

Minireview

Proposed Management Algorithm for Severe Hypoxemia After Liver Transplantation in the Hepatopulmonary Syndrome

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The hepatopulmonary syndrome (HPS) is defined as the triad of liver disease, intrapulmonary vascular dilatation, and abnormal gas exchange, and is found in 10–32% of patients with liver disease. Liver transplantation is the only known cure for HPS, but patients can develop severe posttransplant hypoxemia, defined as a need for 100% inspired oxygen to maintain a saturation of $\geq 85\%$. This complication is seen in 6–21% of patients and carries a 45% mortality. Its management requires the application of specific strategies targeting the underlying physiologic abnormalities in HPS, but awareness of these strategies and knowledge on their optimal use is limited. We reviewed existing literature to identify strategies that can be used for this complication, and developed a clinical management algorithm based on best evidence and expert opinion. Evidence was limited to case reports and case series, and we determined which treatments to include in the algorithm and their recommended sequence based on their relative likelihood of success, invasiveness, and risk. Recommended therapies include: Trendelenburg positioning, inhaled epoprostenol or nitric oxide, methylene blue, embolization of abnormal pulmonary vessels, and extracorporeal life support. Availability and use of this pragmatic algorithm may improve management of this complication, and will benefit from prospective validation.

Abbreviations: ARDS, acute respiratory distress syndrome; ECLS, extracorporeal life support; FiO_2 , fraction of inhaled oxygen; HFOV, high-frequency oscillatory ventilation; HPS, hepatopulmonary syndrome; ICU, intensive care unit; iNO, inhaled nitric oxide; IPVD, intrapulmonary vascular dilatation; IV, intravenous; L, liters; L-NAME, N(G)-nitro-L-arginine methyl ester; L-NMMA, N(G)-monomethyl-L-arginine; LT, liver transplantation; MB, methylene blue; min, minutes; mo, months; N/A, not available; NO, nitric oxide; O_2 , oxygen; PaO_2 , partial pressure of arterial oxygen; PAVM, pulmonary arteriovenous malformation; P/F, partial pressure of arterial oxygen/fraction of inhaled oxygen; POD, postoperative day; R/A, room air; RRT, registered respiratory therapist; SaO_2 , arterial hemoglobin oxygen saturation; SVO_2 , mixed venous oxygen saturation; VQ, ventilation-perfusion

Received 29 October 2014, revised 08 December 2014 and accepted for publication 19 December 2014

Introduction

The hepatopulmonary syndrome (HPS) is defined as a triad of liver disease, intrapulmonary vascular dilatation, and abnormal gas exchange, and is found in 10–32% of patients with cirrhosis (1–4). This disease is associated with progressive hypoxemia and a high mortality (3,5). Although liver transplantation (LT) is curative in HPS, these patients have an elevated postoperative complication rate (6–9). In particular, “severe posttransplant hypoxemia,” defined as a need for 100% inspired oxygen (FiO_2) to maintain a saturation of $\geq 85\%$ (out of proportion to any other concurrent lung process) (10), has been identified as a major complication leading to prolonged ICU stay and death in this population (6,9–12). Although survivors have a complete normalization of gas exchange over time, severe posttransplant hypoxemia occurs in 6–21% of HPS patients, carries a mortality of 45%, and accounts for the majority of peri-operative deaths in this population (10). A variety of strategies to attempt to manage this complication have been described in the literature, but these have never been reviewed and summarized and are used inconsistently, which has led to calls for a systematic approach (6,9,10,13). We sought to review available evidence in order to develop a practical clinical management algorithm for severe posttransplant hypoxemia in HPS.

Methods and Materials

Literature search

We searched MEDLINE (from inception to October 20, 2014) for English language studies involving human subjects with "hepatopulmonary syndrome" as a medical subject heading or keyword. We supplemented this with a manual search of reference lists from all retrieved articles and by consulting experts in the field. We included studies which described outcomes of strategies expected to rapidly (<72 h) reverse hypoxemia either posttransplant, or in a nontransplant context which could be applied posttransplant (in patients with HPS). Two reviewers (DN, SG) screened all abstracts and categorized them as definitely, possibly, or definitely not meeting inclusion criteria. We retrieved and reviewed full manuscripts for abstracts categorized as definitely or possibly meeting inclusion criteria by one or both reviewers, review articles, and reports of LT outcomes in HPS (adults and children).

Algorithm development

The treatment algorithm was developed iteratively by a multidisciplinary team from two quaternary care LT centers (the University Health Network, University of Toronto and Hôpital St-Luc, Université de Montréal). Evidence suggests that protocol-driven care can improve ICU care-related outcomes (14), and that early involvement of multidisciplinary teams in the protocol development can foster a sense of ownership, autonomy, and increased adherence (15). Accordingly, we involved all relevant multidisciplinary stakeholders in the iterative development and approval of the algorithm. The team included five ICU physicians, one respirologist with an interest in HPS, two transplant hepatologists, and one ICU respiratory therapist. The algorithm was further reviewed and modified based on suggestions from ICU, transplant hepatology, liver transplant surgery, respiratory therapy, nursing, and extracorporeal life support (ECLS) team members.

We determined which treatments to include in the algorithm and their recommended sequence of use based on their relative likelihood of success, invasiveness, and risk, based on available evidence from our literature search. Where evidence was not available, we relied on common sense and our practical experience in using these strategies at our specialized HPS center, where reported mortality from this complication was 28.6%, versus 75% in other reports (10).

Results

Literature search

We retrieved 416 citations using the medical subject heading "hepatopulmonary syndrome," and an additional 156 citations using the keyword "hepatopulmonary syndrome," for a total of 572 citations. Of these, 18 definitely met, 149 possibly met, and 405 definitely did not meet inclusion criteria. Upon full manuscript review, of the 149 citations possibly meeting inclusion criteria, 15 met inclusion criteria. We identified an additional 23 citations of interest from the manual search of reference lists and from experts, nine of which met inclusion criteria upon full manuscript review, for a total of 42 manuscripts (7%) meeting inclusion criteria. Of these, 27 studies reported therapies that were included in the algorithm (Table 1). Given that this is an infrequent complication in a rare disease, evidence was limited to case reports and case

series and could not be formally meta-analyzed. A small number of patients have been reported for any one therapy, with inhaled nitric oxide (iNO) being the best studied (19 patients), followed by methylene blue (MB) (10 patients), inhaled epoprostenol (four patients), embolization of abnormal pulmonary vessels (four patients), combined iNO and MB (two patients), ECLS (three patients), and Trendelenburg positioning (one patient). Mechanisms and time-courses of action for these agents are summarized in Table 2. Therapies that were not included in our algorithm, along with their mechanisms of action and reasons for exclusion are summarized in Supplemental Table S1.

Algorithm

Using the existing definition of severe posttransplant hypoxemia in HPS (a need for 100% FiO₂ to maintain a saturation ≥85%) (10), we designated the threshold for triggering the algorithm as a saturation <85% despite 100% FiO₂. We further required these conditions for at least one hour, and with a PEEP of ≥10 mmHg, corresponding to existing standards for use of ECLS in acute respiratory distress syndrome (ARDS) (16). Given rapidly changing PaO₂ (P) and FiO₂ (F) in ICU patients, we chose PF ratio as the index for monitoring responsiveness in gas exchange. This is a common metric of choice for describing the severity of hypoxemic respiratory failure in the ICU literature and has previously been used in HPS (10,17). We defined a response to therapy as a change in PF ratio of ≥20%, based on 3 factors: (1) this is an accepted threshold for minimal clinically relevant change (18,19); (2) smaller percentage changes could result from simple fluctuations in PaO₂, given baseline PaO₂'s of <65–70 mmHg (corresponding to a saturation of <85%) in patients entering the algorithm (20); and (3) the previously reported top range for mean coefficient of variation for PaO₂ is 10–11% over a 1-h period in medically stable ICU patients, whereby a 20% change approximates the variation expected by 2 standard deviations (as a proportion of baseline value) (21).

The proposed management algorithm is presented in Figure 1.

Discussion

Severe hypoxemia accounts for a majority of postoperative deaths in patients with HPS undergoing LT. We reviewed existing literature to develop a systematic management algorithm for this complication, informed by best evidence and expert opinion.

This complication tends to occur early in the postoperative period (usually within 24 h of LT). It is thought to be related to postoperative pulmonary vasoconstriction resulting from an abrupt change in the vascular mediators entering the lung from the hepatic effluent (10,22). Due to possible remodeling and impaired vasoconstriction in dilated HPS

Table 1: Summary of reports describing included strategies for management of severe posttransplant hypoxemia in HPS

Treatment and study	Number of patients	Outcome ¹	Treatment duration	Pre- or post-LT	Post-LT survival ²	Effect ³
Trendelenburg positioning Meyers et al., 1998 (13)	1	SaO ₂ increase from 80% to 91% (FiO ₂ 1.0) (immediate)	3 days	Post-LT	Alive 1 yr post-LT	Positive
Inhaled nitric oxide Karnatovskaia et al., 2014 (56)	1	PaO ₂ increase from 48 to 83 mmHg (30L/min O ₂) (1 h)	2 weeks	Post-LT	Alive 1 yr post-LT	Positive
Nayyar et al., 2014 (10)	4	3/4 improved gas exchange, 1/4 no effect	1–29 days	Post-LT	2/4 died (POD 77, 19), 2/4 alive > 4 yrs post-LT	Variable
Santos et al., 2014 (57) ⁴	1	PaO ₂ increase from 50 to 154 mmHg (FiO ₂ 1.0) (1 h)	4 days	Post-LT	Alive 2 months post-LT	Positive
Monseil et al., 2011 (45)	1	No improvement in gas exchange	N/A	Pre-LT	N/A	No effect
Al-Hussaini et al., 2010 (8)	1	SaO ₂ increase from 75–80% to >90% (FiO ₂ 1.0)	13 days	Post-LT	N/A	Positive
Schiller et al., 2010 (29)	1	SaO ₂ increase (immediate) ⁵	9 days	Post-LT	Alive 1 yr post-LT	Positive
Elias et al., 2008 (58)	1	Gradual improvement in gas exchange ⁵	N/A	Post-LT	Alive >4 mo post-LT	Positive
Fleming et al., 2008 (59)	1	No improvement in gas exchange ⁶	N/A	Post-LT	Alive >1 yr post-LT	No effect
Taille et al., 2003 (6)	3	3/3 improved gas exchange	N/A	Post-LT	N/A	Positive
Taniai et al., 2002 (60)	1	PaO ₂ increase from ~70 to 110 mmHg (FiO ₂ 1.0) (12 h)	2 days	Post-LT	N/A	Positive
Diaz et al., 2001 (61)	1	Improvement in gas exchange, allowing extubation ⁵	N/A	Post-LT	Alive 7 mo post-LT	Positive
Alexander et al., 1997 (62)	1	SaO ₂ increase from ~50% to 85% (2 h)	15 days	Post-LT	Alive 42 days post-LT	Positive
Durand et al., 1997 (28)	1	PaO ₂ increase from 44 to 75 mmHg (FiO ₂ 1.0)	12 days	During and post-LT	Alive 100 days post-LT	Positive
Orii et al., 1997 (63)	1	PaO ₂ increase from 44 to 54.3 mmHg (FiO ₂ not reported)	14 days	Post-LT	Alive 1 yr post-LT	Positive
Inhaled iloprost ⁷ Krug et al., 2007 (33)	1	PaO ₂ increase from 43 to 48 mmHg (R/A) (15 min)	8 weeks pre-LT; 3 months post-LT	Pre- and Post-LT	Alive 3 mo post-LT	Positive
Inhaled epoprostenol Nayyar et al., 2014 (10)	3	3/3 improved gas exchange	1 – 4 days	Post-LT	2/3 died (POD 77, 19), 1/3 alive > 4 yrs post-LT	Positive
Saad et al., 2007 (39)	1	SaO ₂ increase from 76% (FiO ₂ 1.0) to 90% (FiO ₂ 0.5)	N/A	Post-LT	Alive 100 days post-LT	Positive
Methylene blue Roma et al., 2010 (17)	1	PaO ₂ increase from 35 (FiO ₂ 0.7) to 39 mmHg (FiO ₂ 0.45) (4 h)	Single dose	Post-LT	Alive 58 days post-LT	Positive
Almeida et al., 2007 (64)	1	Reproducible, reversible decrease in PaO ₂ by 3–4 mmHg	Two doses	Pre-LT	N/A	Negative
Schenk et al., 2000 (36)	7	7/7 improved gas exchange (mean PaO ₂ increase from 58 to 74 mmHg) (5 h)	Single dose	Pre-LT	N/A	Positive

(Continued)

Table 1: Continued

Treatment and study	Number of patients	Outcome ¹	Treatment duration	Pre- or post-LT	Post-LT survival ²	Effect ³
Rolla et al., 1994 (65)	1	PaO ₂ increase from 56 to 68 mmHg (RA) (20 min)	Single dose	Pre-LT	N/A	Positive
Methylene blue + inhaled nitric oxide						
Nayyar et al., 2014 (10)	1	No improvement in gas exchange ⁸	Single dose	Post-LT	Died POD 19	No effect
Jounieaux et al., 2001 (66)	1	No improvement in gas exchange; decrease in cardiac output	N/A	Pre-LT	N/A	Negative
Embolotherapy ⁹						
Lee et al., 2010 (38)	1	SaO ₂ increase from 65% to 75% (5L O ₂) (immediate)	-	Post-LT	Alive 2 yrs post-LT	Positive
Saad et al., 2007 (39)	1	SaO ₂ increase from 76% (FI _O ₂ 1.0) to 95% (3L O ₂) 4 days after and 86% (R/A) 12 days after 2nd embolization	-	Post-LT	Alive 100 days post-LT	Positive
Ryu et al., 2003 (40)	1	PaO ₂ increase from 65 to 72 mmHg (2L O ₂) (24 h)	-	Pre-LT	N/A	Positive
Felt et al., 1987 (41)	1	PaO ₂ increase from 38 to 53 mmHg (R/A) (5 weeks)	-	Pre-LT	N/A	Positive
Extracorporeal life support						
Auzinger et al., 2014 (44)	1	Successfully weaned off sedation, tolerated minimal respiratory support	21 days	Post-LT	N/A	Positive
Monsel et al., 2011 (45)	1	"Stabilized" gases (patient also had ARDS) ⁵	5 days	Pre-LT	N/A	Positive
Fleming et al., 2008 (59)	1	"Stabilized" SaO ₂ ; decreased oxygen requirements (patient also had ARDS) ^{5,6}	18 days	Post-LT	Alive >1 yr post-LT	Positive

ARDS, acute respiratory distress syndrome; FI_O₂, fraction of inspired oxygen; L, liters; min, minutes; LT, liver transplant; mo, month; N/A, data not available; O₂, oxygen; PaO₂, partial pressure of arterial oxygen; POD, postoperative day; R/A, room air; SaO₂, arterial hemoglobin oxygen saturation; yr, year.

¹FI_O₂ and time to initial improvement were included in brackets when available.

²Reports all deaths during transplant hospitalization/or and reported survivals > 30 days post liver transplant.

³Given variable reporting, a uniform criterion could not be used to determine effectiveness; accordingly, we report authors conclusions regarding effect.

⁴Case 1 from this report was excluded because hypoxemia did not develop until 13 days post liver transplant.

⁵Quantitative details of improvement in gas exchange were not reported.

⁶Acute hypoxemia occurred on postoperative day 8, at which time patient had ARDS; inhaled NO tried first, followed by ECMO.

⁷This agent is not in the treatment algorithm, but may be considered in place of epoprostenol in centers where the latter is not available.

⁸A single dose of MB was given on postoperative day 17 in a patient on inhaled NO who had suffered from ventilator-associated pneumonia and had severe hypercapnia and acidemia.

⁹Reports of embolotherapy were limited to those in patients with diffuse intrapulmonary vascular dilatation, as opposed to frank arteriovenous malformations.

Table 2: Time course and mechanisms of action for included therapies

Treatment	Onset of action	Timing of peak effect	Mechanism of action
Trendelenburg positioning	Minutes	Minutes	Intrapulmonary vascular dilatations are predominantly basilar. Gravitational redistribution of blood flow to upper and mid lung zones decreases flow through intrapulmonary vascular dilatations
Inhaled vasodilators (epoprostenol or nitric oxide)	Minutes	Minutes	Preferentially vasodilates normal vessels, redirecting flow from (maximally vasodilated) intrapulmonary vascular dilatations
Methylene blue	~1 h	5 h	Guanylate cyclase inhibitor; blocks nitric oxide-induced vasodilation, which may vasoconstrict and reduce flow through intrapulmonary vascular dilatations (particularly in areas of impaired hypoxic vasoconstriction)
Inhaled vasodilator + intravenous methylene blue	Minutes	5 h	Preferentially vasodilates normal vessels in well-ventilated areas, and vasoconstricts intrapulmonary vascular dilatations in poorly ventilated areas with impaired hypoxic vasoconstriction
Embolization of lower lobar pulmonary vessels	Minutes to 24 h	Unclear	Redistributes blood flow away from intrapulmonary vascular dilatations, to mid and upper lung zones
Extracorporeal life support	Hours	Sustained	Sustains tissue oxygenation until intrapulmonary vascular dilatations begin to reverse and pulmonary gas exchange improves

vessels, normal (nondilated) pulmonary vessels may vasoconstrict disproportionately, resulting in further increases in flow through dilated HPS vessels, and consequently, a transient worsening in the underlying diffusion-perfusion defect and ventilation-perfusion (VQ) mismatch of HPS (10). Accordingly, selected therapies work through a variety of mechanisms to reduce flow through these dilated vessels (Table 2). The overall goal of therapy is to: (1) mitigate early mortality; and (2) maintain oxygenation for long enough such that the expected posttransplant reversal of HPS pathology (and hypoxemia) can begin to take place. The rationale for inclusion of each treatment in the algorithm and other considerations are summarized below.

Rationale and Considerations for Included Therapies

Trendelenburg positioning

Dilated vessels are predominantly found at lung bases in HPS (23), and Trendelenburg positioning (−10°) aims to redistribute blood flow away from these basilar lung units. This was effective not only in HPS (13), but also in non-HPS patients with orthodeoxia (24). Due to the increased risk of aspiration in Trendelenburg position, we recommend advance placement of a post-pyloric feeding tube at the time of LT. Port suction for gastric decompression and a cuffed endotracheal tube may further mitigate this risk.

Inhaled nitric oxide

Nitric oxide has been theorized to be the primary vasodilator responsible for HPS (25). However, paradoxically, due to the regional nature of these dilatations (23), administration of exogenous iNO appears to have a

beneficial effect in HPS. This was the most widely reported agent used for severe posttransplant hypoxemia, and the vast majority of reports noted a beneficial effect (Table 1). Inhaled NO likely acts by mitigating the postoperative pulmonary vasoconstriction of normal vessels described above. In addition, by preferentially vasodilating normal vessels in the mid and upper portions of the lung, it may effectively divert pulmonary blood flow away from the dilated basilar vessels which are responsible for hypoxemia. The reason for preferential dilatation of mid and upper zone vessels is two-fold. Firstly, some of the pathologically dilated basilar vessels may already be maximally dilated through remodelling (26), and therefore not susceptible to any further vasodilatation by NO. Secondly, the inhaled route preferentially distributes the NO to the areas of the lung that are already well ventilated. Given that micro-atelectasis with impaired ventilation is more prominent at lung bases (27), and that impaired hypoxic vasoconstriction has been well described in HPS (28–30), avoidance of poorly ventilated areas prevents any further dilatation of HPS vessels that are already relatively over-dilated due to impaired hypoxic vasoconstriction. It is considered to be safe and highly selective for the pulmonary circulation, with no adverse effects, including no effect on systemic hemodynamics at doses that we have recommended (31), and rapid reversibility (111–130 millisecond half-life) (32).

Inhaled epoprostenol

Inhaled epoprostenol likely acts through a mechanism similar to that of iNO (33), and is similarly fast- and short-acting, with a half life of approximately 5 min (34). Although clinical experience with inhaled epoprostenol in HPS is limited (Table 1), it was used successfully in all four reported

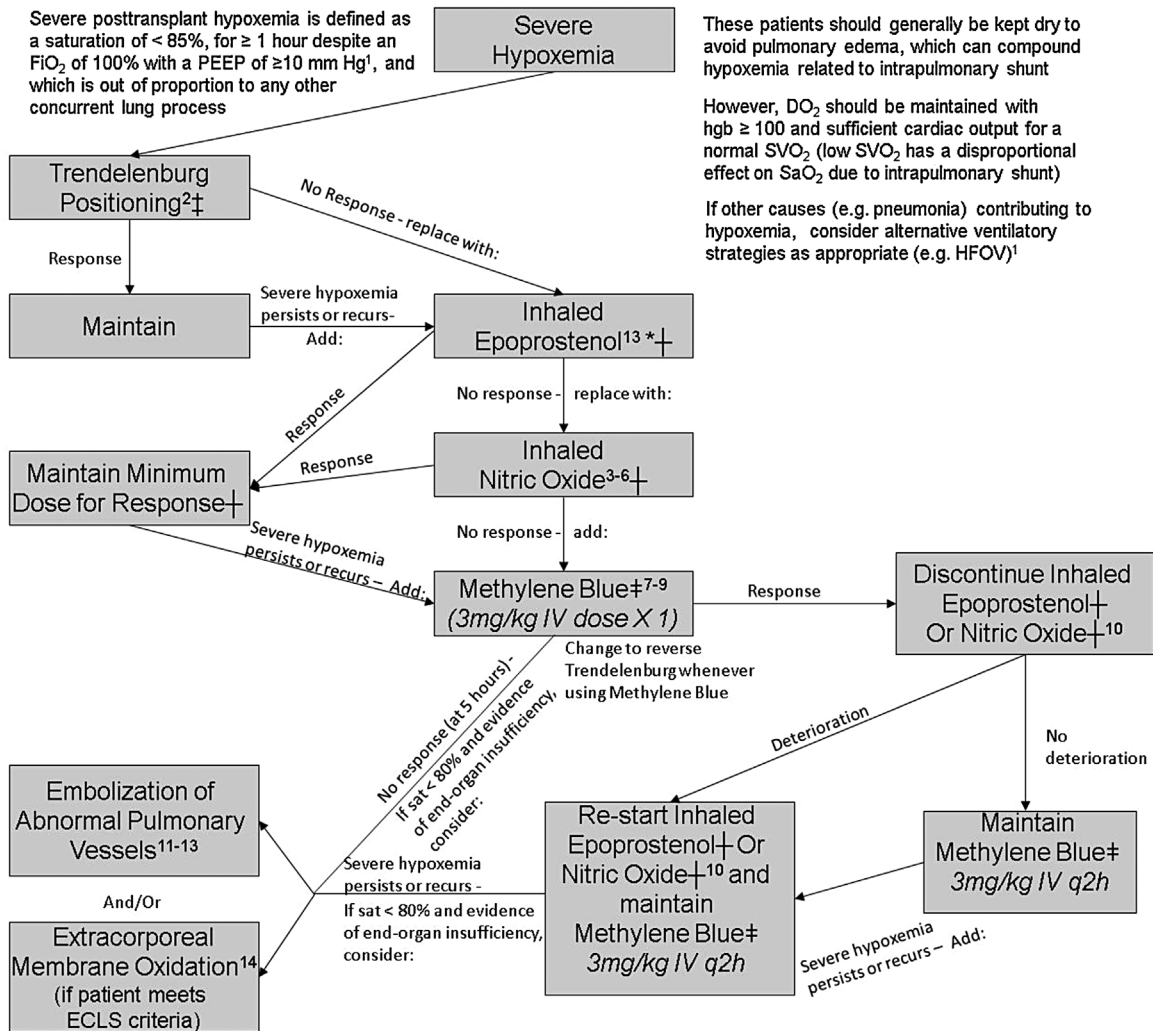


Figure 1: Proposed management algorithm for severe post-liver transplant hypoxemia in patients with hepatopulmonary syndrome. Response is defined as a 20% improvement in P/F ratio (and deterioration a 20% drop in P/F ratio), as measured at 30 min for all other interventions, and at 5 h for methylene blue (MB) (MB response can be seen as early as 30 min, but peak effect is at 5 h). [†]If feeding in this position, ensure that patient has a post-pyloric feeding tube. *If ventilated with high frequency oscillatory ventilation (HFOV), skip this step and go directly to inhaled nitric oxide. [†]In accordance with the modified University Health Network Inhaled Pulmonary Vasodilator Policy (see Supporting Information 1). [†]MB 3 mg/kg in 50–100cc’s normal saline IV over 15 min; change to reverse Trendelenburg for MB (if not possible, place supine). Hold MB after every 3 doses to assess ongoing need. Maximum recommended duration: 24–48 h (effects of larger cumulative doses unknown) (15, 16). Notes: hold any selective serotonin reuptake inhibitor (SSRI) and await appropriate washout if using MB (risk of serotonin toxicity) (17); MB can cause spuriously low pulse oximetry (verify oxygenation with ABG). Algorithm should be adapted in accordance with any available pre-operative testing results of Trendelenburg positioning, inhaled nitric oxide and/or IV MB, and any prior pulmonary angiography identifying embolizable pulmonary vessels. FiO₂ denotes fraction on inspired oxygen; DO₂ denotes systemic oxygen delivery; SVO₂ denotes mixed venous oxygen saturation; HFOV denotes frequency oscillatory ventilation. See Supporting Information 2 for figure References.

HPS patients posttransplant. Inhaled therapy is selective for the pulmonary circulation and has minimal adverse effects (35).

Intravenous methylene blue

Methylene blue is a potent vasoconstrictor which acts through inhibition of the cyclic GMP pathway. As noted, in

cirrhosis, impaired hypoxic pulmonary vasoconstriction with corresponding VQ mismatch is likely most prevalent at lung bases (30), where the majority of intrapulmonary vascular dilatations (IPVDs) are found (23), and where micro-atelectasis with resulting regional ventilation impairment is also more prominent (27). Methylene blue may induce vasoconstriction of these dilated basilar pulmonary arterioles (36) (non-remodeled vessels may still be capable

of vasoconstriction), thereby improving VQ matching. Although this vasoconstriction may also affect normal pulmonary vessels, dilated basilar pulmonary arterioles receive a higher proportion of pulmonary blood flow and therefore a higher total MB dose. Given its IV administration, we recommend that the patient be switched to a *reverse* Trendelenberg position to further favor basilar delivery by gravity. Given its systemic vasoconstrictive effects and corresponding possible reductions in cardiac output, hemodynamic monitoring is required to ensure that any drop in cardiac output is sufficiently offset by an improvement in oxygen saturation, for a net increase in tissue oxygen delivery.

Although gas exchange improved in seven patients with HPS given MB in a controlled, nontransplant setting, another case report noted a (reversible) deterioration in gas exchange with MB, and posttransplant experience is limited to a single (successful) use (Table 1). This interpatient variability in responsiveness to MB may be related to the relative contributions of reduced vascular tone and vascular remodeling in each patient's HPS pathophysiology (26). Specifically, patients with pulmonary vascular remodeling may be less likely to respond to agents attempting to increase vascular tone, given frank morphologic vascular enlargement as opposed to an imbalance of vasodilators and vasoconstrictors affecting vessel size (26).

Although little is known about the effects of large cumulative doses of MB, case reports suggest that the therapy is safe and effective at the doses that we have recommended. The drug was also shown to be safe post-LT, where it has been used for its potential anti-inflammatory effects (37).

Combined intravenous MB and inhaled vasodilators

Although there are only two reports of use of MB in conjunction with inhaled vasodilators in HPS, we included this strategy due to its low risk (given that inhaled vasodilators are rapidly reversible) and the hypothesized synergistic effect of these therapies. As noted, inhaled vasodilators preferentially vasodilate vessels in regions with good ventilation, as they have limited access to poorly ventilated areas. With MB, we seek to preferentially induce vasoconstriction in these poorly ventilated areas, where HPS vessels are inappropriately dilated due to impaired hypoxic vasoconstriction. When used in combination, inhaled vasodilators may also mitigate any possible vasoconstrictive effect of MB on pulmonary vessels in well ventilated areas, and thereby maximize the desired heterogeneity of its vasoconstrictive effect. The goal of this strategy is to redistribute blood flow away from inappropriately dilated HPS vessels. Since inhaled epoprostenol mediates vasodilatation through cyclic AMP rather than cyclic GMP, it is less susceptible to blockade by MB, and may thus be superior to iNO in achieving this effect.

Embolization of lower lobar pulmonary vessels

Embolotherapy of diffuse IPVDs has been shown to improve oxygenation in HPS, likely also through a mechanism of pulmonary blood flow redistribution (38–41). This is further supported by a large series reporting similar improvements in patients with the diffuse form of Hereditary Hemorrhagic Telangiectasia, in which patients have diffuse, basilar-predominant IPVDs which are morphologically similar to those seen in HPS (42). However, given the lack of a reliable way to predict a response, and the risks of transporting a severely hypoxemic patient to a fluoroscopic procedure suite, embolization has been included in the algorithm as a "last resort" approach, and access may be limited to specialized centers.

Extracorporeal life support

The use of ECLS (using the veno-venous configuration) in adult patients remains controversial and represented only 12% of all cases in the ECLS Organization registry report (43). Recently, Auzinger et al reported the first adult case of veno-venous ECLS in posttransplant hypoxemia in HPS (44). The profoundly hypoxemic patient (PF ratio 40–60) was supported on ECLS for 21 days and eventually discharged home off supplemental oxygen. Monsel, et al described successful use of ECLS for 13 days pre- and 5 days posttransplant in a 51 year-old man with alcoholic cirrhosis, ARDS and intrapulmonary shunting (45). As a supportive therapy designed to function as a bridge to recovery, ECLS is theoretically well suited to patients with HPS, given that shunt reversal and corresponding improvement in gas exchange occurs in nearly 100% of LT survivors (9,46). Given the known complications of prolonged ventilation, including ventilator-associated pneumonia and lung injury, early initiation of ECLS would be preferable, as it could both reduce ventilation requirements and mitigate end-organ hypoxia (47). Accordingly, our algorithmic approach seeks to rapidly guide clinicians through various therapeutic approaches, in order that ECLS is considered early in patients who are unresponsive to other therapies. However, timing of improvement in HPS-related hypoxemia is highly variable between patients and difficult to predict (9). Given this and the high risk of complications and mortality associated with prolonged ECLS in adults (44,48), ECLS is suggested as a "last resort" approach, as above.

Sequence of Therapies in Algorithm

We recommend maintaining any initially effective therapy and adding others sequentially thereafter for recurrent hypoxemia. Trendelenburg positioning is the first therapy in the algorithm because it carries low risk, and is the easiest to both implement and reverse. We followed this with inhaled vasodilators because they have been most widely studied in HPS, have a rapid onset, and are quickly reversible. Inhaled epoprostenol is recommended before

iNO because it is just as effective as iNO in critically ill patients with refractory hypoxemia (49), is lower in cost, and may have a stronger synergistic effect with MB than iNO (as detailed above). If a positive effect is seen with combination therapy, we recommend attempting to wean the inhaled vasodilator to determine if the observed effect is due to MB alone or to the combination. If all other treatments have failed, we recommend embolization of abnormal pulmonary vessels or ECLS. Since these are invasive, non-reversible treatments with a high risk of complications and very limited evidence, we recommend that patients have a $\text{SaO}_2 < 80\%$ with evidence of end-organ insufficiency in order to justify these risks.

Pretransplant Testing

Our review suggests that there is variability in responsiveness to various therapies (Table 1). This is likely due to variations in the timing, dose and duration of their administration, and unique patient factors related to HPS pathophysiology and any co-existing lung disease. A previous report noted increased risk of severe posttransplant hypoxemia in patients with a baseline $\text{PaO}_2 \leq 50$ mmHg and/or $\geq 20\%$ anatomic shunting (10). In these "high-risk" patients, preoperative testing for responsiveness to these approaches may be beneficial in predicting their relative effectiveness. These data could be used to tailor and adapt the algorithm to each patient, and positive results may be used to justify listing of candidates otherwise considered at too high a risk for this complication (6).

Other Considerations

We recommend advance involvement of the surgical anesthesia team, as anaesthetic induction alone also worsens hypoxemia in patients with HPS (50), and use of the algorithm may be considered intra-operatively. Hemodynamic monitoring aids may facilitate optimal use of the algorithm. Given that, by definition, patients in the algorithm have a saturation $< 85\%$, a high hemoglobin target can also help to preserve tissue oxygen delivery (9). Furthermore, impaired tissue oxygen delivery results in reduced mixed venous oxygen saturation, which may have a disproportionate effect on arterial hypoxemia in the presence of intrapulmonary shunting. Finally, allograft function requires particularly close monitoring in these patients. Although patients with HPS generally demonstrate good allograft function even in the context of severe posttransplant hypoxemia (10,46), there is a theoretical risk that prolonged posttransplant hypoxemia will adversely impact allograft function. This could then delay the reversal of pulmonary vascular abnormalities, resulting in a vicious cycle of severe hypoxemia and poor allograft function. Along these lines, "extended-criteria" allografts have been associated with increased graft dysfunction (51), and their use must be

considered judiciously, on a case-by-case basis in HPS patients at high risk of developing severe posttransplant hypoxemia. However, given that the risk of severe posttransplant hypoxemia increases with the severity of baseline hypoxemia (10), and that hypoxemia is rapidly progressive in HPS (7,9), this risk must be weighed against the benefit of reduced transplant wait times afforded by use of extended-criteria organs. This is an area that requires further research.

The role of MELD exception points in reducing the incidence of this complication also deserves mention. Although select, highly specialized centers have demonstrated good posttransplant outcomes in very severely hypoxemic patients with HPS (9,52), in addition to the increased risk of posttransplant hypoxemia (10), studies have demonstrated increased overall posttransplant mortality in patients with a pretransplant $\text{PaO}_2 \leq 50$ mmHg (7,11,53). These data, along with the expected decline in PaO_2 of 5.2–13.5 mmHg per year in patients with HPS (7,9) coupled with expected delays to transplantation, form the basis for the UNOS MELD exception threshold of $\text{PaO}_2 < 60$ mmHg in HPS. In centers with transplant waiting times that routinely result in a drop in PaO_2 to ≤ 50 mmHg by the time of transplant in these patients (despite allocation of MELD exception points), even more aggressive prioritization approaches may be required to reduce the incidence of this complication. Future studies should also address whether the length of time from MELD exception to transplant is independently associated with posttransplant outcomes.

Limitations

Our algorithm was intended for use in intubated patients. However, severe hypoxemia may also occur after early extubation (10,52), and strategies in the algorithm might be considered in an effort to avert re-intubation. Previous authors have reported alternative ventilatory strategies such as high frequency oscillatory or jet ventilation (10), or airway pressure release ventilation (APRV) in this population (10,54), however results have been inconsistent. Accordingly, we have not addressed ventilator strategies, nor routine ICU management issues in LT recipients and ventilated patients, which have previously been well described. Similarly, we do not discuss management of other potential contributors to posttransplant hypoxemia (e.g. atelectasis, pulmonary edema, transfusion related acute lung injury, and ventilator-associated pneumonia), which is also described elsewhere (55). Although our search was systematic, there may also have been a publication bias in favor of reports demonstrating positive results. Also, given the rarity of HPS and the fact that this complication is only seen in a fraction of patients who actually receive LT, evidence was limited to case reports and case series. However, we were able to include findings from 27 reports and 43 patients in whom these therapies

were used, and we do not believe that the lack of high quality evidence invalidates the benefit of reviewing and summarizing these data to guide management. We acknowledge that this algorithm has not been validated prospectively. However, we have used the approach in this algorithm in our center, and as noted above, have demonstrated superior outcomes to those reported in other literature (9,10). Also, we believe that the benefits of an algorithm based on best currently available evidence and expert opinion outweigh the risks of the status quo, which is an unacceptably high mortality from this complication, a lack of any recommended systematic approach, and lack of awareness and consistent use of these strategies among clinicians.

Conclusions

Severe posttransplant hypoxemia is associated with an unacceptably high mortality in HPS. We used best evidence and expert opinion to develop a practical management algorithm for this complication. Future research should prospectively measure the impact of this algorithm on posttransplant outcomes in this population.

Acknowledgments

We would like the following team members who had important input in the management algorithm: Kayode Adeniji (ICU), Ruane Walton (RRT), Francois Carrier (ICU), Pierre Aslanian (ICU), and members of the divisions of anaesthesia, ICU (physicians, respiratory therapists, and nurses), hepatology, extracorporeal life support, and liver transplant surgery at the University of Toronto.

Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. John Granton is a member of the scientific steering committee for a clinical trial sponsored by Ikaria. Other authors have no conflicts of interest.

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Supporting Information

Additional Supporting Information can be found in the online version of this article.

Supporting Information Material S1: Modified University Health Network Inhaled Vasodilator Policy.

Supporting Information Material S2: Figure References.

Supporting Information Table S1: Mechanisms of Action and Reasons for Exclusion of Excluded Therapies.