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Acute liver failure (ALF) is a relatively rare and potentially fatal disease. It represents a heterogeneous condition with numerous etiologies in which the pathophysiology is diverse and frequently unclear, preventing substantial advances in specific therapy. Recognized etiologies include infections, toxins, metabolic disorders, infiltrative diseases, autoimmune hepatitis, ischemic, or irradiation damage, although a proportion of cases are unable to be diagnosed and fall into the cryptogenic group. For the pediatric intensivist, the mainstay of therapy consists of meticulous supportive measures, with a focus on anticipation and prevention or treatment of complications and early consideration for liver transplantation. With the onset of cerebral edema in children with acute liver failure, the risk for permanent disability increases dramatically. Thus the timely intervention to prevent the metabolic derangements associated with acute liver failure is pivotal in preventing progression and the morbidity associated with this condition. The rewards of bridging children with end-stage liver failure are reflected in the recent publication of the Pediatric Acute Liver Failure (PALF) Study Group, in which 53% of patients survived with medical therapy alone and an additional 30% survived with the aid of liver transplantation.

**Definition**

Liver failure is defined as the loss of vital functions of the normal liver that entails synthesis of serum proteins including clotting factors and albumin, bile production and excretion, detoxification of organic anions, metabolism and storage of glucose and fatty acids and elimination of ammonia and other byproducts of energy utilization and protein metabolism. The significant compromise of these functions implies loss of a critical mass of hepatocytes, and the clinical manifestations of liver failure are dependent on the extent and time course of liver cell death.

The clinical syndrome of acute or “fulminant” liver failure is defined as the onset of hepatic encephalopathy and coagulopathy within 8 weeks of the onset of liver disease in the absence of preexisting liver disease in any form. This narrow definition does not adequately address children with new-onset liver disease who develop encephalopathy more than 8 weeks after presentation or children with subclinical chronic liver disease such as autoimmune hepatitis or Wilson disease who present initially with liver failure. Although the management principles of children are similar for most etiologies of liver failure, it is important for the intensivist to recognize that the prognosis can be remarkably different for the different underlying causes.

**Epidemiology**

The cause of ALF in children continues to be age dependent with viral hepatitis probably the most common cause of ALF in all age groups overall. Severe hepatitis from echovirus and adenovirus is seen almost exclusively in the neonatal population. Liver failure can be one of the manifestations of overwhelming herpes infection in the newborn or immunocompromised patient. Metabolic liver disease and familial erythropagocytosis are most commonly found in infants. Acute hepatitis A and B infections are rare causes of ALF in North America, but are a common cause of ALF in school-aged
children in developing countries. Drug-induced liver disease is more common in older children especially that secondary to intentional acetaminophen overdose. Acute liver failure of indeterminant cause is common in all age groups, accounting for 40% of ALF among patients younger than age 3 years and indeterminant cause is common in all age groups, accounting for 40% of ALF among patients younger than age 3 years and in 49% of the cases. Overall survival in this group was 84% at 3 weeks after presentation with 36% of the survivors receiving liver transplantation. Considering the infrequency of this diagnosis and the frequent associated morbidity and mortality it is not unexpected that few pediatric subspecialists are comfortable managing patients with this diagnosis.

Clinical Presentation by Etiology

The clinical presentation varies with etiology but, in most cases admitted to the pediatric intensive care unit (PICU), there is hepatic dysfunction with hypoglycemia, coagulopathy and encephalopathy. Jaundice may be a late feature, particularly in metabolic disease. The clinical onset may be within hours or weeks. Most pediatric patients who develop ALF are previously healthy, with no history of major medical problems and no clear exposure to hepatitis or toxins.

Beyond the acute stabilization and attempts at detoxification of children with ALF, subsequent diagnosis and management of these patients must occur at a center familiar with the needs of this subset of critically ill children and with the resources (e.g., blood banking, continuous renal replacement therapy) necessary to provide optimal care until either recovery or transplantation occurs. The decision to transfer a patient with evolving signs of progressive liver failure must be made in a timely manner, because the risks of transporting patients in a deteriorating condition with advanced hepatic encephalopathy or uncontrolled bleeding can be monumental. When liver transplantation is not possible due to geography or other considerations, such transfer to a distant center may be a futile effort and a very disruptive experience for the terminal patient (and family) with advanced liver failure.

Family Support

Families of children with acute liver failure are naturally devastated by the development of potentially fatal, acute organ failure in their child. Such families require a considerable amount of psychological support and counseling, particularly as many families will not be able to grasp the seriousness of their child’s condition and the implications of liver transplantation. Living donor transplantation is a reasonable option for families who are able to quickly assimilate the broad implications of ALF. The family’s ability to comply with long-term care and medication regimens, should liver transplantation be necessary, is critical to the ultimate success of the process. The particular problems of suicide attempts and gestures in adolescents may require additional psychiatric help.

Management

Initial Assessment and Care

There is no specific therapy for acute and end-stage liver failure except hepatic replacement. Management therefore is directed toward early consideration for liver transplantation, hepatic support, treatment of acquired infections, and prevention and treatment of complications while awaiting recovery or a suitable donor for liver transplantation. The key elements in managing patients before transplantation are meticulou medical support in the setting of an intensive care unit and rapid referral to a transplant center. It is essential to take a full history from the parents; this would include establishing appropriate risk factors such as information on intravenous injections, infusions of blood products, foreign travel or contact with individual exhibiting jaundice. It is important

### Box 88–1 Investigations in Fulminant Hepatic Failure

<table>
<thead>
<tr>
<th>Baseline essential investigations</th>
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<tbody>
<tr>
<td>Biochemistry</td>
</tr>
<tr>
<td>• Bilirubin, transaminases</td>
</tr>
<tr>
<td>• Alkaline phosphatase</td>
</tr>
<tr>
<td>• Albumin</td>
</tr>
<tr>
<td>• Urea and electrolytes</td>
</tr>
<tr>
<td>• Creatinine</td>
</tr>
<tr>
<td>• Calcium, phosphate</td>
</tr>
<tr>
<td>• Ammonia</td>
</tr>
<tr>
<td>• Acid-base, lactate</td>
</tr>
<tr>
<td>• Glucose</td>
</tr>
<tr>
<td>Hematology</td>
</tr>
<tr>
<td>• Full blood count, platelets</td>
</tr>
<tr>
<td>• PT, PTT</td>
</tr>
<tr>
<td>• Factors V or VII</td>
</tr>
<tr>
<td>• Blood group cross-match</td>
</tr>
<tr>
<td>Septic screen</td>
</tr>
<tr>
<td>Omitting lumbar puncture</td>
</tr>
<tr>
<td>• Radiology</td>
</tr>
<tr>
<td>• Chest radiograph</td>
</tr>
<tr>
<td>• Abdominal ultrasound</td>
</tr>
<tr>
<td>• Head CT scan or MRI</td>
</tr>
<tr>
<td>Neurophysiology</td>
</tr>
<tr>
<td>• EEG</td>
</tr>
<tr>
<td>Diagnostic investigations</td>
</tr>
<tr>
<td>Serum</td>
</tr>
<tr>
<td>• Acetaminophen levels</td>
</tr>
<tr>
<td>• Cu, ceruloplasmin (&gt;3 years)</td>
</tr>
<tr>
<td>• Autoantibodies</td>
</tr>
<tr>
<td>• Immunoglobulins</td>
</tr>
<tr>
<td>• Amino acids</td>
</tr>
<tr>
<td>• Lactate</td>
</tr>
<tr>
<td>• Pyruvate</td>
</tr>
<tr>
<td>• Hepatitis A, B, C, E</td>
</tr>
<tr>
<td>• EBV, CMV, HSV</td>
</tr>
<tr>
<td>• Other viruses</td>
</tr>
<tr>
<td>Urine</td>
</tr>
<tr>
<td>• Toxic metabolites</td>
</tr>
<tr>
<td>• Amino acids, succinylacetone</td>
</tr>
<tr>
<td>• Organic acids</td>
</tr>
<tr>
<td>• Reducing sugars</td>
</tr>
</tbody>
</table>

CMV, Cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; PT, prothrombin time; PTT, partial thromboplastin time.
to establish what medications the child has taken, including over-the-counter preparations, folk remedies and herbal supplements, what medications might be in the household, and in adolescents to inquire about the use of illicit drugs and sexual contact. Folk remedies, some Chinese herbs, and herbal supplements (e.g., pennyroyal) in particular are often overlooked by parents giving a medical history but may be vital information in establishing an etiology. Until a diagnosis is made (Box 88–1), it is assumed that all children are infectious and that all blood, excretions and secretions are potentially capable of transmitting viral hepatitis. Enteric isolation procedures must be enforced (http://www.cdc.gov/ncidod/dhqp/pdf/isolation2007.pdf) until an infectious etiology has been ruled out.

The initial physical examination should determine the status of major organ systems including hepatic, cerebral, cardiovascular, respiratory, renal, and acid–base balance. The patient’s level of consciousness and degree of hepatic encephalopathy (Table 88–1) should be established using a reliable scale and a complete central nervous system examination performed including examination of reflexes and mental status. Progression of coma may be assessed by serial examinations. Evidence of chronic liver disease or other signs which may suggest an etiology, such as Kayser-Fleischer rings, caput succedaneum, cataracts, and needle marks, should be established. Liver size and consistency should be determined and documented. The presence of impaired central nervous system function with acute liver disease is an indication for immediate hospitalization independent of any other clinical or biochemical findings. Observation in a suitable facility to intervene immediately with mechanical ventilation, intracranial pressure monitoring, if deemed beneficial, rapid availability of blood products and the ability to maintain acid–base/fluid and electrolyte balance is critical. Typically, this level of support warrants referral to a transplant center where greater experience and availability of emergency transplantation may prove lifesaving.

A central venous catheter is useful for assessment of right heart function and volume status, but must be placed with care in patients with significant coagulopathy or thrombocytopenia. Use of a multilumen catheter, which enables simultaneous administration of blood products, dextrose solutions to maintain normal serum glucose levels, intravenous fluids and drugs, is helpful and may be replaced if needed to facilitate exchange blood transfusions or renal replacement therapy when required. An indwelling arterial line for continuous measurement of blood pressure and for biochemical and acid-base monitoring is frequently helpful especially in patients with evolving cardiopulmonary instability or in whom intracranial pressure monitoring is planned. A nasogastric tube is passed and placed to gravity, with regular gentle saline lavage to detect upper gastrointestinal hemorrhage. The urinary bladder is catheterized and strict output measured to help in the evaluation of fluid status and renal function. Ideally, the patient is placed on a bed that permits the body weight to be recorded frequently.

Baseline biochemical and other investigations should be performed and management initiated as in Box 88–2. Frequency of biochemical monitoring will depend on the severity of illness, ranging from daily in mild cases to every 4 to 6 hours in patients in stage III and IV coma, and should include complete blood count, blood gases, electrolytes, aminotransferases, and prothrombin time, plus daily monitoring of plasma creatinine, bilirubin, and ammonia. A baseline chest radiograph is useful to diagnose cardiac dysfunction or aspiration.

### Table 88–1 Clinical Stages of Hepatic Encephalopathy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Asterixis</th>
<th>EEG Changes</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (prodrome)</td>
<td>Slight</td>
<td>Minimal</td>
<td>Mild intellectual impairment, disturbed sleep-wake cycle</td>
</tr>
<tr>
<td>II (impending)</td>
<td>Easily elicited</td>
<td>Usually generalized</td>
<td>Drowsiness, confusion, coma/inappropriate behavior, disorientation, mood swings</td>
</tr>
<tr>
<td>III (stupor)</td>
<td>Present if patient cooperative</td>
<td>Grossly abnormal slowing of rhythm</td>
<td>Drowsy, unresponsive to verbal commands, markedly confused, delirious, hyperreflexia, positive Babinski sign</td>
</tr>
<tr>
<td>IV (coma)</td>
<td>Usually absent</td>
<td>Appearance of delta waves, decreased amplitudes</td>
<td>Unconscious, decerebrate or decorticate response to pain present (stage IVA) or absent (stage IVB)</td>
</tr>
</tbody>
</table>

### Box 88–2 Management of Fulminant Hepatic Failure

No sedation except for procedures

Monitor

- Heart and respiratory rate
- Arterial BP, CVP
- Core/toe temperature
- Neurological observations
- Gastric pH (>5.0)
- Blood glucose (>4 mmol/L)
- Acid-base
- Electrolytes
- PT, PTT

Fluid balance

- 75% maintenance
- Dextrose 10%–50% (provide 6–10 mg/kg/min)
- Sodium (0.5–1 mmol/L)
- Potassium (2–4 mmol/L)

Maintain circulating volume with colloid/FFP

Coagulation support only if required

Drugs

- Vitamin K
- H<sub>2</sub> antagonist
- Antacids
- Lactulose
- N-acetylcysteine for acetaminophen toxicity
- Broad-spectrum antibiotics
- Antifungals

Nutrition

- Enteral feeding (1–2 g protein/kg/day)
- PN if ventilated

**BP, Blood pressure; CVP, central venous pressure; FFP, fresh frozen plasma; PN, parenteral nutrition; PT, prothrombin time; PTT, partial thromboplastin time.**
An abdominal ultrasound may indicate liver size and patency of hepatic and portal veins, particularly if liver transplantation is being considered.

**Fluid Balance**

The aim of fluid balance is to maintain hydration and renal function while not provoking cerebral edema. Maintenance fluids consist of 10% dextrose in 0.25 normal saline, and intake should be 75% of normal maintenance requirements unless cerebral edema develops. A total sodium intake of 0.5 to 1.0 mmol/kg/day is usually adequate. Potassium requirements may be large, 3 to 6 mmol/kg/day, as guided by the serum concentration. As patients may become hypophosphatemic, intravenous phosphate may be given as potassium phosphate. Maintenance of euglycemia is critical and may require 3 to 6 mg/kg/min of dextrose infusion or greater.

Attempts should be made to maintain urinary output using loop diuretics in large doses (furosemide at 1 to 3 mg/kg dosed intravenously every 6 hours), vasoactive-inotropic agents and colloid/fresh frozen plasma (FFP) to maintain adequate preload and renal perfusion. Should profound oliguria occur, early consideration should be given to hemofiltration or dialysis prior to the development of hemodynamic instability (see section below on hemofiltration).

Anemia should be corrected, maintaining the hemoglobin concentration above 10 g/dL to provide acceptable oxygen delivery to tissues. Coagulopathy should be managed conservatively; the massive requirements for fresh frozen plasma may result in fluid overload requiring the institution of renal replacement therapy. In addition, the use of frequent FFP when not essential to control bleeding may confuse the signs of clinical recovery, which is often best reflected in an improving prothrombin time.

**Nonspecific Adjunctive Therapy**

It is usual to administer a single dose of vitamin K (2 to 10 mg intravenously) although it is frequently not effective. Proton pump inhibitors and antacids (see below) should be administered prophylactically to minimize the risk of gastrointestinal hemorrhage from stress erosions. The role of N-acetylcysteine in the management of ALF other than acetaminophen poisoning has been investigated with promising results. A multicenter, randomized trial of a continuous infusion of N-acetylcysteine over the first 72 hours after presentation in adult patients with ALF suggests that N-acetylcysteine may improve spontaneous survival in patients with early stages of encephalopathy.31,32

**Antibiotic Therapy**

The results of surveillance cultures can be used to guide antibiotic therapy in the event of suspected infection, but broad-spectrum antibiotics (amoxicillin, cefuroxime, metronidazole, and prophylactic fluconazole) are only prescribed if sepsis is suspected or parenteral transplantation is anticipated.

**Nutritional Support**

The role of parenteral nutrition in the management of patients with acute liver failure is controversial. The main aims of therapy are the following:

1. To maintain blood glucose (>40 mg/dL) and ensure sufficient carbohydrates for energy metabolism.
2. To reduce protein intake to 1 to 2 g/kg/day, either enterally or parenterally.
3. To provide sufficient energy intake to reverse catabolism, either enterally or parenterally.

Children who are mechanically ventilated should receive parenteral nutrition to minimize negative nitrogen balance because it may be 7 to 10 days before full normal diet is resumed after transplantation.

**Central Nervous System Monitoring**

A baseline electroencephalogram may be helpful to stage coma; however, the findings are typically nonspecific. Computed tomography scans may be useful early in encephalopathy as a baseline examination to be compared with subsequent imaging to evaluate for signs of progressive, cerebral edema later in the disease. Frequent evaluation of neurological function with serial examinations and blood ammonia is essential to follow the progress of hepatic encephalopathy. Continuous or frequent electroencephalography may demonstrate abnormal electrical activity as a heralding sign of progressive hepatic encephalopathy or subclinical seizure activity. The role of intracranial pressure monitoring remains controversial (see Cerebral Encephalopathy and Edema sections in the following sections). The choice of intracranial pressure monitoring system is dependent on the standards of the individual institution and neurosurgeon consulting on the case (see also Chapter 59). All forms of intracranial monitoring are potentially hazardous in patients with severe coagulopathy, but they may provide helpful information on changes in intracranial pressure and improve selection for liver transplantation.30

**Prevention and Management of Complications**

The clinical course before transplantation of patients with advanced hepatic failure is dominated by the myriad complications affecting a wide range of organ systems. Monitoring for evidence of those complications and their skillful and timely management should be the focus of the intensivist in the preoperative period. The following discussion covers the most common organ system dysfunctions seen in this critically ill patient population.

**Hypoglycemia**

Hypoglycemia (blood glucose <40 mg/L) develops in the majority of children. It may contribute to central nervous system impairment and other organ dysfunction. Factors contributing to hypoglycemia include (1) failure of hepatic glucose synthesis and release, (2) hyperinsulinemia (due to diminished of hepatic degradation), (3) increased glucose utilization (due to anaerobic metabolism), and (4) secondary bacterial infection.33-36

Frequent bedside monitoring of blood glucose concentrations (every 2 to 4 hours) and the intravenous administration of glucose (10% to 50% dextrose) are required to prevent this complication. Patients may typically require 5 to 8 mg/kg/min of dextrose infused to meet these goals; however, clinicians should avoid excessively high rates of glucose infusion and the resulting hyperglycemia. Increased insulin production, secondary to excess glucose infusion, leads to increased glucose need and net lipogenesis that can be avoided by permitting the blood glucose to remain between 40 and 60 mg/L. Profound refractory hypoglycemia carries a grave prognostic implication and often heralds the imminent death of the patient.
Coagulopathy and Hemorrhage

The management of coagulopathy and hemorrhage is a major challenge in the overall care of the child with acute liver failure. Profound disturbances in hemostasis develop secondary to failure of hepatic synthesis of clotting factors and fibrinolytic factors, reduction in platelet numbers and function, and/or intravascular coagulation. The coagulation factors synthesized by hepatocytes include factors I (fibrinogen), II (prothrombin), V, VII, IX, and X, and a reduction in synthesis leads to the prolongation of prothrombin and partial thromboplastin time.

The prothrombin time is the most clinically useful measure of hepatic synthesis of clotting factors. Prolongation of the prothrombin time often precedes other clinical evidence of hepatic failure, such as encephalopathy, and may alert the clinician to the severity of acute hepatitis; it is a guide to the urgency of liver transplantation. Administering vitamin K parenterally (2 to 10 mg intravenously) assures the sufficiency of this essential cofactor, but rarely improves coagulation in ALF.

The prothrombin time depends on the availability of factor VII, which has the shortest half-life (approximately 4 to 7 hours) of the clotting factors and decreases more rapidly than other liver-derived clotting factors when production does not keep up with its utilization. As a result, measurement of factor VII is a more sensitive indicator than the prothrombin time but is typically not as readily available. Fibrinogen concentrations are usually normal unless there is increased consumption such as in disseminated intravascular coagulation (DIC). The level of factor VIII may help differentiate between DIC and ALF because factor VIII is synthesized by vascular endothelium and therefore is normal or increased in ALF as an acute-phase response or from decreased utilization. Decreased levels of factor XIII may contribute to poor clot stabilization.

A reduction in platelet numbers (80 × 10^3/μL) occurs in up to half of adult patients, although thrombocytopenia is less of a problem in pediatric experience. Severe thrombocytopenia, requiring platelet transfusion, suggests hypersplenism, intravascular coagulation, or aplastic anaemia. Use of extracorporeal support devices may also contribute to abnormally low platelet numbers.

Intravascular coagulation as detected by abnormal concentrations of fibrin degradation products is present in almost all ALF patients, indicating ongoing clot deposition and dissolution, most probably as a consequence of tissue necrosis in the liver. Rarely significant in ALF, DIC can contribute to organ damage. Sepsis may also be present as an additional cause of DIC. With the ready availability of activated Factor VIIa concentrate, the intensivist should recognize that the administration of commercial concentrates containing activated clotting factors may itself precipitate DIC.

Oozing from needle puncture sites and line insertion is common, whereas pulmonary or intracranial hemorrhage may be terminal events. Petechiae reflect decreased platelet function, disturbed vascular integrity, or DIC.

Although in the early stages of assessment prolongation of prothrombin time is a sensitive guide to prognosis and the need for liver transplantation, coagulopathy resulting in significant bleeding should be treated with FFP infusion at a rate of 15 to 20 mL/kg FFP every 6 hours, or by continuous infusion at a rate of 3 to 5 mL/kg/h, with the addition of cryoprecipitate and platelets as needed. Treatment to improve coagulation status should also be attempted prior to invasive procedures. In the very small infant, recombinant Factor VIIa may provide significant hemostasis with less volume loading.

Administration of recombinant factor VIIa (40 μg/kg) reliably corrects the coagulation defect in patients with acute liver failure for a period of 6 to 12 hours and may be useful in preparation for invasive procedures. Double-volume exchange transfusion may also temporarily improve coagulation to control life-threatening hemorrhage, especially in patients with DIC. Hemofiltration may be necessary to control fluid balance and provide fluid “space” if large amounts of coagulation support are required. Platelet counts should be maintained above 50 × 10^3/μL by infusion of platelets. DIC is rarely severe enough to warrant the risks of heparin infusion to break the vicious cycle.

Prevention of Gastrointestinal Hemorrhage

Gastrointestinal tract hemorrhage may be life-threatening and secondary to gastritis or stress ulceration. PPIs (pantoprazole 0.5 to 1.0 mg/kg/day up to 20 mg for children <40 kg) or high-dose H2 antagonists (ranitidine 1 to 3 mg/kg dosed every 8 hours) should be administered intravenously to reduce the risk of upper gastrointestinal tract bleeding. Prevention of gastrointestinal hemorrhage may also prevent further hyperammonemia by eliminating the large protein load to the intestines.

Encephalopathy

Clinically, acute hepatic encephalopathy is defined as any brain dysfunction that occurs as a result of acute hepatic dysfunction and may be exacerbated by sepsis, gastrointestinal bleeding, electrolyte disturbances, or sedation, particularly benzodiazepine administration. Clinical manifestations and progression are highly variable, but acute hepatic encephalopathy usually evolves over days through definable stages. In rare cases, it may progress rapidly with coma and fatal cerebral edema developing within hours of the earliest detectable signs.

A scale for grading clinical encephalopathy is presented in Table 88-1. This scale is useful for assessing encephalopathy in older patients and the table includes guidelines for assessing infants, particularly in the early stages of encephalopathy.

The earliest abnormalities may not be detectable by clinical assessment, but are apparent to family members. Personality changes, reflective of forebrain dysfunction, include regression, irritability, apathy and occasionally euphoria. Younger children are more likely to be irritable and apathetic. Sleep disturbances, such as insomnia or sleep inversion, are often observed.

Intellectual deterioration, observed in stage I of chronic hepatic encephalopathy, is usually not evident in acute encephalopathy. Constructional apraxia related to disturbed spatial recognition may be present. Simple age-related tasks may be clinically useful tools for the day-to-day assessment of inattentiveness and apraxia. Subtraction of serial 7s (in older children and adults), recall of events (such as recently viewed videos), handwriting, and figure-drawing are appropriate tasks that older children can be asked to repeat daily in order to assess early encephalopathy. Younger children when asked to color a figure in a simple coloring book may not complete the task (inattentiveness), or scribble far outside the lines (constructional apraxia).

As the patient progresses into stage II hepatic encephalopathy, drowsiness and lethargy are readily apparent. Mental deterioration is clearly evident—the personality changes and...
behavior becomes inappropriate, with outbursts of anger or crying. Infants exhibit increasing irritability and often produce high-pitched screams. They may refuse to take feedings. Asterixis develops and is a useful sign, but it cannot be elicited with regularity in children less than 8 to 10 years of age. Motor impairment becomes evident, including ataxia, dysarthria and apraxia. Other neuromotor disturbances that can be detected at this stage include hyperreflexia, sustained clonus, rigidity, extensor posturing, and bizarre facial expressions. Electroencephalogram abnormalities are detectable at this stage.

Stage III hepatic encephalopathy is characterized by deepening somnolence and stupor. The patient is arousable by vigorous physical stimuli, but does not respond to commands. Patients are disoriented and often do not recognize family members. School-aged children and teenagers in deepening stage II and stage III coma often exhibit extreme agitation and rage. Biting and aggressive behavior may be a problem, and individuals caring for such children must be aware of the potential health risks involved. Seizures may develop. Neurological findings are more profound (see Table 88-1).

Progression into stage IV hepatic encephalopathy is heralded by the onset of coma. The patient responds only to painful stimuli. At first, the patient is flaccid, but in deeper stage IV the patient will assume decerebrate posturing, and brainstem reflexes are lost. Respiration may become ineffective requiring mechanical support to prevent death.

Acute hepatic encephalopathy is completely reversible after resolution of the hepatic dysfunction as long as neuronal death has not developed due to the consequences of cerebral edema.

Management of Hepatic Encephalopathy

Although the role played by ammonia in the development of encephalopathy is controversial, traditional therapy to reduce ammonia production or accumulation is indicated. The essential components of therapy are (1) restriction of dietary protein, (2) enteral antibiotics, (3) enteral lactulose, (4) continuous hemofiltration in patients with renal insufficiency, and (5) controlling the complications of acute liver failure that contribute to ammonia accumulation.

In the early stages of hepatic encephalopathy, conventional measures are taken to minimize the formation of nitrogenous substances by the intestine. A cathartic, such as sodium-free magnesium sulphate and/or a nonabsorbable disaccharide (lactulose 1 to 2 mL/kg every 4 to 6 hours) may be administered orally or via the nasogastric tube. Enteral neomycin (50 to 100 mg/kg/day) may also be used to reduce ammonia production by colonic bacteria if diarrhea secondary to lactulose is a problem. Protein intake should be limited to 0.5 to 1.0 g/kg/day in this phase and may be administered enterally or parenterally to limit the production of ammonia. Caloric intake is maintained in the early stages with glucose polymers and supplemented by infusion of 10% dextrose solution or greater as needed while frequently monitoring blood glucose.

The older patient with aggressive delirium is a particular risk to care providers. Sedation is not usually needed, except in violent patients to prevent self-injury. Electrolyte imbalances from the gut. A marked increase in blood creatinine concentration may develop from decreased glomerular filtration and/or increased muscle breakdown.

Acute tubular necrosis is seen in the minority of patients and may occur because of hypovolemia or dehydration and may be induced after mannitol infusion or diuretic therapy. Features include: abnormal urinary sediment; urinary sodium concentration greater than 20 mmol/L, reduction in creatinine clearance (urine/plasma creatinine ratio <10), and oliguria (urine output <0.5 mL/kg/h).

Functional renal failure (hepatorenal syndrome) is the most common cause of renal insufficiency. Features include sodium retention (urinary sodium concentration <20 mmol/L), normal urinary sediment, and reduced urinary output (<1 mL/kg/h). The etiology is multifactorial, and electrolyte imbalance, sepsis, and hypovolemia all play a part. Endotoxemia may contribute to renal injury.

The aim of management is to maintain circulating volume to prevent hypovolemia and ensure that urine output is greater than 0.5 mL/kg/h. A fluid challenge with isotonic volume expander (10 mL/kg) may be successful unless central venous pressure indicates fluid overload (>8 to 10 cm H₂O), in which case the use of furosemide (1 to 2 mg/kg intravenously) or (0.25 mg/kg/h by infusion) may be effective. Established renal failure requires hemodialysis or continuous renal replacement therapy as detailed in the following section (see Chapter 72).

Although functional renal failure recovers quickly after liver transplantation, acute tubular necrosis may severely compromise the postoperative management. Although 50% of patients require hemodialysis or continuous renal replacement therapy, renal function returns to normal after successful liver transplantation.

Ascites

Use of ultrasound in the pretransplant assessment has demonstrated excessive peritoneal fluid in most ALF patients, probably from acute portal hypertension, from lobular collapse,
vasodilatation, poor vascular integrity, and reduced oncotic pressure. Clinically evident ascites occurs in less than half the patients but may be a site for secondary bacterial or fungal infection, indicating the necessity for paracentesis in septic patients without an obvious focus of infection. Therapy for ascites is not indicated, other than the correction of oncotic pressure with albumin infusion and general fluid management. Paracentesis may be indicated if peritonitis is suspected if the intra-abdominal pressure leads to impaired renal perfusion or intractable embarrassment of diaphragmatic movement.

**Secondary Bacterial and Fungal Infections**

The majority of adults and 50% of children will develop significant infection that may be related to impairment of cellular and humoral immune systems. The organisms most often implicated are gram positive (Staphylococcus aureus, S. epidermidis, and streptococci), presumably of skin origin. Gram-negative bacteria or a fungal infection is occasionally observed. Urinary tract infections from indwelling catheter, and pulmonary infection, particularly in ventilated children, are common.

Management includes surveillance cultures from the endotracheal tube, indwelling catheters, and urine. Broad-spectrum antibiotics should be started at the first suspicion of sepsis, as the signs may be subtle and fever may be absent as part of the immune paralysis seen with advanced liver failure. Cefuroxime (75 to 150 mg/kg/day divided every 8 hours), piperacillin/tazobactam (240 mg/kg/day; piperacillin component divided every 8 hours), and/or metronidazole (30 mg/kg/day divided every 6 hours), if there is a suspicion of anaerobic infection, are reasonable first-line medications. When fungal infection is suspected, antifungals such as amphotericin (1.5 mg/kg/day) or fluconazole (3 to 6 mg/kg/day) should be included, although are potentially nephrotoxic. Positive cultures in the absence of clinical infection should result in removal or replacement of the infected catheter and administration of the appropriate antimicrobials, with close attention to the possibility of additional, perhaps opportunistic infection. Aminoglycoside antibiotics should be avoided, if possible, because they can contribute to renal failure.

**Hemofiltration for Hepatic Support**

Although the definitive therapy for irreversible hepatic failure is organ transplantation, because of limited organ availability, transplantation may not be available in short enough time to prevent irreversible complications (e.g., cerebral edema, fatal hemorrhage). Therefore therapies have been developed over the last decade intended to temporize and support adult patients suffering from acute fulminant hepatic failure or so-called acute-on-chronic hepatic failure have been used in the adult population. They use a single vascular access with a clearance of toxins resulting from hepatic failure using a charcoal filter. Such techniques have been used less frequently in pediatrics and to date there is very limited pediatric literature to support this therapy. Attempts to create extracorporeal artificial liver systems using living hepatocytes in various configurations have shown promise, however, as yet unsolved technical problems have limited the utility and widespread availability of this approach to research centers only.

As an alternative to extracorporeal hepatic systems, many programs have used continuous hemofiltration as a way to support electrolyte status and ammonia clearance as well as to permit the administration of large quantities of FFP in patients with hepatic failure (see Chapter 72). This has been used in primarily in patients with concurrent renal insufficiency. Such therapy is continued until either the patient recovers or progresses on to irreversible loss of hepatic function with subsequent hepatic transplant or death. The specific techniques of continuous hemofiltration will depend upon the capability of the PICU, but all such approaches depend on optimizing clearance of medium and small molecular weight compounds as well as maximizing nutritional and anticoagulation support.

Data have shown that small molecular weight solutes (e.g., urea) can be cleared equally effectively with convective (continuous venovenous hemofiltration [CVVH]) or diffusive (continuous venovenous hemodiafiltration [CVVHD]) approaches. Personal experience has also demonstrated that ammonia, which is not effectively cleared during acute hepatic failure, can be equally cleared by CVVH and CVVHD. In addition, exogenous amino acids delivered via total parenteral nutrition can be equally cleared with both the modalities with a slightly greater clearance in convective methods.

Therefore the choice of CVVH versus CVVHD is based on the preferences, capabilities, and experience of each center. Using this therapy requires controlled anticoagulation in spite of the prolonged clotting times associated with liver failure. Because of the underlying coagulopathy, such patients may require little to no anticoagulation. It should be remembered that the prolonged clotting times resulting from liver failure are due to decreased factor levels rather than to direct antagonism of clotting mechanisms (i.e., anticoagulation). Thus, some patients may have a paradoxical coagulation status in which they appear “anticoagulated” based on clotting times but yet have a tendency to be hypercoagulable partially due to depressed levels of anticoagulation factors and intravascular coagulation as well. Most programs have used citrate or no therapy for this population for anticoagulation.

Citrate is intended to bind calcium within the hemofiltration circuit decreasing its availability as a cofactor in the clotting cascade. Calcium then is infused back to the patient distal to the hemofiltration circuit to rescue the patient from potential risk of hypocalcemia. Citrate is cleared both via the dialysis membrane as well as the residual hepatic function. Hepatic citrate metabolism results in bicarbonate production, which typically results in metabolic alkalosis. However, in patients with hepatic failure, citrate may be poorly metabolized and may accumulate over time. This condition may result in so-called citrate lock that represents residual citrate in the patient as the delivery of citrate exceeds its hepatic clearance. This can be accentuated if the patient receives banked blood products containing citrate such as FFP, although this is becoming less common in contemporary blood bank practice. Citrate can be used nonetheless in this population by minimizing citrate infusion and watching closely for the signs and symptoms of citrate lock (i.e., clinical hypocalcemia). Laboratory evidence for citrate lock is a rising total of calcium with a falling ionized calcium level when measured in the patient’s blood rather than a sample drawn from the hemofiltration circuit. The decision to use no anticoagulation, heparin anticoagulation, or citrate anticoagulation is based on local experience and preference. In the hands of an experienced hemofiltration program, any of these approaches can be successfully used.
In undertaking either CVVH or CVVHD, one must use an appropriate solution to provide for either convective or diffusive clearance. Since the mid 2000s, the Food and Drug Administration—approved the use of dialysis solutions as drugs, paving the way for commercially produced solutions to be used for convective clearance in the mode of CVVH. This has allowed programs to replace “custom” mixed solutions in the hospital’s own pharmacy that have been associated with significant complications due to errors in mixing.66

For diffusive methods (CVVHD), multiple solutions are available that commonly are bicarbonate based, some with calcium and some without. The calcium free solutions are more commonly used in a citrate anticoagulation protocol. Use of Normocarb HF as a replacement solution creates options of bicarbonate-based solutions for either convective or diffusive clearance.67 Lactate is normally hepatically metabolized but in this population lactate from the dialysis solution may rise due to the diminished hepatic clearance. Whereas lactate is not thought to be directly toxic except at exceedingly high levels, rising lactate levels may prompt the clinician to undertake unwarranted investigation for sepsis, bowel necrosis, etc. It is well recognized that patients with lactate-based solutions will exhibit lactate concentrations that are detectable68 using conventional clinical lactate assays. One can discriminate between patient and dialysis solution derived lactate by measuring the dextro- and levo- portion of lactate. Unfortunately, this test is not widely available and often will take an average of 4 to 6 weeks for an answer. Data by Barenbrock et al.69 have demonstrated that bicarbonate-based convective solutions result in improved hemodynamics when compared to lactate-based solutions. Therefore many programs prefer bicarbonate-based solution. Clinicians can choose solutions compounded by the hospital pharmacy or the Food and Drug Administration-approved solution Normocarb that is now available for dialysis and continuous therapy. The latter eliminates the risk for pharmacy error and is less expensive.70

Once continuous hemofiltration has been initiated, the goals for hepatic support are several: The first goal is fluid management of the patient. An edematous patient at the time of liver transplant will have difficulty with closure of the abdomen as well as subsequent wound healing. Therefore preoperative maintenance of euvolemia and minimizing tissue edema is desirable. The second goal is the correction of electrolyte disturbances. Often patients with fulminant hepatic failure develop sodium perturbations, metabolic acidemia as well as other electrolyte disturbances. CVVHD with bicarbonate-based solutions can maintain normal electrolytes and minimize the adverse effects of electrolyte changes on the central nervous system. The third goal is to optimize nutrition and minimize the loss of visceral and somatic protein pools. Because liver failure often represents a catabolic state, the provision of nutrition in these patients benefits not only their postoperative care, but also helps support them during the period of organ failure before transplantation. Providing excess protein ammonia and may worsen hepatic encephalopathy, but modest amounts (0.75 to 1.50 g/kg/day) of high bioavailable protein or amino acids with suitable nonprotein calorie source will enhance wound healing, antibody synthesis and support body protein pools until transplantation can be performed. By balancing nutrition with the clearance of amino acids and ammonia through continuous hemofiltration, one optimizes the nutritional status that will benefit both the pretransplant and posttransplant status of the patient. The fourth goal is to maintain a balanced state of anticoagulation while noting the predisposition of the patient to bleeding. Many programs use frequent or continuous FFP therapy to reduce the risk of spontaneous bleeding from the underlying coagulopathy as well as to improve the response to anticoagulation therapy. The last benefit of continuous therapy is for control of ammonia levels and removal of potentially toxic substances not eliminated by the failed liver. Although hyperammonemia is not the sole cause of hepatic encephalopathy, the use of continuous hemofiltration is an effective adjunct in controlling the ammonia level in patients with hepatic failure.

If the condition of the patient necessitates ongoing continuous hemofiltration preoperatively, one may need to consider its intraoperative use as well. Intraoperative fluid flux with blood products, as well as other fluid management may need to be addressed during the operation. Blood transfusion can expose the patient to large potassium loads that may not be tolerated well by oliguric patients. Experience has shown that the use of intraoperative hemofiltration during liver transplantation can be safely and effectively undertaken.71 The use of hemofiltration without anticoagulation provides optimal intraoperative support, whereas continuing to infuse calcium to offset the risk of hypocalcemia associated with intraoperative FFP and blood administration.

Continuous hemofiltration represents an important adjunctive support modality for patients with advanced hepatic failure and multiorgan dysfunction. By virtue of its ability to provide both a modicum detoxification as well as create a more desirable fluid balance, continuous hemofiltration may be a life-sustaining bridge to transplant for patients.

**Extracorporeal Hepatic Support**

Extracorporeal hepatic support has been under development for over two decades.55,59 In general such systems are composed of immobilized living hepatocytes or multiphase dialytic and plasma exchange/absorber systems. There have been obstacles with each of these approaches and both systems have been used in clinical trials in adults and children with mixed results. Given the complexity of each system neither approach has gained widespread adoption although in Europe, there appears to be greater acceptance in particular for supporting adults with hepatic failure.72 Because of the limitations in availability, expertise, and adaptation to smaller pediatric patients, extracorporeal support cannot be considered a standard of care at this time, although in centers where it is available for use, it may be a valuable bridge to either recovery or transplant. In lieu of specific extracorporeal liver support systems, the use of continuous renal replacement therapy as described above in conjunction with continuous FFP infusion can achieve many of the goals of support in the patient with advanced liver failure.

**Liver Transplantation**

Liver transplantation should be considered in all children who develop a stage III or IV hepatic coma, as spontaneous survival in this group is only 40%.20,73,74 Transplantation is indicated for all forms of ALF, namely viral hepatitis (including of hepatitis B), drug-induced liver injury including acetaminophen overdose and halothane hepatitis and liver injury of indeterminant
cause. It is also appropriate for certain forms of inborn errors of metabolism, for example Wilson disease and tyrosinemia type I, although contraindicated for some children with multisystem disease or mitochondrial DNA deletions. Because the certainty of a successful outcome after liver transplantation is less likely than with other forms of liver disease selection is critical and is based on previous experience of mortality in the pretransplant era. Transplantation using a living donor can accelerate the process and is associated with better outcome in the setting of acute liver failure. Relative contraindications for transplantation include progressive terminal extrahepatic disease, irreversible or rapidly degenerative central nervous system or mitochondrial DNA deletions. Because the pretransplant era. Transplantation using a living donor can accelerate the process and is associated with better outcome in the setting of acute liver failure.

Etiology of ALF is an important factor in determining whether transplantation is appropriate. The highest mortality is seen in children with indeterminate hepatitis, particularly those with a rapid onset of coma and progression to stage III or IV hepatic coma, a shrinking liver, falling transaminases associated with an increase in bilirubin, and coagulopathy. Such children should be immediately considered for transplantation. Children with fulminant Wilson disease are unlikely to recover with medical treatment and require transplantation.

In contrast, children with hepatitis A and children with drug-induced liver disease, particularly acetaminophen poisoning, may make a complete recovery with intensive medical therapy. Thus, careful monitoring for poor prognostic factors is required before selection.

In practical terms, it is appropriate to list for emergency liver transplantation all children who have reached stage III hepatic coma as the shortage of donor organs may mean a considerable wait for transplantation, or death on the waiting list.

As the development of irreversible brain damage is a major contraindication to transplantation, it is essential to be certain that brain damage has not occurred before the operation. Current techniques are inadequate, but include intracranial pressure monitoring, the identification of cerebral infarction or intracranial hemorrhage by cerebral computed tomography or magnetic resonance imaging scans and establishing evidence of mid-brain herniation, such as fixed, dilated pupils.

Auxiliary transplantation, in which the recipient liver is left in situ to regenerate, is controversial treatment for acute liver failure, but may have the benefit that the graft may be removed if the original liver regenerates. It is not suitable for transplantation for acute liver failure secondary to metabolic liver disease because there is no potential for these livers to recover and there may be a risk of hepatoama in the cirrhotic liver.

Relative contraindications for transplantation include untreated sepsis, HIV infection, and the presence of vascular thrombosis. Absolute contraindications for isolated hepatic transplantation include progressive terminal extrahepatic disease, irreversible or rapidly degenerative central nervous system disease, intestinal failure, or untreated metastatic diseases.

Technical Aspects of Liver Transplantation

A detailed discussion of the techniques of liver transplantation is beyond the scope of this chapter. Several aspects of intraoperative management, however, are pertinent to the intensivist in managing the patient postoperatively.

First and foremost in reducing intraoperative and postoperative morbidity is to send the patient for transplantation in the best condition possible. This means that (1) infections have been treated, (2) excess edema has been avoided, (3) cardiopulmonary and renal systems are functioning well, and (4) the brain has been spared irreversible damage.

Table 88–2 Common Postoperative Issues After Liver Transplantation

<table>
<thead>
<tr>
<th>Postoperative Condition</th>
<th>Intraoperative Cause</th>
</tr>
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<tbody>
<tr>
<td>Fluid overload</td>
<td>Intraoperative crystalloid, fluid shifts</td>
</tr>
<tr>
<td>Capillary leak syndrome</td>
<td>Altered perfusion state, multiple blood products, venous congestion</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>Atelectasis, edema, mucus plugging</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Altered perfusion, impaired venous return, renal vasoconstriction secondary to calcineurin inhibitor exposure</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Inadequate fresh frozen plasma/platelets transfusion</td>
</tr>
</tbody>
</table>

Limited availability of donor organs has led to the development of techniques for using “technical variant grafts” (reduced size, living donors, and split liver) to expand the donor pool and reduce waiting time. The ability to provide a reduced segment allows smaller children to receive grafts from larger donors, increasing the availability of organs for younger patients. Although technical variant grafts may reduce waiting list mortality in the setting of acute liver failure, they are associated with a higher rate of postoperative complications. However, patient survival for recipients of technical variant grafts is similar to that seen with whole liver transplants, thus leading to a favorable risk/benefit ratio for selection of these types of grafts. Intraoperative issues affecting the postoperative course are listed in Table 88–2. In general, these issues can be managed with conventional approaches while adhering to two critical, postoperative principles: (1) maintain patency of vascular anastomoses, and (2) maintain normal to slightly supraphysiologic arterial pressure to provide adequate perfusion of the graft. Avoidance of excessive hemococoncentration and rapidly correcting all clotting parameters is key to successful care.

Immune Suppression

Currently, calcineurin inhibitors (e.g., cyclosporine [Neoral], tacrolimus [Prograf]), comprise the initial approach to immunosuppression. Tacrolimus is usually combined with low-dose steroids. Cyclosporine-based protocols may incorporate steroids and a third agent (e.g., azathioprine or mycophenolate [CellCept]).

Most centers have tended to reduce the use of corticosteroids because of the poor growth and infectious risks associated with their use. The practice of steroid withdrawal varies between centers with weaning often started at 3 to 12 months posttransplant. The exception to this rule pertains to children who were transplanted for autoimmune hepatitis who have a high incidence of recurrence.

Postoperative Management Issues of Concern to the Intensivist

The postoperative period is critical due to the need to anticipate predictable complications and to detect unexpected issues as early as possible. The intensivist must be aware of the...
risk for early complications including primary nonfunction, bleeding, hepatic artery or portal vein thrombosis, and bile leak. Later complications include infections, rejection, hypertension, renal dysfunction and lymphoproliferative disease.

As in all other organs, prolonged ischemia because of vascular compromise will potentially lead to the loss of graft function. It is impossible to overly stress the need for close and rapid communication between the PICU team caring for the postoperative transplant patient and the surgical and hepatology teams responsible for the operative interventions and managing the immunosuppression following transplantation. Joint rounding in the immediate postoperative period of at least once a day with all teams caring for the patient will facilitate the best communication during the critical postoperative period.

**Primary Nonfunction**

Primary nonfunction of the graft is a disastrous complication necessitating immediate retransplantation. Of children with graft failure within 30 days, primary graft dysfunction accounted for 25.6%. Evidence of primary nonfunction includes worsening coagulopathy, acidemia, rising liver enzymes, and cholestasis. All measures used to support a patient with minimal liver function must be considered and instituted since the condition will become rapidly fatal in the absence of retransplantation.

**Bleeding**

Postoperative bleeding occurs due to the profound coagulopathy and thrombocytopenia that many patients have going into liver transplantation as well as the dilutional coagulopathy and thrombocytopenia that can occur intraoperatively. Bleeding should abate as the function of the graft returns postoperatively. In addition, patients may return to the pediatric intensive care unit on heparin infusions in an attempt to maintain patency of the hepatic artery and portal vein anastomoses. Monitoring drainage devices for trends in the amount and the characteristics of the drainage is critical to detect postoperative bleeding at the surgical site. Additionally, monitoring of the hemoglobin is important as an indirect sign of bleeding and to assure adequate oxygen carrying capacity, optimally 8 to 10 g/dL. Platelet count should be followed and maintained in a suitable postoperative range as agreed on by both surgical and medical teams. Attempts to achieve perfect clotting function are generally avoided due to the high potential to promote thrombosis of the vascular anastomoses. Worsening coagulopathy suggests hepatic dysfunction, sepsis with DIC, or unrecognized internal bleeding and requires rapid, aggressive diagnosis with treatment of the underlying cause.

**Monitoring Vascular Anastomotic Patency**

Progress in microsurgical techniques has led to improvements in maintaining vascular patency. During the first 30 days after transplant, vascular complications are a major cause of graft failure. Forty-three percent of liver graft loss in children is directly attributable to either hepatic arterial or portal vein thrombosis. Of the vascular complications, hepatic artery thrombosis occurs most commonly, 10% overall and is probably the most important, because it can lead to biliary leaks, strictures, and intra-abdominal infection. Routine assessment of hepatic artery patency using color Doppler ultrasonography at the bedside is critical during this period. Magnetic resonance angiography or computed tomography angiography can be helpful in defining the status of vascular structures but can be technically difficult to perform in critically patients. Attempts at revascularization may be successful, if performed early. The intensivist should work closely with the surgical and radiology team to detect early signs of vascular occlusion. Avoidance of excess hemoglobin (hyperviscosity) and overzealous transfusion of platelets and clotting factor replacement in the immediate postoperative period is essential. Once again, detailed discussion with the other members of the transplant team will achieve consensus and minimize risks.

**Infection**

Sepsis continues to be the most frequent final pathway leading to death in liver transplant recipients. The presence of arterial thrombosis or biliary leak significantly increases the risk of infection as well as abscess formation. Patients having undergone previous abdominal surgery and those who have received pretransplant steroid therapy are at increased risk for postoperative infection. Percutaneously drainage of intra-abdominal abscesses can be an effective method to treat these infections provided there is no evidence of an enteric leak. A high index of suspicion for postoperative infection in the immunosuppressed patient must be maintained with early culture and institution of antibiotic treatment including antifungal and anti-cytomegalovirus as indicated by the patient and donor status. Children are at particular risk for cytomegalovirus and Epstein-Barr virus infections because many are naive to these viruses at the time of transplantation. Passenger donor lymphocytes in the graft are a frequent source of primary infection. Prophylactic therapy with antiviral medication can delay infection and monitoring active viral replication by polymerase chain reaction can be a useful tool to assist in adjustment of immunosuppressive medications in patients with early, acute infection.

**Biliary Complications**

Biliary complications include biliary anastomosis dehiscence and bile leaks from the cut surface of the liver. Approximately 15% of patients experience biliary complications within the first 30 days and 25% or more will experience this complication in long-term follow-up. Early bile leaks may be diagnosed by the appearance of bile in the abdominal cavity drains, by nuclear scan or transhepatic contrast studies. Cut surface leaks from minor biliary radicals may resolve spontaneously, but leaks from the biliary anastomosis or from larger cut surface ducts require operative management. Bile duct ischemia secondary to hepatic artery thrombosis that results in a stricture or leak will likely require retransplantation. Bile leaks increase the risk of postoperative infections that require aggressive attempts to diagnose and treat with targeted antibiotic therapy when possible.

**Rejection**

The median time to first rejection after transplant in one series was 16 days with 40% to 70% of children experiencing a first episode of rejection 7 to 10 days after successful transplantation. Laboratory findings including elevation in AST and γ-GTP followed by elevations in bilirubin. Liver biopsy is important to confirm the diagnosis of acute rejection and distinguish patients with viral infection, biliary obstruction, or graft ischemia who may have a similar clinical presentation. Early detection of rejection is critical to allow the initiation
of intensified immunosuppression to reverse the process and minimize graft loss.

**Complications of Immune Suppressive Medications**

Each of the immune suppressant agents in common use has potential undesirable side effects. The most common issues are listed in Table 88–3. The majority of patients will receive a calcineurin inhibitor and corticosteroids setting the stage for postoperative hypertension with or without deterioration in biochemical renal function. Hypertension is treated with conventional pharmacologic agents and may remain a persistent problem. Diabetes is also relatively common in patients receiving tacrolimus with a prevalence of 25% at 3 months posttransplant. Hyperglycemia in the immediate postoperative period can be controlled by insulin drip and should not limit the clinician’s ability to deliver adequate caloric intake. Cyclosporin and tacrolimus-related encephalopathy and seizures occur in 11% and 8% of patients, respectively, with the most common onset in the first 2 weeks after transplantation. Both can be managed by reduction or elimination of the calcineurin inhibitor exposure. Seizure control will frequently require short-term treatment with antiepileptic medications.

### Table 88–3 Adverse Effects of Immunosuppressants

<table>
<thead>
<tr>
<th>Agent</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>Hypertension, headache, infection, seizures, hyperglycemia, insulin resistance/diabetes, renal failure, PTLD, cardiomyopathy</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Hypertension, infection, seizures, hyperglycemia, renal failure, hirsutism, gingival hyperplasia, PTLD</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Hypercholesterolemia, infection, edema, poor wound healing, PTLD</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Hypertension, increased appetite, Cushing syndrome, acne, gastritis, poor wound healing, osteoporosis, poor linear growth</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>Intestinal hypermotility, cramping, diarrhea, infection, leucopenia, depressed WBC/plt counts</td>
</tr>
</tbody>
</table>

PTLD, Posttransplant lymphoproliferative disorder; WBC, white blood cell; plt, platelet.

References are available online at http://www.expertconsult.com.