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ADULT RESPIRATORY DISTRESS SYNDROME SECONDARY TO END-STAGE LIVER DISEASE—SUCCESSFUL OUTCOME FOLLOWING LIVER TRANSPLANTATION¹

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Abstract

The adult respiratory distress syndrome (ARDS) complicating liver failure carries a 100% mortality. Two cases of ARDS that resolved following liver transplantation have been reported, one associated with acute allograft rejection, and the second due to sepsis. There is, however, a great reluctance to transplant these very-high-risk patients. We report the first series of patients with ARDS secondary to liver failure who successfully underwent OLTX. No patient had sepsis or pneumonia. Posttransplant mechanical ventilation was required for a median of 14 days (range 6–37 days). All patients in this series are alive and well, with a follow-up of 6–15 months. This demonstrates that ARDS associated with liver failure, an otherwise uniformly lethal complication, can respond dramatically to OLTX.

The adult respiratory distress syndrome (ARDS)^{*} is frequently seen complicating liver failure. Once established, it is irreversible, despite the most aggressive medical management (1). There have been two cases reported in the literature in which resolution of this syndrome followed orthotopic liver transplantation. The first case was that of a patient who underwent OLTX at our institution, and who developed ARDS in association with severe rejection of the allograft. This resolved completely after retransplantation (2). The second patient had sepsis and ARDS complicating liver failure. After the sepsis was brought under control, the patient underwent a successful OLTX and eventually recovered (3).

Most clinicians, however, are usually reluctant to consider OLTX in the presence of ARDS. This is because these patients are always desperately ill, and an underlying septic focus can be difficult to exclude. Recently, we managed several patients who developed an ARDS picture in association with end-stage liver disease (ESLD), and who successfully underwent OLTX. The excellent results in this small series suggest that, in carefully selected patients, OLTX will lead to the resolution of an otherwise lethal combination of failing organs.

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^{*}Abbreviations: ARDS, adult respiratory distress syndrome; ESLD, End-stage liver disease; LIS, lung injury score; PBS, protected brush specimen.

MATERIALS AND METHODS

During a period of nine months extending from June of 1990 to March of 1991, five patients with ESLD and associated ARDS underwent primary OLTx at Presbyterian University Hospital, Pittsburgh. During the perioperative period they were all under the care of one of the authors (H.R.D.). Follow-up ranged from 4 to 15 months. The data were gathered retrospectively through a review of the patients' charts.

All patients were admitted preoperatively to the Liver Transplant Intensive Care Unit, and required mechanical ventilation. Four patients had a pulmonary artery catheter inserted upon arrival at the ICU to monitor filling pressures and cardiopulmonary profiles. The fifth patient, a 13-year-old boy, was managed with a central venous line. Besides routine monitoring of blood chemistries (4), a thorough search for sepsis was conducted. This included an abdominal CT scan, as well as sputum, urine, and blood cultures. If indicated, a paracentesis was performed and the ascitic fluid sent for routine cultures and cell count. Four of the patients underwent bronchoscopy, and either a quantitative bronchoalveolar lavage or a protected brush specimen (PBS) of a radiographically diseased lobar segment. Since all patients had diffuse infiltrates, the choice of a specific segment was left to the individual operator. The fifth patient was a Jehovah's Witness who had a coagulopathy that could not be corrected prior to transplant due to religious objections to the administration of blood products. Also, the size of his endotracheal tube (6.0) would not allow fiberoptic bronchoscopy. Under these circumstances we thought that airway manipulation would pose an unjustifiable risk of hemorrhage—and, as such, only sputum cultures were obtained. The anesthetic management was uniform. Anesthesia was maintained with the use of an oxygen air mixture, isoflurane, fentanyl, lorazepam, and vecuronium. A Siemens 900D ventilator was used intraoperatively, which allowed for continuous assessment of peak airway pressures, fraction of inspired oxygen, expired tidal volume, and level of positive end-expiratory pressure. Venovenous bypass was used in all cases.

Definitions

Spontaneous bacterial peritonitis was defined as a positive ascitic fluid culture and/or an absolute neutrophil count $>250/\text{ml}$ (5).

Ventilator-associated pneumonia was defined as persistent pulmonary infiltrates that did not clear after vigorous pulmonary toilet, together with purulent sputum and a positive quantitative culture obtained by either BAL or PBS. A quantitative BAL was positive if it grew $>10^5$ colonies/ml, whereas the cut-off point was $>10^3$ colonies/ml for a quantitative PBS. Lower colony counts were considered to reflect colonization (6,7), whether or not the patient was receiving systemic antibiotics at the time.

ARDS was defined as the combination of bilateral diffuse infiltrates on chest radiography, decreased pulmonary compliance, and hypoxemia requiring supplemental oxygen. In addition, the pulmonary artery occlusion pressure had to be <18 mmHg. A lung injury score (LIS) was determined according to the method of Murray et al. (8), as shown in Table 1.

Statistical analysis

The data are presented as the median and the range. Statistical comparisons were made using the Wilcoxon rank sum test. Significance was defined at a $P < 0.05$ level.

RESULTS

The general patient characteristics are presented in Table 2. All patients were male, and the median age was 45 years (range 13–55). Three patients had alcoholic cirrhosis, one had post-

necrotic cirrhosis due to hepatitis B, and one had fulminant hepatic failure of unknown etiology. Advanced liver failure was noted in all, with a median total bilirubin of 18.7 mg/dl (range 8.7–26.0), and a median prothrombin time of 17.4 sec (range 16.7–18.6). Four patients were receiving frequent infusions of fresh frozen plasma to permit invasive instrumentation. Patient D.W. was in grade IV coma, while the remaining patients were intentionally sedated to facilitate their management.

Table 3 shows the respiratory system data. An LIS was calculated for each patient by assessing four parameters: magnitude of the infiltrates seen on chest roentgenogram, respiratory system compliance, hypoxemia index, and the level of PEEP (8). This index has a maximum value of 4. The median LIS within 24 hr prior to undergoing OLTx was 2.3 (range 2.3–3.5). No patient was turned down for transplantation based on the severity of the LIS. Mechanical ventilation was required after transplantation for a median of 14 days (range 6–37). As can be seen in Figure 1, on the day mechanical ventilation was stopped the median LIS had decreased to 1.0 (range 0.5–1.5 [$P < 0.005$]).

An important concern prior to transplantation was to establish whether any of the patients was infected. As can be seen in Tables 2 and 4, all patients for whom data are available had a clinical picture compatible with sepsis (patient D.W. was a Jehovah's Witness in whom laboratory work was strictly limited). Two patients were febrile. All had thrombocytopenia and a left shift in the differential leukocyte count. As is characteristic of liver failure, these patients had hyperdynamic circulation, with a cardiac index that ranged between 6.0 and 9.7 L/min/m², and systemic vascular resistance index from 492 to 636 dyne/sec/cm⁵/m² (Table 4). Pulmonary artery occlusion pressures were maintained between 14 and 15 mmHg. Blood, urine, and ascitic fluid cultures were consistently negative. The absolute neutrophilic count in the ascitic fluid was below 250 in every case examined. Sputum cultures in patient D.W. had a light growth of coagulase-negative *Staphylococcus*. Due to the particular organism, the light growth, and the chest roentgenogram pattern, it was thought that this represented colonization rather than infection. Table 2 shows the respiratory cultures. Two patients had protected brush specimens that failed to grow any organisms, and two other patients had a quantitative BAL that grew fewer than 10³ organisms. They were all on systemic antibiotics at the time the cultures were obtained. All patients underwent a successful liver transplant. The effective dynamic lung compliance and alveoloarterial oxygen difference (AaDO₂) remained the same throughout the operation, without improvement upon graft reperfusion.

The time to resolution of the pulmonary infiltrates was variable, but improvement was evident by the end of the first week posttransplant. In one case residual changes were still present at the end of one month. Mechanical ventilation was required for a median of 14 days posttransplant (range 6–37). All patients are doing well, and are back in their communities 6–15 months after transplantation.

DISCUSSION

The prognosis for patients suffering from ESLD who require mechanical ventilation for any reason is poor, with a mortality approaching 90% (9,10). ARDS is a frequent complication of advanced liver failure, whether chronic or acute. Matuschak et al. retrospectively studied 29 patients with advanced nonalcoholic ESLD who were in an ICU for at least 24 hr (1). Of these, 23 eventually developed ARDS (79%), compared with only 3 of 44 control patients (6.8%). Sepsis was the most common risk factor for the development of ARDS in both groups, with 18 of 23 (78%) ESLD patients being clinically septic before ARDS developed. More important, the course of the respiratory failure was irreversible regardless of the presumed etiology. Nonresolving ARDS was a direct or indirect cause of death in 12 of 23 (52%) patients, and a contributing cause of death in the remaining patients (1). The combination of liver failure and

ARDS, therefore, carries a mortality of 100%, as compared with 60–70% for ARDS in a variety of other settings (11–14).

Patients with advanced liver disease appear to be at high risk for irreversible ARDS, probably because of the central role the liver plays in host defenses (15). Although the pathogenesis of ARDS is still not completely understood, certain key elements have emerged. The role of circulating endotoxin in initiating an inflammatory cascade that will eventually lead to panendothelial injury has been suggested (16). This injury is probably initiated by activated neutrophils, but it can also take place through neutrophil-independent mechanisms (16,17). The liver, specifically the Kupffer cell mass, is critical in the detoxification of gut-derived bacteria and their products. Liver failure or Kupffer cell blockade can lead to a “spillover” of toxins into the systemic circulation (18, 19). Severe hepatic dysfunction can not only increase the likelihood of ARDS, but may also modulate its resolution (1). There have been several studies performed by our group looking at the relationship between perioperative endotoxemia and outcome following OLTx. Yokoyama et al. have recently emphasized the deleterious consequences caused by the wave of endotoxemia that follows the anhepatic phase, which can lead to profound graft dysfunction and decreased patient survival (20), and in a separate study by Miyata et al., addressing specifically the issue of pulmonary complications, a significant correlation was found between high levels of endotoxin and the need for prolonged postoperative ventilatory support (21). We did not perform endotoxin determinations in any of our patients.

In keeping with the preceding discussion, OLTx has been reported to lead to resolution of established ARDS associated with preexisting liver failure (2,3). In the first case, respiratory failure was caused by severe liver allograft rejection (2). Hepatic retransplantation started approximately 9 hr after the diagnosis of ARDS was made, and the patient was extubated 48 hr after the completion of the operation. In another case (3), a patient with cirrhosis and ulcerative colitis developed ARDS following *Bacteroides* sepsis. Although the sepsis was brought under control, she continued to have nonresolving ARDS. At this point she underwent a successful OLTx and the ARDS eventually resolved. In contrast to these two cases, none of our patients had any known predisposing factor such as sepsis, aspiration, multiple transfusions, pancreatitis, or drugs. Therefore, they appear to have developed ARDS solely on the basis of advanced liver failure.

Besides the patient we already mentioned (2), we have sporadically in the past performed a primary OLTx in patients having both liver failure and a picture consistent with ARDS. However, these patients did not undergo the complete and systematic evaluation to rule out infection that we performed in the present series, and are, therefore, not included in this report. The decision to proceed with transplantation in these cases has always been taken reluctantly. This is because the sepsis syndrome that accompanies advanced liver failure can be very difficult to differentiate from that due to a serious infection, which is a formal contraindication to transplantation. As can be seen from Tables 3 and 4 our patients demonstrated the hyperdynamic state characteristic of either condition. They were also thrombocytopenic, coagulopathic, and had a significant left shift. In trying to determine whether the patients had a concomitant infection, we performed repeated cultures of blood, urine, and ascitic fluid. Given the uncertainty of the clinical situation, once the appropriate samples had been collected the patients were placed empirically on broad-spectrum antibiotics. These were continued until the final cultures were back, and found to be negative. In addition, abdominal CT scans were performed to exclude the possibility of an abscess, and liver ultrasounds obtained to evaluate the biliary tree and the patency of the hepatic vessels. None of the patients had bacteremia, urinary tract infections, or spontaneous bacterial peritonitis. The imaging studies were unrevealing, except for the expected presence of a small liver and ascites. At this point the most difficult challenge was to rule out an underlying pneumonia. Since positive sputum

cultures are common in intubated patients, and the chest roentgenogram pattern is unreliable when trying to distinguish infectious from noninfectious infiltrates, we performed fiberoptic bronchoscopy and quantitative BAL or PBS in four of the five patients. We used a colony count of $>10^5$ /ml for quantitative BAL, and $>10^3$ /ml for PBS to differentiate between colonization and infection (6,7). As can be seen in Table 2 none of our patients met these criteria for pneumonia. Patient D.W. did not have a bronchoscopy due to his uncorrectable coagulopathy and relatively small endotracheal tube. He had a light growth of coagulase-negative *Staphylococcus* from sputum, which was thought to be a contaminant. We recognize that the respiratory cultures were obtained while the patients were receiving empiric systemic antibiotics, which may have diminished their accuracy (6). However, since these patients received only routine postoperative antibiotic prophylaxis (intravenous ampicillin and cefotaxime for 72 hr), and the pulmonary picture resolved in all despite being immunosuppressed, we are confident that our initial interpretation of the culture results was correct.

Regarding the magnitude of the lung injury, the lung injury scores (8) ranged from 2.3 to 3.5 on the day of transplantation, and improved significantly after the operation (Fig. 1). The most salient clinical features were those of diffuse bilateral pulmonary infiltrates in the presence of relatively normal filling pressures—and, accompanied by a significantly reduced compliance, all were consistent with ARDS. However, in contrast to ARDS in other groups of patients, oxygenation was easily maintained on mechanical ventilation, except for patient J.G. (Table 3). We used the effective dynamic compliance, instead of the static compliance, to calculate this score. This is because we do not routinely measure plateau pressures in our ICU. Although these compliances are not necessarily identical, we have no reason to believe that they would be significantly different in the particular case of our patients. Except for patient D.W., who was a 13-year-old boy and had a 6.0 endotracheal tube (which may offer some resistance to flow), all other patients had large-diameter endotracheal tubes (8.0 in two patients, 9.0 in the remaining two). Furthermore, none had a history of airway hyperreactivity or copious secretions, and they did not develop clinical bronchospasm during their ICU stay. More important than the degree of lung injury at the time of transplantation is the dramatic improvement seen after these patients received a well-functioning liver allograft, which is in sharp contrast to the grim natural history this combination of failing organs has had until now.

We believe it is extremely important to obtain quantitative respiratory cultures prior to proceeding with the transplant operation. Standard clinical criteria are simply too unreliable to distinguish ARDS from an infectious process in this difficult setting, and quantitative BAL or PBS should be a part of the diagnostic work-up in this population.

It is important to recognize that the scope of our observations is limited to a very specific patient population—that is, those with ARDS secondary to liver failure. Extreme care should be taken not to extrapolate our findings to other patients, such as those with ARDS secondary to sepsis or pancreatitis, who most likely account for a larger number of patients awaiting liver transplantation. We need to define the conditions under which OLTx can be carried out with a reasonable expectation of success, but as our experience with this small series of patients demonstrates—and given careful selection criteria—ARDS secondary to liver failure does not necessarily follow an inexorable progression to death.

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Figure 1.
Lung injury scores on the day of OLTX and on the day mechanical ventilation was stopped.

Table 1Components and individual values of the lung injury score^{a,b}

1	Chest roentgenogram score:
	No alveolar consolidation: 0
	Alveolar consolidation in 1 quadrant: 1
	Alveolar consolidation in 2 quadrants: 2
	Alveolar consolidation in 3 quadrants: 3
	Alveolar consolidation in 4 quadrants: 4
2	Hypoxemia score (PaO ₂ /FIO ₂):
	>300: 0
	225–299: 1
	175–224: 2
	100–174: 3
	<100: 4
3	PEEP score (when ventilated):
	<5 cm H ₂ O: 0
	6–8 cm H ₂ O: 1
	9–11 cm H ₂ O: 2
	12–14 cm H ₂ O: 3
	>15 cm H ₂ O: 4
4	Respiratory system compliance score:
	>80 ml/cm H ₂ O: 0
	60–79 ml/cm H ₂ O: 1
	40–59 ml/cm H ₂ O: 2
	20–39 ml/cm H ₂ O: 3
	<19 ml/cm H ₂ O: 4

^aThe final score is the aggregate sum divided by the number of components used: 0 = no lung injury; 0.1–2.5 = mild-to-moderate lung injury; >2.5 = severe lung injury (ARDS); PaO₂/FIO₂ = arterial oxygen tension to inspired oxygen concentration ratio; PEEP = positive end-expiratory pressure.

^b(SOURCE: Murray JF, et al. Am Rev Respir Dis 1988; 138:720 [by permission from the publisher]).

TABLE 2

Clinical and microbiological features^a

Patient	Age/sex	Dx	Bili (mg/dl)	Temp (°C)	WBC/%bands	Platelets (per ml)	PT (sec)	Cultures
E.C.	45/M	PNCE	15.1	37.5	11,300/15%	93,000	16.7	<10 ³ /ml <i>E. faecalis</i> and <i>C. albicans</i> (BAL)
J.G.	41/M	CAHB	18.9	38.4	11,500/15%	39,000	18.6	<10 ³ /ml coagulase (–) <i>Staphylococcus</i> (BAL)
D.W.	13/M	FHF	26.0	37.9	N/A	N/A	N/A ^c	Light coagulase (–) <i>Staphylococcus</i> (sputum)
D.R.	47/M	PNCE	8.7	37.2	7,800/18%	46,000	16.8	Sterile (PBS)
E.F.	55/M	PNCE	18.7	38.1	7,400/12%	48,000	18	Sterile (PBS)

^aLaboratory values obtained within 24 hr prior to transplant. All cultures performed within one week prior to transplant.

^bAbbreviations: Dx = diagnosis; Bili = bilirubin; Temp = temperature; PT = prothrombin time; PBS = protected brush specimen; BAL = bronchoalveolar lavage; PNCE = postnecrotic cirrhosis due to ethanol; FHF = fulminant hepatic failure; CAHB = chronic active hepatitis B.

^cPT 14 days prior to transplant = 22.3 s.

Table 3

Respiratory system parameters^a

Patient	CXR ^b score	EDC	PaO ₂ /FIO ₂	PEEP	LIS
E.C.	4	16	226	5	2.3
J.G.	4	20	103	15	3.5
D.W.	4	14	260	10	2.8
D.R.	4	20	255	10	2.3
E.F.	4	21	210	5	2.3

^aWithin 24 hr prior to transplantation.

^bAbbreviations: CXR = chest roentgenogram; EDC = effective dynamic compliance (ml/cmH₂O) PaO₂/FIO₂ = arterial oxygen tension:inspired oxygen concentration ratio. LIS = lung injury score; PEEP = positive end-expiratory pressure (cmH₂O).

Table 4Hemodynamic parameters^a

Patient	PaO ^b	CI	SVRI
E.C.	14	7.8	492
J.G.	14	6.0	636
D.W.	N/A ^c	N/A	N/A
D.R.	15	9.7	533
E.F.	16	7.7	541

^aWithin 24 hr prior to transplantation.^b Abbreviations: PaO = pulmonary artery occlusion pressure (mmHg); CI = cardiac index (L/min/m²); SVRI = systemic vascular resistance index (dyne·s/cm⁵·m²).

CVP = 10.