2.31; 95%CI 1.31–4.07; P=0.001). Furthermore, in patients with BA, HPS developed earlier after the diagnosis of the underlying disease compared to those with other CLD (mean time 32.1 x 132 months; P=0.002)[13].

TABLE 2. Prevalence of Hepatopulmonary syndrome in pediatric studies.

Study	Population	Diagnostic criteria	Prevalence
Noli et al. 2008[49]	301 children with liver disease screened by pulse oximetry ≤97% or cirrhosis or severe PH (n=26)	PaO_2 <70 mmHg or A-aO_2 ≥15 mmHg and IPVD (CE-TTE or ^{99m}Tc-MAA)	Overall: **0.66%** Cohort selected in screening: **8%**
Gupta et al. 2007[21]	211 children referred to LT	PaO_2 <70 mmHg and IPVD (CE-TTE or ^{99m}Tc-MAA)	**3.3%**
Raza et al. 2023[23]	3082 children listed for LT	Patients accepted by SRTR for extra PELD/MELD HPS points	**4%**
Mushtaq et al. 2021[28]	203 children with PH (48 with EHPVO)	Pulse oximetry <96% or PaO_2 <70 mmHg and IPVD (CE-TTE or ^{99m}Tc-MAA)	**7%**
Sari et al. 2012[26]	40 children with PH (60% cirrhotic)	ERS/ILTS	Overall: **10%** Cirrhotic: **16%** Non-cirrhotic: **0%**
Awad et al. 2014[25]	120 children with CLD (65% cirrhotic)	ERS/ILTS	Overall: **11.7%** Cirrhotic: **12.8%** Non-cirrhotic: **9.5%**
Tumgor et al. 2008[24]	172 cirrhotic children (22% with BA)	ERS/ILTS	**19%**
Borkar et al. 2015[27]	135 children with PH (25% cirrhotic /75% EHPVO)	ERS/ILTS	Overall: **20%** Cirrhotic: **40%** EHPVO: **13%**
Hoerning et al. 2014[15]	45 cirrhotic children referred for LT (64% with BA)	ERS/ILTS	**40%**
Pandey et al. 2020[13]	104 children with CLD (40% with BA)	ERS/ILTS	Overall: **42.3%** BA: **57%** Successful-Kasai: **42%** Unsuccessful-Kasai: **81%** Other CLD: **32%**
Ceza et al. 2018[14]	40 cirrhotic children (48% with BA)	ERS/ILTS	Cirrhotics: **42.5%** BA: **63%**

PH: portal hypertension; PaO_2: arterial partial oxygen pressure; A-aO_2 alveolar-arterial oxygen gradient; IPVD: intrapulmonary vascular dilations; CE-TTE: contrast enhanced transthoracic echocardiography; ^{99m}Tc-MAA: ^{99m}technetium-macroaggregated albumin perfusion lung scan; EHPVO: extrahepatic portal vein obstruction; SRTR: Scientific Registry of Transplant Recipients; PELD: Pediatric End-stage Liver Disease; MELD: Model for end-stage liver disease; HPS: hepatopulmonary syndrome; LT: liver transplantation; CLD: chronic liver disease; BA: biliary atresia; ERS: European Respiratory Society; ILTS: International Liver Transplant Society.

Ceza et al. published a study that included 40 cirrhotic children, of which 47.5% had BA. HPS was diagnosed in 17 patients, 12 of whom were in the BA group. In bivariate analysis, the diagnosis of BA was associated with the development of HPS (P=0.033), however this was not confirmed in multivariate analysis[14].

Some authors have also evaluated risk factors for HPS among children with BA. Pandey et al. analyzed patients undergoing Kasai surgery and data suggested a 10-fold higher cumulative risk of HPS in the unsuccessful-Kasai children when compared to the successful ones[13]. Hoerning et al. enrolled a sample of 45 cirrhotic patients, 64% of whom with BA. Among these, 51% had IPVD. The authors observed that BA children with IPVD underwent Kasai surgery later than the others (58±11 days x 74±30 days, P<0.04)[15].

The reason for the more frequent and earlier development of HPS in BA patients might be the rapid and progressive evolution of cirrhosis in BA, a pattern that is not observed in other CLD[16]. This also explains the greater risk of HPS in children without reestablished bile flow following Kasai portoenterostomy and the higher frequency of IPVD in those undergoing Kasai surgery at a later stage, as cirrhosis tends to have a more aggressive progression in these patients[15].

Studies by Al-Hussaini et al.[17] and Warner et al.[18] also had some important findings. The investigators observed that patients with HPS had a higher prevalence of polysplenia than the described in literature for the overall patients with BA (37.5–56% vs 10–15%). Al-Hussaini et al. also observed a tendency towards early development of HPS among these individuals, with lower oxygenation parameters and greater shunt fractions on scintigraphy[17,18]. More recently, Kim et al. corroborated this finding: in a study comparing children with BA with and without HPS, in multivariate analysis, the presence of polysplenia and interrupted inferior vena cava (IIVC) were independent risk factors for the development of HPS (OR: 142.66 95%CI 4.59–4433.76 P=0.005)[19].

In a case series of 10 patients described by Bulut et al., polysplenia and IIVC were found exclusively in patients with HPS when compared to the control group. This investigation also draws attention to the presence of these malformations in patients with liver diseases other than just BA, including two non-cirrhotic children[20].

The authors explain these findings by suggesting that HPS is related to a reduction in intrahepatic blood flow in patients with non-cirrhotic PH. Within polysplenia/IIVC malformation, this abnormality occurs more aggressively, justifying the higher incidence of HPS. The occurrence of HPS in patients with congenital portosystemic shunts and normal liver function suggests that the deviation of intrahepatic flow and the consequent impaired metabolism of vasodilatory mediators derived from the splanchnic circulation may contribute to the development of HPS[17,21].

Regarding the relationship between liver dysfunction severity and the development of HPS, there are many divergences in the literature, even for adults[22].

In children, Gupta et al.[21] and Raza et al.[23] found lower PELD (model for Pediatric End-stage Liver Disease) scores among HPS patients. These two authors conducted retrospective analyses of patients referred for liver transplantation and the results may be associated with the studies' methodology. Raza et al. compared patients on the LT list who received exception points for having HPS with individuals listed for other causes (severe cirrhosis) and Gupta et al. found 42% of non-cirrhotic patients in the HPS group[21,23]. Tumgor et al.[24] and Awad et al.[25] described, respectively, higher PELD scores and higher Child-Pugh C frequency among children with HPS when compared to controls. Sari et al.[26] had similar findings when comparing patients with and without IPVD. These three studies had in common the high proportion of cirrhotic patients and the HPS diagnostic work-up done for the entire sample[24-26]. Other series with pediatric patients did not find statistical differences in the severity grading of the underlying disease between groups[13-15,19,27,28].

This discrepancy in findings may be related to the multiple pathophysiological mechanisms involved in HPS. The occurrence of HPS in cirrhotic patients or in those with extrahepatic portal vein obstruction (EHPVO) (conditions that have PH as a common finding) reinforces that PH favors the occurrence of this complication. However, the higher prevalence observed among cirrhotic patients suggests that liver dysfunction plays an additional role. As previously des-

cribed, the hemodynamic changes caused by PH lead to higher circulating levels of vasodilation mediators. In EHPVO, these mediators bypass the liver and reach the pulmonary vessels through the portosystemic collateral circulation. However, as they remain in circulation, they are metabolized by the functioning liver. In cirrhosis, although a greater percentage of mesenteric blood flow is taken directly to the liver, impaired function prevents their clearance, justifying the greater frequency and severity of HPS in this population[27].

Child-Pugh and PELD scores were developed to estimate the risk of death related to liver dysfunction, and their results do not directly reflect the intensity of PH. Considering the association of both mechanisms for the development of HPS, it is possible that these clinical prediction scores are not, in isolation, accurate for estimating HPS risk, explaining the discrepant results observed in the different samples tested.

Some studies also evaluated the relationship between the severity of HPS and the underlying liver disease. Borkar et al. observed greater severity of HPS among cirrhotic patients compared to those with EHPVO (moderate to severe HPS: cirrhotic 12% vs EHPVO 1% $P<0.01$)[27] and Al-Hussaini et al. found no correlation between the severity of HPS estimated by ^{99m}technetium-macroaggregated albumin perfusion lung scan (^{99m} Tc-MAA) shunt fraction and the severity of the underlying liver disease[17].

Clinical manifestations

Patients with HPS may be asymptomatic in the initial stages of disease and as hypoxemia worsens, symptoms develop[1]. Dyspnea, which tends to be progressive, is the most prevalent symptom. However, as a non-specific finding, it can be caused by other conditions associated with liver disease, such as ascites, fluid overload, anemia, and muscle weakness. Platypnea (worsening of dyspnea in the standing position), as well as orthodeoxia (4 mmHg drop in PaO_2 or 5% drop in pulse oximetry in the standing position), are more specific findings of HPS, although not pathognomonic. They occur due to the gravitational effect that leads to greater perfusion of the lung bases in the standing position, worsening the V/Q ratio. Fatigue, clubbing, cyanosis, spider veins, and telangiectasias are also clinical findings associated with HPS[5,29].

In children, dyspnea (up to 70%), cyanosis (70%) and clubbing (85%) were the most frequently described clinical findings[19,20,27].

An interesting finding in pediatric population was described by Borkar et al. who demonstrated that HPS in children with EHPVO tends to be less symptomatic than in those with cirrhosis. In a sample of 13 pediatric patients with HPS due to EHPVO, the only clinical finding was digital clubbing in 38%. None of them had cyanosis or dyspnea. Meanwhile, among 14 cirrhotic patients with HPS in the sample, 21% had dyspnea, 21% had cyanosis and 85% had digital clubbing[27].

DIAGNOSIS

Identification of gas exchange impairment

The criteria currently recommended for the diagnosis of HPS (TABLE 1) utilizes the elevation of the alveolar-arterial oxygen gradient ($A\text{-}aO_2$) to diagnose the oxygenation defect. This is because the test can identify the V/Q disorder early, before the development of arterial hypoxemia (defined as PaO_2 <80 mmHg). Furthermore, unlike PaO_2, the gradient is not masked by hyperventilation, a common finding in cirrhotic patients[29]. In children and adolescents, the cutoff to characterize abnormal oxygenation is $A\text{-}aO_2$ ≥15 mmHg[2,3].

Recently, Sneharvardhan et al. questioned the validity of this single cutoff point for the entire pediatric population and tested the use of the $A\text{-}aO_2$ above the normal range for age as a diagnostic criterion. Calculated by the formula 10 + (0.26 x age in years – 0.43), the age-based cutoff identified a greater number of patients than the standard criteria in the study sample (44/104 versus 50/104), although without statistical significance (P=0.405). All additional cases identified were classified as mild HPS[30].

Another relevant aspect related to the diagnosis of HPS in children and adolescents is related to the technical difficulty and associated risks of arterial blood gas sampling in this population, such as hematomas and vasospasm. Several articles cite this limitation, and there are studies in which the diagnosis of HPS in children was done through indirect assessment of hypoxemia through pulse oximetry, without meeting the current diagnostic criteria[18,19,28].

Considering this issue, non-invasive strategies for measuring hypoxemia in the context of HPS, such as the estimation of PaO_2 by transcutaneous oxygen tension[31] and oxyhemoglobin dissociation curve[32], were tested with promising results, but their application has not been validated in cohorts with larger samples. To date, arterial blood gas analysis continues to be the recommended method for diagnosing hypoxemia in HPS[3].

Identification of IPVD

The identification of IPVD can be done non-invasively through contrast enhanced transthoracic echocardiography (CE-TTE) with intravenous injection of agitated saline microbubbles and ^{99m}technetium-macroaggregated albumin perfusion lung scan (^{99m}Tc-MAA). The first is considered the gold standard because it is easy to perform and allows differentiation between intracardiac and intrapulmonary shunts. Lung scintigraphy has the advantage of quantifying the shunt, locating areas with a very low or zero V/Q ratio, and identifying the contribution of IPVD to hypoxemia in patients with HPS who also have chronic lung disease. Its main disadvantage is that it is a more invasive method and does not identify intracardiac shunts[2].

The ILTS guidelines recommend considering the presence of IPVD when CE-TTE identifies intravenously injected microbubbles in the left heart 3 or more cardiac cycles after visualization in the right heart; or, on ^{99m}Tc-MAA, when, after pulmonary perfusion, cerebral radionuclide uptake is greater than 6%[3].

Most centers that retrospectively described pediatric cases, reported the utilization of both methods, alone or combined, in their diagnostic workup[18-21,33,34]. Exceptions were observed in the studies by Obbergh et al. (Belgium)[35], Ueno et al. (Japan)[36], and Al-Hussaini et al. (United Kingdom)[17], in which ^{99m}Tc-MAA was the method of choice. Prospective studies by Borkar et al. (India)[27], Pandey et al. (India)[13], and Mushtaq et al. (Pakistan)[28] preferentially used CE-TTE for diagnosis. These protocols are likely based on local practices and the availability of resources to perform the tests.

Prospective studies cited in TABLE 3 performed both tests in all children and allowed comparative analyses of their diagnostic accuracy in pediatric age group[14,25,26,37]. Some of the differences in their findings can be explained by methodological differences.

CE-TTE

The studies by Sari et al.[26] and Awad et al.[25] found similar accuracies for CE-TTE in diagnosing HPS (92.5% and 95%). These two studies were conducted in similar populations and used a similar methodology: CE-TTE carried out by a single operator, blind to clinical data, with injection of 10 ml of agitated saline solution into a peripheral vein. The exam was considered positive if microbubbles were present in the left cardiac chambers between three and six cardiac cycles after their visualization in the right heart chambers[25,26].

Ceza et al.[14] found a much lower specificity than other investigators[25,26,37]. This may be justified by the fact that the study population was composed exclu-

TABLE 3. CE-TTE versus ^{99m}Tc-MAA in the pediatric population.

Study		El- Shabrawi et al.[37]	Sari et al.[26]	Awad et al.[25]	Ceza et al.[14]
HPS prevalence		17.5% 7/40	10% 4/40	11.7% 14/120	42.5% 17/40
CE-TTE	Sensitivity	42.8%	100%	71.4%	94.1%
	Specificity	100%	91.6%	98.1%	4.3%
	Accuracy	90%	92.5%	95%	42.5%
^{99m}Tc-MAA	Sensitivity	100%	25%	100%	35%
	Specificity	100%	100%	94.3%	87%
	Accuracy	100%	92.5%	95%	65%

CE-TTE: contrast enhanced transthoracic echocardiography; ^{99m}Tc-MAA: ^{99m}technetium-macroaggregated albumin perfusion lung scan; HPS: hepatopulmonary syndrome.

sively of cirrhotic children. The presence of IPVD without abnormal arterial blood gas analysis has been described in a significant proportion of adult cirrhotic patients[38].

Different from other studies, El-Shabrawi et al. observed a low sensitivity of CE-TTE for diagnosing HPS. This is possibly due to the cutoff defined for the test, considered altered only in cases in which microbubbles were visualized in the left chambers six or more cardiac cycles after visualization in the right chambers[37].

^{99m}Tc-MAA

All authors found good specificity for ^{99m}Tc-MAA. Regarding sensitivity, data were conflicting. While Sari et al.[26] and Ceza et al.[14] found low sensitivity for the test, El-Shabrawi et al.[37] and Awad et al.[25] observed the opposite.

This difference in findings was accompanied by different methodologies applied to the exams. In the study by Awad et al., in which greater sensitivity was found, the contrast was injected after the patients remained in the orthostatic position for 10 minutes and the reading was acquired 20 minutes after the injection[25]. Sari et al., who found lower sensitivity, injected the contrast with the patient in the supine position and performed the reading after 2 minutes[26]. To determine the impact of such technical issues on the diagnostic quality of scintigraphy, specific studies are warranted. As for the cutoff point, the three studies used references based on the percentage of brain uptake in relation to lung uptake.

El-Shabrawi et al., on the other hand, found a 100% accuracy of ^{99m}Tc-MAA. However, different parameters were utilized, precluding comparative analyses with other studies. The authors calculated an index that considers radionuclide uptake in all extrapulmonary sites and not just brain uptake. Furthermore, the cutoff point with greater accuracy in the sample was defined, achieving sensitivity and specificity of 100% if extrapulmonary uptake/whole body uptake >0.278[37]. Ten years after, in 2020, a prospective study corroborated El-Shabrawi's findings when comparing brain uptake versus whole body uptake in ^{99m}Tc-MAA for the diagnosis of HPS in adults. The study found a greater area under the ROC curve for whole-body capture (0.75 *x* 0.54; *P*=0.025), with an accuracy of 74% for the cutoff point >0.425. The authors suggest that this may be considered the new standard for ^{99m}Tc-MAA positivity, although they emphasize its use as a complementary method to CE-TTE, due to its lower sensitivity[39].

Other tests

Chest radiographs are useful in HPS to exclude concomitant pulmonary disease but rarely show evidence of dilated vasculature. High-resolution computed tomography can identify large and dilated pulmonary vessels, but its accuracy for this diagnosis has not been adequately established. Pulmonary angiography can reveal two patterns in HPS: type 1, characterized by minimal and diffuse vascular dilations, and type 2, with large arteriovenous communications. Patients who develop type 2 are resistant to 100% oxygen administration. The invasive nature of pulmonary angiography makes it less convenient for diagnosing HPS, being the method reserved for candidates for embolization therapy[2,3,5].

Screening

Screening for HPS is justified because it is an oligosymptomatic condition with variable clinical presentation that negatively influences patients' quality of life and survival. Considering that performing arterial blood gas analysis and/or work-up for the identification of IPVD in all patients with underlying conditions compatible with HPS, more than invasive, is not cost-effective, the ILTS guidelines recommend the use of pulse oximetry (SpO_2) for severe HPS screening in adults[3]. This recommendation is based on the study by Arguedas et al. conducted with cirrhotic adults referred for LT – in which a sensitivity of 100% was observed for SpO_2 <96% for identifying patients with PaO_2 <70 mmHg[40] – and on studies that showed higher mortality, with or without LT, in adults with HPS and severe hypoxemia (PaO_2 <50 mmHg)[41]. This method, despite not identifying patients with HPS in early stages, is recommended by the guideline for its ability to identify the most severely ill patients, eligible for prioritization in the LT waiting list[3].

In the pediatric age group, these findings are extrapolated, and many centers also use SpO_2 to screen children for severe HPS[1]. However, given the greater frequency of living donor LT in pediatric patients,

with no need to wait in list for a donated organ, it is questionable whether the early diagnosis of HPS and the earlier performance of LT in these patients would be beneficial. To date, there are no studies assessing this question.

Regarding other methods proposed for HPS screening, Awad et al. suggest that the difference in SpO_2 measured in the supine and standing positions may have higher sensitivity than the isolated measurement of SpO_2 in any position in pediatric patients. The authors carried out a prospective study with 120 cirrhotic children, of which 14 met the criteria for the diagnosis of HPS. Of these, only 10 had SpO_2 ≤97% in the supine position, while all had a drop of ≥4% in SpO_2 when moving from the supine to the standing position. None of the 106 patients without HPS presented this finding[25].

The ILTS guideline cites the pediatric study by Hoerning et al. and suggest that the analysis of hiperemic capillary blood gases (CBG) may be a better method compared to SpO_2 for HPS screening in cirrhotic children[3]. This study, based on a meta-analysis that showed a correlation between arterial PaO_2 and CBG PaO_2 collected from the ear lobe[42], tested CBG analysis in 45 cirrhotic children. Eighteen patients with IPVD were found on CE-TTE. Of these, 17 had A-aO_2 >15 mmHg measured by CBG. None of them would have been identified by pulse oximetry, as they all had SpO_2 >98%. The analysis showed good sensitivity (94%) of the method for detecting patients with IPVD, however with low specificity (54%), especially in the age group of 6–24 months, in which 75% of patients with normal CE-TTE had abnormal gradient[15]. The limitation of this work was the absence of PaO_2 measurement in arterial blood gas samples, which precluded the quality evaluation of CBG analysis for hypoxemia detection and HPS diagnosis, as the comparison with the gold standard method was not possible. There are no recent studies to date comparing this method with conventional blood gas analysis in the context of HPS.

Prognosis

As previously mentioned, the natural history of HPS is best described in the context of liver cirrhosis. It is believed that the hemodynamic changes presented by these patients lead to the development of IPVD, initially, without blood gas abnormalities, a stage named by some authors as subclinical HPS. Subsequently, with the progression of IPVD, the gas exchange becomes impaired and changes in A-aO_2 are observed even with normal PaO_2. Then there is a worsening of oxygenation with concomitant onset and progressive hypoxemia[11,38,43].

This natural evolution has been demonstrated in children in several studies. In the case series described by Warner et al., during the waiting time for LT, 81% of patients with HPS became progressively more dyspneic, and a trend toward decreasing $SatO_2$ on room air was observed from 91% to 88%[18]. The study by Al-Hussaini et al. repeated the ^{99m}Tc-MAA in six patients with HPS after a mean time of 9 months and observed a mean increase of 4.7% in the shunt fraction, indicative of progressive worsening of IPVD over time[17]. Barbé et al., in 1995, described a series of 26 children with HPS. During follow-up, those not transplanted developed worsening symptoms severity (dyspnea and cyanosis), a drop in PaO_2, and an increase in the shunt fraction quantified by scintigraphy[44].

Regarding morbidity and mortality, in adults, lower 5-year survival rates were demonstrated in patients with HPS and native liver when compared to controls matched by age, underlying disease, MELD and Child-Pugh. (23% vs 63%, P=0.0003)[11]. In pediatric patients, there are no case-control studies comparing patients with and without HPS who did not undergo LT. Survival with the native liver can be assessed based solely on descriptions of how patients not referred for transplant evolved in small case series prior to 2010, with high mortality rates[17,24,44], and rare cases of spontaneous resolution reported in literature, generally related to improvement of the underlying liver disease[13,34,36].

Still, although data suggest poor outcomes for non-transplanted HPS patients, the lack of controlled prospective studies with this aim in the pediatric group precludes unbiased conclusions. It is possible that the reasons for not performing LT in referred cases were associated with the presence of comorbidities that may have contributed to mortality.

Management

Management of HPS is supportive with oxygen therapy and treatment of underlying liver disease.

The use of supplemental oxygen is indicated for patients with SpO_2 <89% and/or PaO_2 <55 mmHg[29]. In addition to clinical improvement and the impact on patients' functional capacity, some authors suggest that the use of supplemental oxygen slows the increase in hematocrit resulting from hypoxemia, reducing the risk of hepatic artery thrombosis after LT[17].

Drugs aimed at interfering in the pathophysiological processes of the disease, such as angiogenesis inhibitors and mediators involved in vascular tone control, have been extensively studied. Garlic extract (vasodilator and angiogenesis inhibitor), methylene blue (NO synthetase inhibitor) and pentoxifylline (vasodilator and angiogenesis inhibitor) have proven somewhat effective in improving oxygenation in some studies in adults[3,29,45]. In children, a trial published in 2006 evaluated the effect of garlic extract on the PaO_2 of 15 patients with HPS, observing a 10-mmHg increase in the average PaO_2 in 53.3% of cases[46]. However, controlled trials are still required to prove these benefits.

Invasive approaches have also been tested. Reducing portal pressure through intrahepatic transjugular shunt has an uncertain effect on HPS. Coil shunt embolization has already been described in case reports as a measure to improve hypoxemia, before or after LT, especially in patients with large arteriovenous communications. Although, there is a lack of evidence for its routine recommendation. In practice, to date, no intervention has shown sustained efficacy for improving hypoxemia other than LT, regarded as the only definitive treatment that reverses HPS and improves survival in all age groups[3,5].

Liver transplantation

The role of LT in patients with HPS has evolved over the years. The presence of an intrapulmonary shunt was initially considered a contraindication to LT given the perception that such patients had worse outcomes. In the first half of the 1990s, cases of normalization of the V/Q ratio and resolution of HPS after LT were reported and, as a result, hypoxemia became a formal indication for the procedure. At the end of that decade, case series were published documenting the benefit of transplantation for this patient profile and, in 2002, severe and very severe HPS began to configure special criteria for the indication of LT in some countries. This strategy was proposed with the aim of balancing results between patients with and without HPS, given that the prognosis of HPS appears to be worse than predicted by PELD/MELD scores alone[3,22].

The impact of implementing this measure was evaluated in some studies, such as that by Goldberg et al. which enrolled a large cohort of adults and revealed greater survival in the LT waiting list for patients listed due to HPS as an exception criterion when compared to chronic liver disease patients without HPS (HR 0.53)[41]. In children, a similar analysis was performed by Raza et al. and showed that there were no differences in waitlist mortality between children listed for LT due to HPS and those listed for other reasons. In this study, patients with HPS (n=124) had a cumulative incidence of death on the waiting list at 250, 500, 750, and 1000 days similar to that observed for patients without HPS (n=3776) (P=0.69), suggesting the effectiveness of special criteria in mitigating the risk of death from HPS while waiting for an organ donation[23].

Published evidence shows excellent post-transplant results in children with HPS, with survival rates similar to or slightly lower than those of patients without HPS[15,17,23]. Furthermore, as demonstrated in TABLE 4, most studies showed complete normalization of post-LT arterial oxygenation in 100% of patients[15,17,18,33-35]. Al-Hussaini et al. demonstrated that there is a correlation between the time required for HPS resolution after LT and the severity of HPS, with later resolution in patients with lower PaO_2 in room air and higher shunt fractions at ^{99m}Tc-MAA[17].

Regarding the impact of implementing the exception criterion on post-LT mortality, a systematic review published in 2021 compared transplant patients before and after the strategy. An improvement in survival rates of adults was demonstrated, reinforcing the adequacy of the criteria for this age group, however, there was no difference between the groups among pediatric patients. In children, survival at 30 days, 1 year, and 5 years was respectively 92.9%, 85.7%, and 85.7% before the special criteria and 97.4%, 97.4%, and 97.4% after its implementation (P=0.09)[22].

This discrepancy may be related to the cutoff point defined for granting priority for LT. According to current criteria, special status is only granted to

TABLE 4. Post-transplant evolution in the pediatric population.

Study	N	MV time	O_2 time	ICU stay	Hospital stay	Improvement of hypoxemia	Survival	Follow-up
Obbergh et al.[35]	7	58h (13–145)	-	8.7 days (3–24)	-	100% Average time: 6 months (0.5–16)	–	–
Al- Hussaini et al.[17]	14	1 day (1–12)	9 days (1–75)	3 days (2–13)	19 days (9–71)	100% Average time: 14 days (3–80)	85.7%	2–12.5 years
Willis et al.[34]	6	–	–	–	–	100% in 2 months	100%	2.9–10.6 years
Warner et al.[18]	16	1 day (1-23)	12 days (2-139)	3 days (2-25)	20 days (11-168)	100%	87.5%	5–20 years
Turine Neto et al.[33]	21	1 day (1-23)	21 days (1-437)	PaO_2 ≥50 7 days (4-10) PaO_2 <50 24.5 days (14.7–37)	PaO_2 ≥50 16 days (12-21) PaO_2 <50 31.5 days (26.2-–80.2)	100%	81%	90 months
Hoerning et al.[15]	15	4.9 days	–	–	–	100% Average time: 14 months (6–18)	80%	1 year

MV: mechanical ventilation; O_2: necessity of supplemental O_2; ICU: intensive care unit.

patients with HPS with PaO_2 <60 mmHg, and this is questionable. While studies carried out with large cohorts of adults demonstrated worse post-transplant survival for patients with HPS with PaO_2 <45–50 mmHg[41,47], justifying their prioritization, in pediatric patients this observation was not confirmed. In children, three studies compared outcomes between HPS patients with different PaO_2 ranges, and all of them revealed similar post-transplant survival rates between groups[23,33,48]. Differences were observed in intermediate outcomes, with longer times of mechanical ventilation, ICU stay, hospital stay, longer time to wean from supplemental O_2, higher rates of reintubation, and other postoperative clinical complications in patients with more severe HPS, however, there were no differences in mortality[33,48].

These data suggest that children probably behave differently compared to adults concerning post-transplant recovery, since the severity of previous hypoxemia is not significantly related to a greater risk of death[23,48]. Raza et al. question the existence of other preponderant factors that may increase the risk of death among children with HPS, other than PaO_2 <60 mmHg. In their study, patients with PaO_2 60–69 mmHg – who would not be included in the exception criteria – presented survival rates of, respectively, 82.4%, 76.5%, and 76.5%, 1, 3, and 5 years after LT. Although not statistically significant (P=0.13), these rates were paradoxically lower than those observed in individuals with PaO_2 <50 mmHg (93.6%, 89.4%, and 89.4%) and PaO_2 50–59 mmHg (97. 4%, 92.1% and 92.1%). Therefore, the authors suggest that children with mild and moderate HPS may be at greater risk because they are not being prioritized according to the current criteria[23].

The only finding suggesting the influence of PaO_2 on post-LT mortality in children was reported by Pinto et al. in a systematic review that pointed towards better survival among patients who presented a positive hyperoxia test (PaO_2 >300 mmHg collected using an inspired fraction of O_2 equal to 100% (P=0.045)[22].

The TABLE 5 shows the highlights of this narrative review.

TABLE 5. Highlights in Pediatric Hepatopulmonary Syndrome.

FACTORS RELATED TO THE INCREASED OCCURRENCE OF HPS		
• More common in cirrhotic than in non-cirrhotic portal hypertension. • More common in Biliary Atresia than in other chronic liver diseases. • More common in patients with polysplenia/interrupted inferior vena cava. • There is no established relationship between the severity of liver disease measured by Child-Pugh, MELD or PELD scores and the occurrence of HPS.		
SCREENING AND DIAGNOSIS		
	What do we know?	**New perspectives**
Screening	SpO_2 <96% has low sensitivity in the pediatric age group.	CBG collected from the ear lobe may be a less invasive screening method than arterial blood gas analysis (but has low specificity, especially in children under 2 years of age). The saturation differential between the supine and standing positions ≥ 4% may be promising as a screening method.
Diagnosis of gas exchange failure	Arterial blood gas analysis is the recommended method, but it is invasive and painful.	Other methods such as transcutaneous oxygen tension and the oxyhemoglobin dissociation curve have not yet been validated.
	Cutoff point in pediatrics: A-aO_2 ≥15 mmHg	A- aO_2 above that expected by age group may be more sensitive.
Diagnosis of IPVD	CE-TTE has good accuracy ^{99m}Tc-MAA has good specificity.	The relationship of lung uptake to whole body uptake may be more sensitive than the percentage of brain uptake.
PROGNOSIS		
Mortality list	Similar among children listed by HPS as a special criteria when compared to those listed for other reasons.	
Post-LT survival	Similar or slightly lower in children with HPS when compared to those without HPS.	
Influence of pre-LT PaO_2 on post-LT evolution	No difference was observed in post-LT survival between children with HPS of different PaO_2 ranges. Longer MV time, ICU stay and hospital stay were observed in children with PaO_2 <50 mmHg. A longer time was observed for the resolution of hypoxemia and O_2 weaning in patients with lower PaO_2 and higher shunt fractions. Greater survival was observed in children with PaO_2 above 300 mmHg when collected using an inspired fraction of O_2 equal to 100% (type 1 HPS).	

HPS: hepatopulmonary syndrome; CBG: capillary blood gases; A- aO_2:alveolar-arterial oxygen gradient; IPVD: intrapulmonary vascular dilations; CE-TTE: contrast enhanced transthoracic echocardiography; ^{99m}Tc-MAA: ^{99m}technetium-macroaggregated albumin perfusion lung scan; LT: liver transplant; MV: mechanical ventilation; ICU: intensive care unit; PELD: Pediatric End-stage Liver Disease; MELD: Model for end-stage liver disease.

CONCLUSION

HPS is not an uncommon complication of cirrhosis in children and adolescents, especially in those in whom biliary atresia is the underlying condition. Its evolution is progressive, impacting quality of life and worsening survival with the native liver. Despite several studies investigating drug therapeutic options, LT remains the only definitive treatment for this condition. There are still many gaps to be filled related to the disease, and this article demonstrates that not all findings from adult studies reflect the behavior of HPS in pediatric patients, especially about prognosis. For further conclusions on this topic, additional research is required.

Authors' contribution

Alberto LD, Fagundes EDT, Rodrigues AT and Ferreira AR: conceptualized the study and literature search. Alberto LD, Fagundes EDT, Rodrigues AT, Ferreira AR, Queiroz TCN and Castro GV: contributed equally to drafting the article and making critical

revisions related to important intellectual content of the manuscript. All authors have read and approved the final version of the article to be published.

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Alberto LD, Fagundes EDT, Rodrigues AT, Queiroz TCN, Castro GV, Ferreira AR. Síndrome hepatopulmonar em pacientes pediátricos com hipertensão portal – uma revisão integrativa. Arq Gastroenterol. 2024;61:e24040.

RESUMO – Contexto – A síndrome hepatopulmonar (SHP) é caracterizada pela tríade de oxigenação arterial anormal causada por dilatações vasculares intrapulmonares (DVIP) no contexto de doença hepática ou hipertensão portal, com impacto na qualidade de vida e sobrevida dos pacientes. Há ainda muitas lacunas na literatura sobre este tema, especialmente na Pediatria, cujas práticas são frequentemente extrapoladas de dados obtidos entre pacientes adultos. **Objetivo –** Apresentar uma síntese do conhecimento atual sobre a SHP na faixa etária pediátrica. **Métodos –** Trata-se de uma revisão narrativa. As bases de dados para pesquisa foram Medline, Embase, Elsevier, Lilacs e Scielo. As palavras-chave utilizadas foram "*hepatopulmonary syndrome" AND child, children, infant, preschool, pediatric*. **Resultados –** Nas crianças cirróticas, a prevalência da SHP pode chegar a 42,5%, sendo ainda mais comum naquelas com atresia biliar, atingindo até 63%. A triagem com oximetria de pulso (saturação de O_2 <96%), diferentemente dos adultos, tem baixa sensibilidade na faixa etária pediátrica. O manejo envolve cuidados de suporte com oxigenoterapia; o transplante de fígado é o único tratamento definitivo para reverter o quadro e a SHP é considerada situação especial para alocação na lista de espera. A mortalidade em lista é semelhante entre as crianças com SHP elencadas como situação especial quando comparada àquelas elencadas por outros motivos. As taxas de resolução completa da hipoxemia após o transplante de fígado são próximas de 100% em crianças. A sobrevida pós-transplante de fígado é semelhante ou ligeiramente menor em crianças com SHP quando comparadas àquelas sem SHP. Ao contrário dos achados em adultos, não foi observada diferença na mortalidade pós-transplante nas crianças de diferentes faixas de gravidade da hipoxemia, embora tenha sido observado maior tempo de ventilação mecânica e internação hospitalar em crianças com PaO_2<50mmHg. **Conclusão –** A SHP não é uma complicação incomum na cirrose em crianças e adolescentes, principalmente quando a atresia biliar é a condição subjacente. Ainda há muitas lacunas a serem preenchidas em relação ao quadro, e este artigo demonstra que nem todos os dados obtidos em estudos com adultos refletem o comportamento da doença na pediatria, principalmente no que diz respeito ao prognóstico.

Palavras-chave – Síndrome hepatopulmonar; hipertensão porta; cirrose hepática; hipoxemia; transplante hepático; pediatria.

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