Acute Liver Failure: Early Referral is the Key

Acute liver failure (ALF) is a rare but devastating condition which requires immediate recognition and management in experienced centers. The etiology of this syndrome is most frequently drug toxicity, with acetaminophen on top of the list, and acute viral hepatitis declining over the years. This condition is rapid and unpredictable, and the outcome is related to the etiology (acetaminophen and Hepatitis A, better than other drugs and Hepatitis B, and Wilson’s disease the worst) and the degree of liver damage and hepatic encephalopathy at the time of presentation. Management includes supportive care in intensive care units, and specific treatments in certain conditions, such as delivery for acute fatty liver of pregnancy, N-Acetylcysteine for acetaminophen overdose, and silibinin for mushroom poisoning, among others. Liver transplantation is the standard of care for patients with a low chance of spontaneous survival. Bridging techniques with liver support devices are still experimental and none have proven benefit to date. A randomized controlled trial of N-Acetylcysteine for non-acetaminophen ALFs is underway. Early referral to experienced centers, and centers where liver transplant is available, is the key to improve outcome.

INTRODUCTION

The estimated number of patients annually affected by acute liver failure (ALF) (or fulminant hepatic failure) in the US is approximately 2000(1). ALF is characterized by the rapid progression or resolution, the unpredictability and severity of its complications, and by high morbidity and mortality. The need for prompt recognition and early referral to tertiary specialized centers cannot be overemphasized. Delay in referral and lack of offering a life-saving procedure such as liver transplantation, may result in poor outcome.

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Acute Liver Failure

A SPECIAL ARTICLE

This review will provide some basic guidelines in the management of ALF and most importantly, we will illustrate a network of sites and contacts within the US, where medical providers can call for advice or refer patients needing immediate and specialized care.

Although ALF cases related to acetaminophen tend to be a distinct group in terms of management and survival, because of their more homogenous and predictable outcome, no single patient with ALF can be satisfactorily “framed” in a “standard” critical care pathway. Each patient must be managed individually with close attention to the potential and variable life-threatening complications.

One single take-home message from this review to all providers in the community involved in the management of these difficult patients is: early referral to an ALF study group site or a transplant center.

Acute Liver Failure Study Group

During the last few years the National Institute of Diabetes and Digestive and Kidney Diseases has funded an important study group, the Acute Liver Failure Study Group (ALFSG), coordinated by Dr. William Lee and coworkers at the University of Texas Southwestern (2). Twenty-six US academic centers are currently participating in collecting information on all cases of adult acute liver failure seen at their institutions. In addition, since 2000, 17 pediatric sites have been added to the group. Moreover, the group is actively enrolling patients in a prospective, randomized, double-blind placebo-controlled clinical trial on the use of intravenous N-Acetylcysteine (NAC) for ALF not caused by acetaminophen toxicity. This study will be an invaluable resource for viral discovery and genetic and immunologic approaches to defining the causes of idiopathic ALF. More information on this consortium is available at www3.utsouthwestern.edu/liver. Table 1 and Table 2 list all participating centers, for adult and pediatric patients, with the contact e-mail addresses and phone numbers. Figure 1 illustrates the US map with center location, divided by pediatric and adult. Please make a copy of these tables for your practice and consider contacting the center closest to you if you see a patient with ALF.

DEFINITION

ALF develops as a result of acute necrosis of hepatocytes, without previous evidence of hepatocellular disease (3). Hepatic encephalopathy (HE) must be present for the diagnosis of ALF, in addition to elevated liver enzymes and coagulopathy (PT-INR >1.5). The interval between the onset of HE and the onset of symptoms can be as long as 24 weeks, but commonly within 8 weeks. HE is a syndrome that describes all neuropsychiatric symptoms occurring in patients with acute or chronic liver diseases in the absence of other neurological disorders. Making a diagnosis of HE and staging the severity is clinically fundamental, since early recognition can be life saving by initiating specific management and by alerting for potential transfer to tertiary or transplant center. It is important to recognize that subtle changes in mental status, such as slow speech and changes in sleeping patterns, may not be detected by the standard “mini-mental” status assessment (“where are you?”, “which is today’s date?”, etc). The presence of asterixis (“flapping tremor”) should be properly checked and monitored over time.

ETIOLOGY

The causes of ALF can be subdivided into four categories: 1) drugs, 2) infections, 3) ischemia, 4) miscellaneous, and 5) indeterminate (Table 3) (4). In the last 5–10 years, acetaminophen has become the number one cause of ALF in the US, approximately half of which are actually due to unintentional “overdose,” where acetaminophen is taken to relieve pain, without suicidal intent (5). It has been suggested that the combination of acute alcohol intake may actually protect from acetaminophen liver toxicity. Recent study has shown that chronic alcohol intake actually worsens liver toxicity from acetaminophen, while acute alcohol does not affect the clinical outcome (6). Viral hepatitis is declining as the cause of ALF in the US, with only one-eighth of the total cases as reported by the ALFSG (7). Acute hepatitis B is more frequent than hepatitis A, and others such as herpes simplex, Epstein-Barr, cytomegalovirus are rare and usually associated with immunocompromised patients. Occult hepatitis B

(continued on page 19)
Table 1  
Adult Acute Liver Failure Study  
Group Sites by State  

<table>
<thead>
<tr>
<th>State</th>
<th>Site</th>
<th>Principal Investigator</th>
<th>Phone Number</th>
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<tbody>
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infection does not appear to be a cause of ALF, at least in the US (8). Prompt recognition of the cause of ALF is important not only because it determines prognosis, but also because specific treatments are available in certain diseases (9). Antidotes to acetaminophen (i.e. NAC) and mushroom poisoning (i.e. silibinin and penicillin) need to be given immediately in order to obtain maximum benefit. Acute fatty liver of pregnancy may require termination of pregnancy, cardiogenic shock requires prompt correction of fluid balance and aggressive hemodynamic monitoring, and patients with Wilson’s disease need to be referred immediately to liver transplant centers.

OUTCOME

Approximately one third of patients with ALF survive without liver transplantation, one third receive liver transplantation, and one third will die either because they are not transplant candidates or while waiting for a donor graft (9). The etiology and the severity of encephalopathy at presentation are the major determinants of outcome. Patients with hepatitis A, acetaminophen, cardiogenic shock, and pregnancy have the highest chance of spontaneous survival (50%–70%). Those with idiosyncratic drug reactions, hepatitis B, autoimmune, Budd-Chiari, and indeterminate cause have intermediate or low chance of spontaneous survival (15%–25%). ALF patients with malignancies and with Wilson’s disease have practically zero chance of spontaneous survival (1,4,7,9).

Infections during the course of ALF are associated with worsening encephalopathy, especially in the acetaminophen cases, although the role of indiscriminate use of prophylactic antibiotics in this condition is still controversial (10). Survival with liver transplantation in ALF patients is between 60% and 80%, and not different from other indications for transplant (1,11,12). It is recommended that patients with ALF be referred to experienced centers with access to liver transplantation in order to optimize outcome.

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Figure 1. The map of the US with the location of the Acute Liver Failure Study Group sites: in red circle, the adult sites; and in green diamond, the pediatric sites. See Table 1 and 2 for details and contact numbers/addresses.

Indicators to determine prognosis in ALF include the King’s College Hospital criteria (13), APACHE II scoring system (14), alfafigoprotein (15), coagulation factor V (16), and Gc proteins (17). The King’s criteria are probably the most widely used. They differ between acetasminophen toxicity, in which the arterial pH <7.30 is the best predictor of poor survival, and other causes of ALF, in which coagulopathy (PT-INR >6.7) appears to be more reliable (13). None of the above scoring systems have proven to be conclusively effective in predicting outcome in ALF (18). The ideal scoring system would allow predicting with great sensitivity and specificity which patient with ALF needs a liver transplant and which one will spontaneously survive. Until more reliable parameters are available, our recommendation is to evaluate each patient individually with the expert advise of a liver specialist.

ADMISSION TO THE EMERGENCY ROOM
AND GENERAL MANAGEMENT

The patient with suspected acute liver failure should be evaluated immediately in the emergency room with consultation of the gastroenterologist or the liver specialist. The first priority is to assess the need for admission to the medical intensive care unit or the need and timing for transfer to a liver transplant center.

The prompt availability of a liver specialist and the level of expertise provided with the initial evaluation are crucial in order to prevent poor outcomes. If a local gastroenterologist or liver specialist is not readily available, a phone call to the nearest liver transplant or experienced center is strongly recommended (see list in Table 1 and Table 2, alphabetically ordered by State).

Sometimes patients with ALF do not declare themselves with severe symptoms right at the time of presentation to the hospital. They may have elevated liver enzymes and mild coagulopathy, but the mental status changes may be subclinical. They will answer correctly to the mini-mental status assessment questions and their hepatic encephalopathy will be detected only with the use of more sensitive tests such as the number connection test (19) or other psychometric testing.

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In any case, if an immediate decision for transferring the patient to a transplant center cannot be made, and admission to the medical intensive care unit is indicated, Table 4 illustrates an example of admission orders.

General management varies depending on the grade/stage of hepatic encephalopathy. Patients with early (stage I–II) should have strict monitoring of intake and output (I & O’s), and hemodynamic monitoring using a central line, central venous pressure at a minimum. Swan-Ganz placement should be considered in patients who are hemodynamically unstable. Laboratory tests should be performed for both diagnostic and monitoring purposes.

In patients with more advanced encephalopathy (stage III–IV), the addition of urinary bladder catheterization (Foley), insertion of Swan-Ganz for more accurate hemodynamic monitoring, and more frequent laboratory assessment are recommended. These patients require intubation for airway protection prior to transfer to a liver transplant or experienced center.

Nutrition assessment is important, and serum protein, albumin, prealbumin, and transferrin should be ordered. Measures of nitrogen balance, and indirect calorimetry to evaluate proper nutrition have been used. In patients with prolonged admissions and severe encephalopathy, enteral tube feeding or parenteral nutrition should be considered. If diarrhea develops, *C. difficile* should be excluded with appropriate testing.

### Special Considerations

Patients with ALF who present concomitant history or laboratories consistent with *alcoholic liver disease* most likely already have chronic liver damage or cirrhosis, and do not usually fit the criteria of ALF, which requires absence of “chronic liver disease.” Physical findings and stigmata of chronic liver disease, such as spider angiomatas, ascites, collateral veins and signs of portal hypertension should alert the provider of the chronicity of the process. Those with alcoholic liver disease are also usually malnourished and should be treated with: (a) multivitamins, (b) thiamine 100 mg daily for 5 days, (c) folate 1 mg IV/po daily for 5 days, and (d) vitamin K 10 mg sc daily for 3 days, to ensure that vitamin K deficiency is not a contributing factor to the coagulopathy.

### Table 3

<table>
<thead>
<tr>
<th>Principal Causes of ALF</th>
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<tbody>
<tr>
<td>1) Drugs</td>
</tr>
<tr>
<td>Acetaminophen</td>
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<td>Idiosyncratic drug reactions</td>
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<tr>
<td>Drugs that cause ischemia (i.e. cocaine, methamphetamine)</td>
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<tr>
<td>2) Infections</td>
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<tr>
<td>Viral hepatitis</td>
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<tr>
<td>Type A</td>
</tr>
<tr>
<td>Type B</td>
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<tr>
<td>Type D (always associated with hepatitis B)</td>
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<tr>
<td>Type E (rare)</td>
</tr>
<tr>
<td>Others (very rare)</td>
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<tr>
<td>3) Ischemia</td>
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<tr>
<td>Hepatic vascular occlusion (i.e. Budd-Chiari)</td>
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<tr>
<td>Cardiogenic ‘shock’</td>
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<tr>
<td>Heat stroke</td>
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<tr>
<td>Gram-negative bacteremia with shock</td>
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<tr>
<td>4) Miscellaneous</td>
</tr>
<tr>
<td><em>Amanita phalloides</em> (mushroom poisoning)</td>
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<tr>
<td>Acute fatty liver of pregnancy</td>
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<tr>
<td>Autoimmune hepatitis</td>
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<tr>
<td>Reye’s syndrome</td>
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<tr>
<td>Wilson’s disease</td>
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<tr>
<td>Metabolic hereditary diseases (i.e. tyrosinemia)</td>
</tr>
<tr>
<td>Malignancy with massive liver replacement (i.e. breast cancer, melanoma, lymphoma)</td>
</tr>
<tr>
<td>5) Indeterminate</td>
</tr>
</tbody>
</table>

### Hypophosphatemia

Hypophosphatemia is common in patients with ALF and normal renal function. It should be monitored and treated accordingly.

### Hypomagnesemia

Hypomagnesemia is more common than previously thought. If there is any doubt it should be treated. Patients after liver transplantation who develop ALF, those malnourished or with alcoholic liver disease should receive magnesium supplements prophylactically.

### Stress ulcer prophylaxis

Stress ulcer prophylaxis is generally indicated by using an H₂ blocker such as famotidine 20 mg IV bid or one of the proton pump inhibitors. Intragastric pH should be maintained > 5.0.

Avoid sedation or narcotics in these patients since they can affect the neurological status and interfere with the diagnostic and prognostic indexes.
COMPLICATIONS AND SPECIFIC MANAGEMENT
The purpose of this review is to provide general guidelines for the management of ALF and not a comprehensive tool for the management of complications which should be handled in the setting of experienced centers.

The complications associated with ALF involve multiple organ systems and need to be promptly recognized and managed. These include: a) acute hepatic encephalopathy, b) cerebral edema, c) seizures, d) psychomotor agitation and delirium, e) infections, f) renal dysfunction, g) fluid and electrolyte imbalance, h) acid-base disturbances, i) hypotension, j) coagulopathy, and k) hypoglycemia.

Acute Hepatic Encephalopathy
The neurological exam is fundamental in the diagnosis of HE and in the assessment of severity of the neurological disturbances. When encephalopathy is present with hepatocellular injury, without evidence of chronic condition, the patient fits the criteria for ALF, and the gastroenterologist or the hepatologist should be consulted immediately.

Daily observation of HE and assessment of stage/grade is very important in the management of ALF. Correction and avoidance of factors aggravating or causing encephalopathy, such as: constipation, hemorrhage, sepsis, hypoxia, electrolytes and acid-base disturbances, hypoglycemia, and drug toxicity. Opiates and acetaminophen should be avoided, while short acting benzodiazepines are allowed only for patients on respiratory support.

We recommend a step-wise approach to the management of HE. For patients with stage I–II, lactulose up to 30 mL three times daily per nasogastric tube titrated to 3–4 bowel movements/day or by enema is the first line of therapy. In severe coagulopathy avoid enema because of the risk of lower gastrointestinal bleeding. In patients with more severe encephalopathy, stage III–IV, airway protection (intubation) should be instituted prior to transfer to experienced centers. The decision for, intracranial pressure monitoring (ICP) to detect and manage cerebral edema should be made only if a patient is a liver transplant candidate and be performed within the setting of a transplant center.

Head CT scan should be considered in the setting of worsening HE to rule out mass lesion such as intracranial hematoma, or prior to ICP monitor placement for baseline. Discussion of ICP monitoring is beyond the purpose of this review.

Cerebral Edema
Patients with ALF who proceed to stage/grade III/IV coma are at risk of cerebral edema and raised intracranial pressure. As a result, cerebral herniation is one of the major causes of death in ALF. Cerebral edema has been reported in 50%–80% of cases that progress to grade IV encephalopathy. It had been thought that patients with ALF had pathologically high cerebral blood flow that can contribute to the raised ICP.

In the general management of cerebral edema it is important to avoid factors that increase ICP. In partic-
Seizures
Seizures are more common than previously thought, and a low threshold to request an EEG should be exercised. The first line of treatment is phenytoin, although magnesium, which is frequently low in this condition, should also be considered. Valproic acid should be avoided since it increases NH₃ level, as well as tegretol for its ADH effect. Continuous EEG monitoring may be useful to detect subclinical seizures.

Psychomotor Agitation and Delirium
When present, treatable causes need to be excluded, such as: a) elevated ICP; b) extravascular injection of drugs or fluids; c) painful skin ulcer or noxious stimuli; and d) anticholinergic medications. If agitation is present, the use of fentanyl or morphine works when pain is the main causative factor. If pain is not the cause, the use of short-acting benzodiazepines or haloperidol is the treatment of choice, especially if delirium is present. As an alternative for sedation, propofol can be considered. The pharmacokinetic of propofol is not affected by liver/renal failure. In general, and particularly in ALF, sedation increases the risk of aspiration. As such, the threshold for intubation in these patients should be individually set, and probably kept at a low level. In grade III encephalopathy, short-acting agents for sedation should be preferred.

Infections
The use of aseptic techniques is paramount in the management of ALF. Infection is a potential cause of death in these patients. Close surveillance with blood, urine cultures and chest x-ray every 48 hours during the first week of admission should be performed, and twice a week thereafter or as clinically indicated. Sputum cultures are also important especially in presence of fever or leukocytosis.

Ampicillin plus sulbactam for at least 7–10 days are the usual antibiotics of choice. If after 3–5 days, the patient is still febrile, particularly with increased white cell count, the addition of empiric antifungal therapy should be considered. In the hemodynamically unstable patient but with a still preserved renal function (creatinine <3 mg/dL) amphotericin B is the usual drug of choice. If the patient is more stable or in presence of renal insufficiency fluconazole is the alternative drug.

Aminoglycosides should be avoided because of the increased risk of nephrotoxicity in the setting of severe liver disease.

In all female patients additional prophylaxis with clotrimazole 5 mg (as 10% vaginal cream) on admission and weekly thereafter is recommended.

Renal Dysfunction
Daily assessment of renal function in patients with ALF is important, since renal impairment is frequently observed and needs to be treated. On admission, the most frequent renal dysfunction is pre-renal azotemia, secondary to fluid loss, vomiting, and inadequate hydration. Frequent determination of serum creatinine levels, 24 hour urinary output and periodical 24 hour urinary sodium concentration are recommended.

Adequate cardiovascular filling pressure is provided by IV fluids, keeping particular attention at the need of substituting electrolytes and providing dextrose without overloading the cardiovascular system. Again it is important to avoid aminoglycosides and to limit the use of radiological dyes.

If the intravascular volume needs to be restored, colloids such as FFPs and albumin are the preferred choice. The use of IV dopamine at low doses (2 to 4 mcg/kg/min) has been used by several centers to treat renal dysfunction in this setting but there is no strong scientific evidence to support its use.

Fluid and Electrolyte Imbalance
Proper assessment of fluid and electrolytes is very important in the management of ALF patients, since iatrogenic fluid overload is a common problem. Total intake and output, patient weight, and serum osmolarity should be measured daily. A total fluid intake of 1 to 2 L daily is usually adequate. It is recommended to avoid
Acute Liver Failure

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sodium chloride to IV fluids in presence of hyponatremia unless there is evidence of excessive losses of sodium. Dilutional hyponatremia (Na <120 mEq/L) may require free water restriction or rarely a bolus of hypertonic sodium chloride (3% sodium chloride, 150 mL) for severe cases with serum sodium <115 mEq/L.

Iatrogenic sodium and fluid overload and a low level of ionized calcium may result from the infusion of blood product, such as FFPs, and therefore ionized calcium should be checked every other day.

Supplementation of potassium, calcium, magnesium, and phosphate may be necessary. Some centers use phosphate prophylectically. Severe sodium and fluid overload or hyperkalemia may require correction by hemodialysis.

Acid-base Disturbances

Acid-base disturbances are common in ALF patients, and the causes are different depending on the time and severity of the process. Early in the course of ALF and usually mild or moderate in severity, acid-base impairment is caused by mixed metabolic and respiratory alkalosis due to vomiting, gastric content aspiration, and increased respiratory drive. In the late stages of ALF and in severe cases, acidosis develops due to renal failure, sepsis, lactic acid accumulation, and occasionally hemorrhagic pancreatitis.

Hypotension

Hypotension should raise the suspicion of sepsis, bleeding, pneumothorax, acidosis, or pericardial tamponade. Pressors are used to support blood pressure as in any other critically ill patients.

The indications for placement of pulmonary artery catheter are: a) acidosis not due to late renal failure, b) hypotension, and (c) the need for pressor agents. If patients have coagulopathy (INR >1.5) and/or thrombocytopenia (<30 K), one or two “jumbo” unit of FFPs as well as platelets should be given prior to any invasive procedure.

The aim of hemodynamic monitoring is to ensure adequate perfusion to vital organs, especially the brain. The choice of fluids should favor the ones with high oncotic properties to avoid third spacing and maintain intravascular volumes. FFPs and PRBCs are likely to be most appropriate.

Coagulopathy

The severity of coagulopathy is one of the most important predictive factors for the outcome of ALF, since most of the clotting factors are synthesized in the liver. We need to consider the half life of the different proteins involved in the coagulation process, and we need to know if and when FFPs or other blood products are given in relation to the measurement of clotting parameters, since they obviously interfere with such assessment.

Prothrombin has an half life of 2 days, factor V: 12 hours, and factor VII: 7 hours. Several centers, especially in Europe, use baseline factor V as a prognostic indicator: level <10% are associated with very poor survival, while values between 10% and 30% are borderline predictors.

Administration of vitamin K 10 mg daily subcutaneously, may rule out pre-existing vitamin K deficiency. In patients with active bleeding, the use of FFPs is recommended at 10–15 cc/kg every 12 h, as well as transfusion of packed cells. Platelet transfusion may be helpful in severe thrombocytopenia.

Hypoglycemia

Hypoglycemia is one of the causes of death in patients with ALF which should not occur in the era of modern medicine. This event can occur when patients are prematurely transferred out of the intensive care unit setting, and frequent monitoring of glucose levels is not obtained.

Blood glucose levels are measured at admission and then every hour until glucose requirements can be estimated. Usually, a flow rate of 80–100 mL/hr of 10% dextrose solution is necessary. If not sufficient, boluses of 30% to 50% dextrose solution may be needed. A minimum of 300 g of glucose should be given daily to minimize body protein hypercatabolism. When blood level is lower than 60 mg/dL, 50 to 100 mL of 50% dextrose bolus is recommended immediately.

FUTURE TECHNIQUES

Methods of liver support—while the regeneration of the native liver will allow spontaneous survival or while waiting for a donor liver graft—include extracorporeal liver-assist devices, bioartificial livers,

(continued on page 42)
extracorporeal whole organ perfusion, and hepatocyte transplantation (20–23). To date the efficacy of these methods remains unproven, and controlled clinical trials are in progress.

Hypothermia appears to be a promising method for patients with severe ALF complicated by increased intracranial pressure, although again randomized clinical trials are needed to establish safety and efficacy (24,25).

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References


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