Acute Hepatic Failure in Children

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Many diseases may present as acute hepatic failure in the pediatric age group, including viral hepatitis A and B, adverse drug reactions, both toxic and "hepatitic," and inherited metabolic disorders such as tyrosinemia, α, antitrypsin deficiency, and Wilson's disease. Management is primarily supportive, with care taken to anticipate the known complications of hepatic failure. Few "curative" therapies are known, although attempts at stimulating hepatic regeneration may be helpful.

Acute hepatic failure is a rare but devastating event with a mortality rate of 80 percent or higher in adults [1-4]. For children, survival may be somewhat higher as the liver, particularly the young liver, has remarkable regenerative powers. Full recovery to normal hepatic structure and function is possible, even after massive injury. Because of this potential for full recovery, all patients with acute hepatic failure require intensive care. Only the most meticulous, most intensive support is rewarded, albeit far from invariably, with salvage of patients from this catastrophic syndrome.

Acute hepatic failure is a non-specific term, implying abrupt cessation of hepatic function of any etiology (Table 1). First, it is acute, with signs and symptoms fulminating over a very short period, usually less than two weeks and often only hours. Chronic liver diseases which may terminate in an acute fashion are excluded from this diagnostic category. Some liver diseases may progress in the absence of overt signs or symptoms to an acute termination, however, so that the differential diagnosis of acute hepatic failure should include some chronic liver diseases also, Wilson's disease being a prime example. Not included within this diagnosis (or within this review) are clearly chronic forms of liver disease, such as biliary atresia or chronic hepatitis.

The second requirement for this diagnosis is hepatic failure, the inability of the liver to maintain its major functions (Table 1). Hepatic coma with hyperammonemia is necessary for the diagnosis of acute hepatic failure, as is coagulopathy, with prolongations of the prothrombin and partial thromboplastin times. In acute hepatic failure, the prolonged prothrombin time is not responsive to parenteral Vitamin K; correction of the prothrombin time after Vitamin K administration implies long-standing malabsorption of this fat-soluble vitamin and demonstrates normal hepatic function, once absorption has been bypassed.

Almost invariably, other tests of hepatic function are also abnormal in acute hepatic failure (Table 2). The albumin level is often below 4 g/dl, despite the long half-life of this protein. The level of cholesterol, another product of hepatic synthesis, is also usually low, often below 100 mg/dl. In addition to these defects of
1. Acute: Rapid deterioration from health to coma over a short time course (usually less than two weeks).

2. Hepatic failure:
   a. Coma with hyperammonemia
   b. Coagulopathy: prolonged prothrombin (PT) and partial thromboplastin times (PTT)
   c. Other hepatic dysfunctions: decreased serum levels of albumin and cholesterol, elevations in both direct and indirect reacting bilirubin
   d. Signs of acute hepatic necrosis: elevations in serum transaminases (common but not invariable)

hepatic synthetic function, the excretory function of the liver is also impaired, with elevations in the serum bilirubin (both direct and indirect fractions). As a result, jaundice is common in acute hepatic failure, although it may take several days to become clinically evident. In very fulminant cases, the patient may lapse into coma before becoming obviously jaundiced. Nevertheless, the diagnosis of acute hepatic failure is difficult to support without an elevation, although it may be mild, in the bilirubin.

Conventional "liver function tests" usually include the serum transaminases (SGOT-AST and SGPT-ALT) which are often elevated in acute hepatic failure, although such elevations are not mandatory to confirm the diagnosis. The levels may be very high—for example, up to 6,000–10,000 units in acute viral hepatitis.

| Name             | Normal Range       | Usual Level in Acute Hepatic Failure | Interpretation                                      |
|------------------|--------------------|-------------------------------------|----------------------------------------------------|
| Ammonia          | <150 µg/dl         | 1, >3 seconds prolonged             | Failure of appropriate hepatic metabolism          |
| Prothrombin time | Within 2 seconds of control | Inadequate hepatic production of factors |
| Partial thromboplastin time | Within 5 seconds of control | Inadequate hepatic production of factors |
| Albumin          | 3.7–4.8 g/dl       | 1, <3.4 g/dl                       | Inadequate hepatic production and hemodilution      |
| Cholesterol      | 150–230 mg/dl      | 1, <150 mg/dl                      | Failure of hepatic production and hemodilution      |
| Bilirubin        |                    |                                     |                                                   |
| Total            | <1.5 mg/dl         | 1, >2.0 mg/dl                      | Mixed defect in hepatocyte uptake and excretion     |
| Direct           | <0.30 mg/dl        | 1, >1.0 mg/dl                      |                                                   |
| SGOT             | 15–35 units        | 1, >500 units                      | Acute necrosis (may arise from muscle or heart as well) |
| SGPT             | <32 units          | 1, >500 units                      | Acute necrosis (somewhat more specific for liver)  |
| Alkaline phosphatase | 10–20 units/L    | Modestly ↑ or normal               | Membrane enzyme, elevations more common in chronic cholestasis than in acute hepatic necrosis |
| 5' nucleotidase  | <10 Lu             | Modestly ↑ or normal               | Hepatic fraction of alkaline phosphatase           |
Such elevations reflect acute necrosis but give no hint as to hepatic function or prognosis. Chronic hepatic failure may be associated with normal transaminase values, whereas patients with markedly abnormal transaminases may have intact hepatic function.

Other “liver function tests,” such as alkaline phosphatase, may be abnormal, but less impressively so. It is helpful to monitor enzymes more specific to the liver, for example 5’nucleotidase, as the less specific alkaline phosphatase is usually elevated in children, reflecting bone growth.

In children, the differential diagnosis of acute hepatic coma must include a host of enzyme defects which may be associated with hyperammonemia (Table 3). The most commonly encountered of these is a defect in the urea cycle enzyme ornithine transcarbamylase. These hyperammonemic states all share an important feature which differentiates them from acute hepatic failure: hepatic function is well-preserved, as a rule. Such patients may show transient elevations of transaminase, but have normal coagulation tests, bilirubin, and albumin values. These syndromes of isolated hyperammonemia will not be further discussed herein. Also not included in the discussion which follows is the most common hyperammonemic state seen in children, namely Reye’s syndrome [12].

Acute hepatic failure is a devastating event with high mortality. Although its management is only supportive for the most part, it is crucial to try to identify the cause of the hepatic failure. Specific cures or antidotes are rare in this disease entity, but they do exist and must be proffered where appropriate. Not uncommonly, the “cause” of the hepatic failure is a drug being administered by well-meaning physicians in all good conscience; in these instances, identifying the causative agent, and removing it, is crucial if recovery is to take place.

**DIAGNOSIS OF ACUTE HEPATIC FAILURE**

*Diagnostic Tools*

Determining the cause of acute hepatic failure requires the use of both old and new diagnostic tools. Crucial to arriving at the correct diagnosis is a good history, which often must be obtained from the family, as the patient is in a coma. A history of exposure, either to epidemic hepatitis, blood transfusion, drugs, or toxins is helpful. In children, the history of growth and development, along with a growth chart, may indicate pre-existing disease. A family history of infantile deaths or of members with cirrhosis would suggest genetic disease. Physical examination should
be directed toward detecting signs of chronic liver disease, especially palmar erythema, spider angiomata, and prominent venous pattern over the chest and abdomen. Cutaneous signs of allergic reactions, such as a drug exanthem, or of viral infection are very useful. The liver size is important and both the total span to percussion and the span to palpation below the costal margin should be measured and recorded on admission. Hepatomegaly should suggest genetic disease, whereas a normal-sized liver which progressively shrinks suggests hepatitis with an ominous prognosis (Fig. 1). Splenomegaly is usually not present in acute hepatic failure and, if the spleen is found to be enlarged on admission, chronic forms of liver damage should be considered.

Laboratory tests are helpful in confirming the etiology of acute hepatic failure, but should not supersede experienced clinical input. A differential white count with a pronounced eosinophilia suggests an allergic reaction, and can be very helpful if present. In hypersensitivity, the absence of eosinophilia is the rule, however, and in no way excludes this diagnosis. Standard "liver function tests" (bilirubin, SGOT) are surprisingly non-specific in acute hepatic failure. A very high SGOT (i.e., > 5,000 units) suggests massive necrosis as in viral or drug hepatitis, but both may occur without large SGOT elevations or the peak elevation may be missed. Confirmation of the etiology of viral hepatitis depends on serologic testing (Table 4). This field has seen an explosion of knowledge in the last 15 years, and new serologic tests for new viral hepatitides are reported frequently [16]. Several such markers have yet to be reproduced. Despite this, the promise of further elucidation of the viral hepatitides and their serologic markers is great. The laboratory can also be helpful in confirming drug and toxic hepatitis. All patients admitted with acute hepatic failure should have urine and blood samples taken on admission for possible toxic screening. Except for acetaminophen, however, no correlation has been established between blood levels of drug and degree of hepatic injury.

The percutaneous liver biopsy technique introduced in the 1950s provided a quan-

FIG. 1. Radiographs of the abdomen in a patient with fulminant hepatitis; note the small shrunken liver.
TABLE 4
Hepatitis Serologies [13,14]

| Agent                  | Marker                  | Interpretation                                                                 |
|------------------------|-------------------------|-------------------------------------------------------------------------------|
| Hepatitis B            | HBsAg                   | Excess viral surface protein                                                  |
|                        | anti-HBsAg              | Antibody to surface protein                                                   |
|                        | anti-HBcAg              | Antibody to core antigen                                                       |
|                        | HBeAg                   | A third antigen associated with HB, only present concomitant with HBsAg, usually early in disease, correlates with high HBsAg and with infectivity |
|                        | anti-HBeAg              | Antibody to HBe                                                                |
|                        | anti-HA                 | Confirms exposure (may be distant)                                            |
|                        | IgG                     | Confirms recent infection                                                      |
|                        | IgM                     | Correlates with clinical hepatitis which has been shown serologically to be neither A or B; probably multiple viruses |
|                        | Several preliminary     |                                                                              |
| Non-A, non-B hepatitis | reports                 |                                                                              |
| (HNANB) [16]           |                         |                                                                              |
| EBV [17]               | Monospot                | Screening test—usually + early in infection, false + occur                    |
|                        | (Orth Diagnostics)      | High titer in acute phase, IgG persists for life                              |
|                        | Anti-viral capsid antigen, IgM and IgG | Occurs early, then fades                                                       |
|                        | Anti-early antigen      | Occurs in convalescent phase, persists for life                               |
|                        | Anti-EB nuclear antigen |                                                                              |
| CMV [18]               | CMV antibody            | Widely used but inadequately sensitive; many false — , small rises in titer are non-specific |
|                        | IgM and IgG             |                                                                              |

viral jump in diagnostic accuracy of liver diseases. This technique is suitable for use in infants and children as well as adults. Its limitations are real, however. In our institution, we do not perform this procedure in the face of coagulopathy (prothrombin time > 3 seconds prolonged, platelet count < 60,000, template bleeding time > 9 minutes). Occasionally these problems can be circumvented by infusions of fresh frozen plasma or of platelets, but even a corrected coagulopathy represents a relative contraindication to biopsy. Other limitations of liver biopsy should be remembered: as a rule the findings in viral hepatitis (most kinds) and in drug-induced hepatitis (hypersensitivity) are indistinguishable. Liver biopsy cannot predictably distinguish one type of hepatitis from another.

As a result of these limitations, liver biopsy is rarely performed in patients with acute hepatic failure. Our practice has been to limit the use of this procedure to patients without coagulopathy whose history and course are atypical for viral or drug hepatitis and whose disease evades diagnosis by less invasive means.

**Viral Hepatitis [13,14]**

**Hepatitis B** The identification of this viral agent resulted in a Nobel Prize for Baruch Blumberg in 1976. Trials with a vaccine have been very successful [19] and conquering this disease, the most common cause of liver disease worldwide, would surely rank as one of the premier medical achievements of the second half of the
twentieth century. Hepatitis B is probably the single most common cause of acute hepatic failure. This illness can occur in several other ways as well, including the asymptomatic carrier state, chronic active hepatitis, "cryptogenic" cirrhosis, and in association with hepatocellular carcinoma. The disease is common, with incidences in the general population ranging from about 0.5 percent in the U.S. to 20 percent or more in parts of the Far East and Africa. The most common route of transmission is vertical transmission from mother to infant, presumably occurring at birth [20]. Infants infected in this way are usually asymptomatic, although some will have fulminating hepatitis. Presumably, it is this route of spread which is responsible for the high incidence of the hepatitis B surface antigen carrier state in some populations. Studies have shown that vertical transmission is more likely to occur if the mother is also positive for hepatitis Be antigen (Table 4 and Fig. 2), an antigen associated with hepatitis B whose presence correlates with high titer of hepatitis B surface antigen, high levels of DNA polymerase, and also with greater infectivity. When hepatitis B is transmitted vertically, the infant shows conversion to hepatitis B antigen positivity usually in the third to fourth month, suggesting that the infection was acquired traversing the birth canal or in the immediate peripartum period. It seems unlikely that this virus crosses the placenta, as cord blood is almost invariably negative. Therefore, most cases of infantile hepatitis B occur in or after the third month of life, although fulminant hepatitis B has been observed within one or two months after birth.

In addition to vertical transmission, this virus is also transmitted through blood products. With all volunteer donors and with screening for HBsAg, the incidence of post-transfusion hepatitis B has fallen dramatically but persists at a real but much reduced rate. As the infection is cleared from the body, hepatitis B surface antigen disappears before antibody to hepatitis B surface antigen can be detected (Fig. 2). In this so-called window period, the only marker in the blood indicating persistent viral infection is the IgM antibody to hepatitis B core antigen. Until all transfused blood is routinely screened for this marker, a small rate of post-transfusion hepatitis B will persist.

Finally, hepatitis B occurs commonly as sporadic hepatitis. Infection can occur from ingesting a large viral load orally, despite the fact that the gastric milieu kills the virus in small doses. A common route of transmission is intimate prolonged physical contact with an infected person. Sexual transmission is the usual route and this infection is very prevalent in the male homosexual population. The contact must be intimate, however, as studies in families have shown an increased rate of

FIG. 2. Serologic events in the course of typical hepatitis B. Compare with Table 4 (from [13]. Reproduced with permission of Masson Publishing USA, Inc.).
transmission only between sexual partners and not from parent to child. Spread is also common in residential treatment centers for the mentally retarded, where behavioral problems (biting, sexual promiscuity) are frequent. Recent reports have suggested local spread within the normal classroom setting, but have yet to be confirmed [21].

Once a case of hepatitis B has been confirmed, multiple questions about prophylaxis and isolation arise. As a rule, only sexual contacts of the affected patient need receive immunoprophylaxis. It is difficult to be dogmatic about this stance and some physicians may advise prophylaxis for persons in close contact (kissing, sharing bottles) with the child. For the patient who is hospitalized, the staff should realize that transmission only occurs if blood or other fluids (tears, semen, saliva) from the infected patient penetrate the skin or mucous membranes of the exposed person. The most common route, therefore, is by puncturing the skin with a needle from the patient. Strict needle precautions are in order; there should be a needle-destroying kit at the bedside, and it should be disposed of properly. Blood spills represent a real hazard (this includes menstrual flow), and should be cleaned up with hypochlorite solution (Clorox diluted as a 1:10 solution in water) which kills the virus. Other than this, the patient is not highly infectious and the virus is not transmitted by talking or touching. Despite this, many hospitals persist in requiring gown and glove precautions.

Once the decision to give prophylaxis has been made (and this should be decided as soon as possible after exposure, i.e., within 48 hours), the exposed individual should be checked for both hepatitis B surface antigen and antibody to hepatitis B surface antigen. If either is present, no prophylaxis is needed, as viral infection is or has been present. If neither is present, the exposed person is given 0.06 ml/kg of hyperimmune hepatitis B globulin with a repeated dose in one month. The globulin is very expensive. The best prophylaxis for doctors and nurses at risk is informed care of the patient, with respect to needles and blood. If the exposed individual will be chronically exposed (i.e., health care worker, spouse of a chronic carrier), then he or she should also be actively immunized with vaccine.

The clinical hallmarks of hepatitis B can be very helpful in confirming this infection as the cause of acute hepatic failure. Early in the course of the infection (before any symptoms of hepatitis), the patient may experience a rash which may be either typical hives or the acrodermatitis described by Gianotti and Crosti [22]. These rashes are usually evanescent and, unless they are recognized at the time as the prodrome of acute hepatitis B, are only helpful in retrospect. The patient who is to develop fulminant hepatitis B progresses from well to critically ill within five to ten days, as a rule [23]. The symptoms are those of classical hepatitis: anorexia, nausea, vomiting, and jaundice. Hepatic coma may begin as unusual irritability and personality changes, before the onset of lethargy and frank coma. Initially the liver may be modestly enlarged but it shrinks rapidly in fulminant hepatitis (Fig. 1). Early in the course, the SGOT is usually very high (i.e., > 1,000) but may fall rapidly. The findings on liver biopsy are not specific (Fig. 3).

As a rule, fulminant hepatitis B does not occur in chronic carriers or in patients with chronic liver disease secondary to this virus. One exception to this rule is chronic carriers who have been immunosuppressed (for example, a multiply transfused leukemic). Several reports have documented fulminant hepatitis B in this setting when immunosuppression was discontinued [24].

Serologic testing is the key to confirming this diagnosis (Table 4). All patients with acute hepatic failure should be checked for HBsAg. If it is positive, then, almost in-
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FIG. 3. Histopathology of the liver in fulminant hepatic failure (C = central vein, P = portal triad).

A Fatal Acute Viral Hepatitis: No viable hepatocytes remain. Central and portal areas are joined by massive necrosis and collapsed reticulin. B Fatal Acetaminophen Overdose: Most hepatocytes contain fat. The central areas demonstrate hemorrhagic necrosis. Degenerating ducts in the portal areas are distended with bile.

variably, the patient has fulminant hepatitis B. In that instance, the family members should be checked for HBsAg and anti-HBs. If the mother of an affected neonate is positive for HBsAg, testing for e antigen may be helpful in assessing her infectivity. In the HBsAg-positive patient with fulminant hepatitis, testing for HBeAg, anti-HBe, and anti-HBc is superfluous but may give some indication of the duration of the infection and its prognosis.

Hepatitis A This infection is a less frequent but occasional cause of acute hepatic failure [15]. Most cases of hepatitis A are subclinical. It is very common, particularly in underdeveloped countries but also in the United States, where, by the age of 50, 70 percent of the population show serologic evidence for past infection. Many have no past history compatible with acute hepatitis. The incidence of positive markers for this infection is age-related and it is uncommon in children.

In this infection, viremia is very short-lived, usually less than ten days to two weeks, and the viremia has cleared by the time that the symptoms of hepatitis are recognized, or shortly thereafter. There is no chronic carrier state for hepatitis A. Knowledge of these facts will allow the clinician to accurately predict the epidemiology of this virus. Hepatitis A does not occur as post-transfusion hepatitis, because of the transience of viremia and the absence of the chronic carrier state. It
occurs in common-source water- and food-borne epidemics or by fecal-oral transmission from an infected human. Within one to two weeks of the onset of symptoms of hepatitis A, virus is no longer being shed in the stool and the infected patient is no longer contagious. Immunoprophylaxis, as 0.02 ml/kg of regular gamma globulin, is indicated for all individuals who are not already immune who share exposure with the affected patient—i.e., family members, contacts in a residential situation. Failure to provide this immunoprophylaxis is hardly catastrophic, however, as the infection is usually subclinical and as most of us will encounter it eventually. The hospitalized patient with hepatitis A should be maintained on stool and syringe precautions but does not represent a very great threat, as viremia ceases promptly.

Clinically, fulminant hepatitis A is confirmed serologically, using testing for anti-hepatitis A. The antibody should be classified as to immunoglobulin class: IgG antibody indicates distant infection and should not be used as evidence for acute hepatitis A. In acute disease, the antibody is of the IgM class. This titer falls with time after the infection as the IgG titer rises. As viremia is so evanescent, testing for hepatitis A antigen is neither practical nor clinically available.

Non-A, Non-B Hepatitis This catch-all phrase is used to include any hepatitis which cannot be confirmed to be either A or B. The term is generally restricted to primarily hepatic disorders and is not used to describe systemic diseases which can have hepatic involvement, such as mononucleosis. Confirmed markers for specific viral infections within this group are not yet available. When they become so, they will probably be identified as hepatitis C, hepatitis D, and so forth. Until such time, the designation of non-A, non-B hepatitis remains a wastebasket term.

Within this designation, however, there exists at least one well-defined clinical syndrome, probably resulting from infection with a single virus [25]. This form of non-A, non-B hepatitis is now the most common post-transfusion hepatitis [26]. Usually the disease has its onset approximately three months after the transfusion, is subclinical or very mild, and results in a chronic disease with transaminase values rising and falling within a range of normal to 500 units over two- to five-year period. The biopsy during this period may show chronic active hepatitis and cirrhosis may result, although in most patients the disease eventually resolves. This disease may also present as fulminant hepatitis, and is probably the second most common cause of fulminant viral hepatitis, in children as well as adults. This disease is a "serum" hepatitis and, presumably, when markers become available, it will be shown to have epidemiology more similar to that of hepatitis B than of hepatitis A.

Clinically, fulminant non-A, non-B hepatitis is indistinguishable from other forms of fulminant hepatitis. There is no serologic proof for this infection and this term should be used only as a diagnosis of exclusion, after all other serologies fail to reveal the cause and after ingestion of drugs or toxins has been ruled out.

Infectious Mononucleosis Very rarely, the liver may become severely involved during the course of typical "mononucleosis" [17]. Death in hepatic coma has been reported in this entity [27]. The diagnosis should be suggested by a prodrome compatible with mononucleosis, e.g., fever, sore throat, generalized tender lymphadenopathy. This syndrome may be caused by either Epstein-Barr virus (EBV) or by cytomegalovirus (CMV) [18].

Serologic tests may be helpful (Table 4), particularly in establishing acute infection with EBV. Serologic testing for CMV is available, but in most laboratories is mono-valent, and thereby too specific to be generally useful. In addition, this titer
may rise in the absence of demonstrable disease caused by CMV. Both EBV and CMV can be cultured from infected persons. Recovery of virus depends upon culturing fresh specimens (for example, freshly passed urine) and use of the correct culturing technique. Cultures may take weeks to turn positive [17,18].

**Congenital Hepatitis** Several viruses can infect the neonate *in utero* or in the perinatal period and cause so-called congenital hepatitis [28,29]. Rarely, this type of hepatitis may assume a rapid progression and may result in acute hepatic failure within the first six weeks of life. Often these patients will have other signs suggesting systemic or congenital viral infection: thrombocytopenia with "blueberry muffin" rash, congenital heart disease, cataracts or retinal disease, deafness, or vesicular eruption on the skin or mucous membrane. In all such patients (invariably neonates), serologic proof of the suspected agent should be sought in both infant and mother. Testing for specific immunoglobulin classes of antibody (e.g., IgM, IgG) should be used. Acute infection in the infant cannot be presumed in the absence of IgM antibody, which, unlike IgG antibodies, does not cross the placenta and cannot be of maternal origin. In addition, several of these viruses can be successfully cultured from affected patients.

**Adverse Drug Reactions**

Drugs and chemicals are a common cause of acute hepatic failure [30,31]. The variety of offending agents and the diversity of possible reactions presents a bewildering picture to the clinician. The following working hypothesis (Table 5) can serve as a framework for better understanding of these reactions, even though some do not readily fit into the model. This schema should be taken only as a guide, as in most cases the exact pathogenesis of adverse drug reactions is still unknown.

**Classification**

**Toxins** Drugs and chemicals which predictably produce a typical adverse reaction in both animals and man may be considered toxins. Luckily, few of these reach commercial availability in this era of government regulation and testing in animals. These agents will produce an adverse response in all individuals receiving the threshold dose or more. The lesion begins at a predictable (usually short) time after administration and results in a typical pathologic appearance in the biopsy of either man or animal. Because of this predictability, for at least one toxin (acetaminophen),

| TABLE 5 |
| --- |
| A Method for Classifying Adverse Hepatic Reactions to Drugs and Chemicals [30] |

| Toxins                  | Sensitizers                  |
|-------------------------|------------------------------|
| Predictable             | Idiosyncratic                |
| Dose-related            | Not dose-related             |
| Occurs in all exposed   | Occurs only in a fraction of exposed persons |
| Reproducible in animals | Not identically reproducible in animals |
| Short time of onset     | Onset is variable            |
| Consistent histopathology| Histopathology is variable   |

*Examples:*
- Acetaminophen, CCl₄
- Akee fruit
- Dilantin, INH, Halothane
the mechanism of toxicity has been clearly elucidated and an antidote is known. The agents are poisons to all, given a sufficient dose.

**Sensitizers**  Drugs in common clinical use may rarely cause adverse hepatic reactions. These agents do not cause similar reactions in animals and, thus, are able to reach the public. The reactions are idiosyncratic, occur at a variable (often prolonged) interval after initiation of therapy, result in a variety of histo-pathologic responses, and occur in only a small minority of the exposed population, without regard to dose. Unlike the response to toxins, these reactions may be accompanied by systemic signs of hypersensitivity, including fever, rash, and eosinophilia.

**Toxins—Examples**

**Acetaminophen**  This readily available drug is a common vehicle for suicides in England and overdoses, either intentional or accidental, are becoming more frequent in this country. Acute ingestion of an overdose results in acute hepatic failure. Chronic ingestion of smaller (perhaps even therapeutic) doses can result in chronic hepatitis—at least in adults. Immediately after the ingestion the patient is often remarkably well, although some demonstrate vomiting and shock. For the first one to two days, the liver function tests remain normal. By the third day, hepatic necrosis begins, probably initiated by depletion of hepatic glutathione stores by the overwhelming dose of the drug, leaving no glutathione to bind to a minor product of metabolism, which in turn binds covalently with the liver, causing necrosis [32]. Once initiated, this necrotic process progresses to massive hepatic necrosis, hepatic coma, and death. The pathologic picture is a predictable one of confluent central hemorrhagic necrosis (Fig. 3).

Great gains have been made in the management of this entity and progression to death is now the exception rather than the rule, provided that the ingestion is recognized early and appropriate therapy initiated (see below) [33]. Appropriate therapy should blunt or ablate the necrotic reaction. A single ingestion, regardless of severity, results in no hepatic sequelae, providing the patient survives. If detected early, the average patient with acetaminophen overdose does not require intensive care. Nevertheless, the clinician should be reminded that the hepatic necrosis begins late, three days after ingestion, and should monitor for this.

Other typical hepatic toxins include carbon tetrachloride [34], and amanita phalloides [35], the toxin in the amanita species of mushroom, the "angel of death." Both produce microvesicular fatty infiltration of the liver, predominantly in the central zones. Again, like acetaminophen, the hepatic necrosis peaks at two to three days after ingestion. Death occurs if the dose is large enough.

Many other true toxins for the liver exist. One of particular interest in pediatrics is that in unripe akee fruit, the national fruit of Jamaica. When this unripe fruit is consumed, the patient develops vomiting and hypoglycemia, lapses into coma, and dies—so-called Jamaica vomiting sickness. The illness is similar to Reye's syndrome in many respects, including the presence of microvesicular fat in hepatocytes. The toxic compound present in the fruit is an unusual amino acid, hypoglycin, which interferes with long-chain fatty acid metabolism [36]. This illness may be a model for the coma seen in the organic acidemias.

**Sensitizers—Examples**  Several drugs in widespread clinical use can cause fulminating hepatitis indistinguishable from viral hepatitis. A typical example is diphenylhydantoin [37]. Usually, the hepatitis has its onset within three months of initiating therapy, but the onset may be variable. Many patients will have hepatitis as a part of a generalized "allergic" reaction, including fever, eosinophilia, skin rash, and
lymphadenopathy. The hepatitis may occur in isolation, however. The time course of this illness is fulminant with symptoms typical of hepatitis followed rapidly by coma. The transaminase values may be very high, as in viral hepatitis. The liver biopsy may show eosinophils prominent in the infiltrate, but this is not an invariable finding and the biopsy picture is usually indistinguishable from acute viral hepatitis. If the patient survives, there are no hepatic sequelae as a rule. The single most important step in therapy is to stop the drug, although the hepatic necrosis often progresses despite discontinuing the offending agent. This seems like an easy step, stopping the drug, but it first requires knowing all of the patient's medications and remembering that diphenylhydantoin can cause hepatitis. Drugs must be considered as a potential cause in every case of acute hepatic failure.

Many other drugs (e.g., INH, Halothane) can cause acute hepatic failure from a "hypersensitivity hepatitis." Luckily, these reactions are rare in the younger age group. For example, halothane hepatitis is extremely rare below age of 11 but increases in incidence above that age [31].

Indeterminate Group Some drugs provoke reactions which are not clearly toxic or hypersensitive and which progress to hepatic failure. Examples of this group include aspirin and valproic acid. As a rule, the aspirin lesion occurs only in patients with lupus or rheumatoid arthritis who are taking maximal therapeutic doses of aspirin [38]. The hepatitis in these patients is of variable severity but may cause death. Liver biopsy in such individuals has been reported to show typical eosinophilic intracellular inclusions but this diagnostic clue is rarely detected. The new anti-epileptic agent, valproic acid, produces an indolent liver lesion which may progress to hepatic failure [39]. The liver biopsy findings in these patients are reported to be typical, and are remarkably mild for the degree of hepatic failure. This agent is a short-chain fatty acid. The mechanism by which it is toxic is, as yet, unknown.

The intent in this section has been to provide an overview of drug-induced hepatic reactions, along with a working hypothesis for understanding their pathogenesis. The examples provided are only a few of the many possible offenders. The point to remember is that any drug is a possible cause of acute hepatic failure. The clinician should maintain a high index of suspicion that drugs may injure the liver.

Metabolic/Genetic

Several of the inherited metabolic diseases may terminate with acute hepatic failure superimposed upon chronic liver disease which may have escaped detection. With this group are conditions unique to infancy or childhood (Table 6).

Tyrosinemia [40,41] This rare disorder may present acutely within the first four months of life with hepatic failure and failure to thrive associated with a Fanconi-like syndrome and rickets. The course is progressively downhill. No effective therapy is known, although a diet deficient in tyrosine and phenylalanine may prolong life. The diagnosis is confirmed by amino acid screening of the plasma, which shows a marked increase in tyrosine levels. Both prematurity and any form of hepatic failure in infants may result in alterations in the blood amino acid profile, often with an increase in tyrosine levels. These modest, transient, and non-specific increases should not be mistaken for the persistent changes seen in hereditary tyrosinemia.

Galactosemia [44,45] This disease presents early in infancy with hepatomegaly and failure to thrive in infants ingesting lactose-containing formulas. If the correct diagnosis is not made, the infant goes on to die in acute hepatic failure.
**ACUTE HEPATIC FAILURE IN CHILDREN**

**TABLE 6**

| Metabolic Diseases Which May Present as “Acute Hepatic Failure” |
|---------------------------------------------------------------|
| **Common Name** | **Age at Presentation** | **Pathogenic Defect** | **Best Diagnostic Tests** |
| Tyrosinemia [40,41] (acute form) | Infancy | Not yet identified | Urine and plasma amino acid profiles, R/O fructose intolerance [42], R/O “neonatal hepatitis” [43] |
| Galactosemia [44,45] | Infancy | Galactose-1-phosphate uridyl transferase deficiency | Urine + for reducing substances during milk ingestion, assay of galactose-1-phosphate uridyl transferase in red cells |
| Fructose intolerance [46,47] | Within weeks of adding fructose to diet | Fructose-1-phosphate aldolase deficiency | IV fructose loading test, assay of fructose-1-phosphate aldolase in liver |
| Alpha-l-antitrypsin deficiency [48, 49] | Infancy | Unknown, α-1-antitrypsin accumulates in liver, is diminished in serum | Glucagon stimulation test, assay of fructose-1,6-diphosphatase in liver |
| Wilson’s disease [50–52] | 6–50 years | Unknown; hepatic excretion of copper into bile is impaired | Quantitative α-antitrypsin level testing, phenotype (Pi ZZ homozygotes associated with disease) |

**Fructose Intolerance** [42,46,47] This disease presents within days of weaning the infant or starting dietary fructose supplements. If this occurs in early infancy, the patient goes on to develop vomiting, hepatomegaly, failure to thrive, and, ultimately, death in hepatic failure.

**Alpha-1-Antitrypsin Deficiency** [48,49] This inherited disease is probably the single most common cause of liver disease in infancy and should be ruled out in every child with liver disease. The spectrum of hepatic dysfunction in patients with this illness is broad, ranging from normal or asymptomatic elevations in the SGOT all the way to fulminant hepatic failure. Patients in the latter group usually have some evidence of pre-existing liver disease, such as failure to thrive or splenomegaly. The diagnosis may be suspected in patients with low alpha 1-globulin levels on protein electrophoresis, although this is very non-specific; in order to rule out this diagnosis, the alpha-1-antitrypsin level should be quantitated. If the level is low (i.e., < 200 mg/dl), the patient’s alpha-1-antitrypsin should be phenotyped. Patients homozygous for the Pi Z allele are at risk for liver disease. Some studies suggest that even heterozygotes (i.e., Pi MZ or SZ) have an increased risk of liver disease, at least as adults. For all practical purposes, however, severe Neonatal hepatic dysfunction occurs only in Pi ZZ individuals.

Liver biopsy may be suggestive of the diagnosis of alpha-1-antitrypsin deficiency. The periportal hepatocytes contain bead-like inclusions which may be inconspicuous
on routine stains but which are bright cherry red on PAS-digested stain (Fig. 4). The hepatocytes are also positive on immunofluorescent staining for alpha-1-antitrypsin. Regardless of these biopsy findings, the diagnosis should be confirmed with phenotyping.

There exists no known therapy for this disease. Many patients with mild hepatitis show resolution. If the disease is fulminant, the prognosis is grim, despite maximal supportive care.

Wilson's Disease [51,52] This is an inherited disease of copper metabolism. The exact defect remains undefined, but may be an inability to excrete copper into bile, its normal excretory route [50]. The result is a build-up of copper in various organs, specifically liver (with a chronic active hepatitis progressive to post-necrotic cirrhosis), eye (Kayser-Fleischer rings), brain, and kidney. This disease has myriad forms of initial presentation. One of these can mimic fulminant hepatitis. Usually this occurs in patients who have either a previous history or signs of chronic liver disease. Several clues should suggest Wilson's disease. Hemolytic anemia, presumably induced by sudden release of copper, is one of these; a defect in renal tubular function (with hypouricemia) is another. Wilson's disease is a type of "storage" disease and does not occur in the very young. The usual lower age range is six years, although we have encountered a patient with jaundice at age two. The acute presentation certainly occurs in adolescence and Wilson's disease, as one of the few treatable liver diseases, should be ruled out in any child, adolescent, or young adult with acute hepatic failure.

Proving or disproving this diagnosis is difficult, because the primary defect remains undefined [52]. The single best test is determination of hepatic copper concentration, but this is usually not possible in someone with the coagulopathy of acute hepatic failure. The ceruloplasmin level should be determined in all patients with acute hepatic failure. Ceruloplasmin is decreased, usually as low as 10 mg/dl, in Wilson's disease, but this protein is an alpha 2 globulin and can increase into the normal range during acute "hepatitic" flare in Wilson's disease (we have seen values up to 28 mg/dl). Conversely, in patients with hepatic failure of any etiology, the ceruloplasmin may decrease (as low as 20 mg/dl) along with the decrease in other proteins. The urine copper excretion is helpful, provided that the collection is done in a copper-free vessel. Elevated levels imply long-term excessive copper accumula-

FIG. 4. The liver in α-1-antitrypsin deficiency: The PAS diastase digested stain shows typical rose-colored bead-like inclusions in the periportal hepatocytes.
tion (this occurs in any chronic cholestatic state, as well as in Wilson's). Finally, slit
lap examination of the eye by an ophthalmologist is crucial to rule out the presence
of Kayser-Fleischer rings. Although liver disease can occur in the absence of KF
rings, this is unusual.

The treatment of Wilson's disease is copper chelation, usually with D-penicillamine. Patients who present with acute hepatic failure are often beyond salvage,
however.

Circulatory

Major disruption in the hepatic circulation can result in acute hepatic necrosis,
although this is rarely associated with true hepatic failure. Circulatory failure with
severe hypotension, as in hemorrhagic shock, septic shock, or cardiac arrhythmias,
can result in massive hepatic necrosis, with very high (> 10,000 units) SGOT values,
and occasionally transient hepatic dysfunction (short-lived coagulopathy, low-level
elevation of bilirubin). This diagnosis will be suggested by the history and by the
SGOT level. Similarly, impedance of hepatic outflow, when severe, results in hepatic
failure, although this is usually chronic and invariably associated with ascites and
hepatomegaly. The diagnostic possibilities include Budd-Chiari syndrome, hepatic
veno-occlusive disease associated with radiation of the liver and radiomimetic drugs,
and long-standing right-sided congestive heart failure.

MANAGEMENT OF ACUTE HEPATIC FAILURE

Diagnosing the correct cause of acute hepatic failure is important especially as
some forms are iatrogenic and others have specific therapies. But after all diagnostic
maneuvers have been exhausted, a large residue of cases of unknown etiology will
persist. The clinician should remember that, for the most part, the management of
all forms of acute hepatic failure, regardless of etiology, is the same: support the pa-
tient until the liver regenerates (Table 7).

This support should be the most maximal, the most anticipatory, that the inten-
sive care unit can provide. The liver always has potential for regeneration, so the
physician can never "give up" on the patient with acute hepatic failure. The best sup-
portive care is provided by clinicians who are thoroughly versed in the complications
of acute hepatic failure and who thereby anticipate them (Table 8).

"Complications" of the Acute Hepatic Failure

Hepatic Coma [53] By definition, hepatic coma is present in all cases of acute
hepatic failure. The initial stage of coma may be agitation or a change in person-
ality. Treating this stage with sedatives will result in deepening coma, and narcotics
and other CNS depressants must be avoided in acute hepatic failure. Other precipitants of hepatic coma (see below) include infection, hemorrhage into the GI
tract, hypokalemia, azotemia, rapid shifts in intravascular volume, and excessive
protein ingestion. Each of these precipitants should be looked for in a patient with
coma and corrected if possible. Therapy itself is aimed at lowering blood ammonia,
which may not be the "cause" of hepatic coma, but which serves as a useful index of
it. This is done by cleansing the bowel with cathartics or enemas and by keeping
bowel function good, two to three stools per day. This rate of catharsis can be
achieved with lactulose, which also changes the gut flora and diminishes production
of ammonia in the colon. The initial dose is 1 cc/kg given by mouth and repeated
every six to eight hours, titrating to a daily stool count of two to three. Diarrhea,
TABLE 7
Guidelines to the Management of Acute Hepatic Failure

| General                  | Intensive Care Unit                                                                 |
|--------------------------|-------------------------------------------------------------------------------------|
|                          | Monitor I and O, vital signs, weight, stool guaiacs, electrolytes in urine and blood |
|                          | Intubate early for control of airway                                                |
|                          | Central venous pressure or Swan-Ganz catheter for measuring central pressure if     |
|                          | indicated                                                                          |
| Intake                   | Restrict sodium both IV and PO as required                                          |
|                          | Replace volume as needed with albumin or fresh frozen plasma                        |
|                          | Restrict protein as required                                                       |
| Medications              | No narcotics or sedatives                                                          |
|                          | For coma: Lactulose 1.0 cc/kg q 6 hours as starting dose, titrate to 2-3 stools/day  |
|                          | or neomycin 25 mg/kg q 8 hours as starting dose + a cathartic for 2-3 stools/day     |
|                          | For ascites and edema: Best therapy is salt restriction and no medication           |
|                          | During recovery for chronic ascites: Spironolactone (dose 1-2 mg/kg/day); increase  |
|                          | at 3-5 day intervals                                                               |
| Nutrition                | Use the oral route if possible                                                     |
|                          | High carbohydrate intake                                                          |
|                          | Give as much protein as tolerated                                                  |
|                          | Of questionable value as protein supplement = special amino acid mixtures           |

with its attendant hypokalemia, is to be avoided. Lactulose may also be administered as a high-retention enema (50:50 mixture of tap water and lactulose). Neomycin, the poorly absorbed antibiotic, also changes gut flora and diminishes colonic ammonia production. It can be used as an alternative to lactulose (some patients develop nausea, cramps, and abdominal bloating on lactulose) but must be used in conjunction with a cathartic, such as magnesium citrate or milk of magnesia.

Protein metabolism (and catabolism) is important in hepatic coma. Protein intake should be restricted and added back slowly. Protein is crucial to hepatic regeneration, however, so starvation is to be avoided. Protein intake should be titrated against clinical signs of hepatic coma and blood ammonia levels. The patient should receive as much protein as he can tolerate. Protein ingestion plus lactulose is preferable to no protein ingestion and no lactulose.

TABLE 8
“Complications” to Anticipate in Acute Hepatic Failure

| Hepatic coma           |
|------------------------|
| Coagulopathy           |
| Ascites and edema      |
| Electrolyte imbalance  |
| Hypoglycemia           |
| Infection: Spontaneous |
| bacterial peritonitis,  |
| pneumonia              |
| Renal failure          |
| Cerebral edema         |
| Pancreatitis           |
Special amino acid mixtures designed to reverse the amino acid profile in chronic encephalopathy have been reported to reverse chronic coma. When given either intravenously or by mouth, these have not been shown to be effective in acute hepatic failure and their use in many situations has been questioned. Nevertheless, the mixture is commercially available (as “Hepatic-Aid”) and may have a place in the long-term management of hepatic coma. It should be reserved for patients who are protein-intolerant. It may be useful as a protein supplement in chronically encephalopathic patients who are protein-malnourished.

Coagulopathy An elevation in the prothrombin time is present by definition in acute hepatic failure. All patients should be given a trial of parenteral (not oral) aquamephyton, usually in a dose in children of 1 mg intramuscularly or intravenously repeated daily for three days. Patients with chronic cholestasis, and hypoprothrombinemia on the basis of malabsorption of Vitamin K1, will respond promptly, i.e., within 12 hours. Patients with acute hepatic failure will show little or no change in the prothrombin time. If they show a marked change, the diagnosis should be questioned.

Low-grade DIC, with prolonged PT, PTT and TT, lowered fibrinogen and platelet counts, and presence of fibrin split products, is common in acute hepatic failure. It requires no specific therapy (i.e., no heparin) unless diffuse bleeding is present. If this occurs, it should be treated with infusions of fresh frozen plasma, although it is almost impossible to correct the coagulopathy completely, regardless of how much fresh frozen plasma is used. Severe thrombocytopenia is rare, but may be treated with infusions of platelets. Severe DIC is unusual in uncomplicated acute hepatic failure. When it occurs, it suggests sepsis, which should be ruled out.

Bleeding Gastrointestinal hemorrhage is very common in acute hepatic failure. It should be guarded against by avoiding large, stiff nasogastric tubes, and by placing the patient on a specific regimen to decrease gastric acid. Such a regimen includes antacids and, in most institutions, prophylactic cimetidine, which has been shown to diminish bleeding in acute hepatic failure [54]. If bleeding occurs, efforts to correct the coagulopathy with fresh frozen plasma should be made, and the GI tract emptied of blood with cathartics and enemas as quickly as possible. Persistent massive bleeding must be evaluated using the traditional tools (arteriography, endoscopy). Varices can occur in acute hepatitis and may be the source of bleeding. Treatment of variceal bleeding in the setting of acute hepatic failure is limited to the use of vasoactive drugs (vasopressin) to decrease portal pressure. The inexperienced clinician will often contribute to the problem by over-transfusing the patient, thereby raising his intravascular volume and the pressure in his varices. A hematocrit of 30 to 35 is expected in acute hepatic failure and should not be exceeded. Management of this problem is aided by an accurate measure of central pressure, using either a CVP line or a Swan-Ganz catheter. Surgery carries a high risk in the patient with acute hepatic failure and should be avoided. Varices may be transient and shunt surgery is unwarranted in this setting.

In the face of severe coagulopathy, bleeding at sites other than the gastrointestinal tract may also occur. Intracranial hemorrhage is a rare but dreaded complication and should be considered in any patient with acute hepatic failure who has an abrupt change in level of consciousness.

Ascites This is a common complication of acute hepatic failure and is much more difficult to treat, once it has occurred, than it is to prevent. Sodium retention is to be expected in this setting. The urine sodium excretion reflects this, and in patients who are euvoletic (as indicated by normal heart rate, blood pressure, and
urine output and by normal central pressure measured by CVP or Swan-Ganz), the urine sodium is often inappropriately low. In this setting, sodium intake should be restricted before the onset of ascites and edema. Many of these patients will be moderately hyponatremic (125–135 mEq/L) as a reflection of hemodilution. Despite this, usually they will require no intravenous salt and will still maintain normal serum sodium concentrations. Once edema and ascites occur, thereby documenting total body sodium excess, no further sodium should be administered. Salt restriction extends to oral intake also, and these patients should be on a no-salt-added diet initially, with more strict salt restriction if the urine sodium is low. In the patient with acute hepatic failure, if repletion of serum sodium is necessary, this is best achieved using fluids with high oncotic pressure such as albumin. Most hospital pharmacies now dispense salt-poor albumin only, with a sodium content of 0.5 mEq/g protein. This is much less sodium than is present in the next best choice for intravenous replacement, namely fresh frozen plasma, with a sodium content of 2.8 mEq/g protein.

Once ascites has accumulated, the clinician should be slow to treat it in the setting of acute hepatic failure, as almost any treatment will worsen hepatic coma. Specifically, brisk diuresis, with abrupt shifts in intravascular volume and hypokalemia, will almost invariably precipitate coma. Ascites alone is not dangerous, except as a potential source for infection, and should probably only be treated, in the setting of acute hepatic failure, if respiratory embarrassment occurs. In this setting, the best management is ginger paracentesis of small volumes, following carefully the central pressure and replacing volume as required with albumin.

During recovery from acute hepatic failure, ascites may require therapy if salt restriction alone does not suffice. The single best diuretic is spironolactone, which works slowly and prevents hypokalemia. Even small doses of this drug in the acutely ill patient may result in azotemia and the “hepato-renal” syndrome, however, so it must be monitored closely. Therapy should be begun with low doses, 1–2 mg/kg/day. If, after four days, the BUN and potassium are stable and the patient has not lost weight, then the dose should be doubled and the tests repeated. This schedule of slow increases in dosage may be followed until a gentle diuresis is achieved. The urine sodium value is useful to demonstrate the dose which provides a natriuresis. Spironolactone is a long-acting drug, and it should be stopped, not decreased, if azotemia is noted. When the ascites has diminished, the drug should be tapered off as promptly as is feasible.

Electrolyte Imbalance Hypokalemia is common in acute hepatic failure and should be avoided because it causes an increase in renal ammonia production [55]. Potassium supplements should be given to bring the level to 4.0 mEq/L or greater. Patients on spironolactone may become hyperkalemic and should not receive potassium on any regular basis.

Hyponatremia is also common and probably reflects hemodilution in response to the hypoalbuminemia of acute hepatic failure. Values of greater than 125 mEq/L require no specific therapy. Below the level, free water restriction should be implemented. Water restriction is not necessary in treating acute hepatic failure except in the setting of hyponatremia. Giving saline-containing solutions will only increase the body’s salt overload and aggravate edema and ascites.

Alkalosis is common in hepatic coma, presumably resulting from central hyperventilation. Usually these patients have pH values about 7.45, PCO₂ values in the range of 20–30 mmHg, and high bicarbonate values. The central hyperventila-
tion is a protective mechanism which decreases cerebral edema and should not be circumvented by adding dead space to the respirator or by infusing acidifying solutions.

Hypoglycemia This is a common complication of any acute hepatic injury. Blood glucose values should be obtained frequently, perhaps using frequent dextrostick determinations if indicated. Hypoglycemia may mimic hepatic coma. Some patients will require frequent bolus infusions of concentrated glucose, along with maintenance 10 percent dextrose infusions.

Infection Sepsis is a common problem in any acutely ill, hospitalized patient and is frequently the precipitating cause of hepatic coma in acute hepatic failure. In patients with liver failure, the usual signs of sepsis, such as fever and leucocytosis, may be blunted or absent. Sepsis should be ruled out in any patient with acute hepatic failure who worsens suddenly, particularly if hepatic coma or the hepato-renal syndrome develops.

In patients with ascites, spontaneous bacterial peritonitis is common but may be quite inapparent, without obvious ileus or abdominal tenderness [56]. All patients with ascites who become febrile, hypotensive, oliguric, or comatose should be evaluated for spontaneous bacterial peritonitis. A paracentesis is performed, usually in the linea alba one-third of the way below the umbilicus over an empty bladder, using a small-gauge needle, and a small volume (30 cc) of fluid removed. The fluid is sent for both aerobic and anaerobic cultures, cell count and differential, protein determination, and other studies, such as amylase. If the differential cell count contains more than 500 polymorphonucleocytes/ml, then peritonitis should be assumed to be present, and it should be treated vigorously while results of both blood and peritoneal cultures are awaited.

The other major source of infection in patients with hepatic coma is the lungs. This can be minimized by good supportive care, including early intubation for control of the airway and good pulmonary toilet as well as postural drainage.

Antibiotic use in the jaundiced patient with acute hepatic failure is not without risk. Such patients seem to be particularly susceptible to the nephrotoxic effects of aminoglycoside drugs such as gentamicin, despite maintenance of normal blood levels.

Renal Failure This dreaded complication of acute hepatic failure has been dubbed the “hepato-renal syndrome” and, when fully established, is almost invariably fatal [57,58]. By definition, this is an oliguric form of renal failure and is characterized by a urine sodium concentration of less than 10 mEq/L in a euvoletic patient. The cause of this syndrome is not known but is hotly debated. Functionally, patients with acute hepatic failure behave as if they have depletion of the intravascular volume, rendering them particularly sensitive to any further decrease, such as that associated with septic shock, diuresis, or GI hemorrhage. Any of these events can push these patients over into progressive renal failure. The kidney in such patients is normal histologically and can function normally when transplanted into another patient.

The best treatment for this syndrome is anticipation and prevention. Careful watch of the urine output on an every two- to four-hour basis must be maintained. If oliguria occurs, the central filling pressure must be promptly assessed by CVP or Swan-Ganz line. If the pressure is low, volume must be replenished promptly with high oncotic fluids (e.g., albumin, FFP). Time is of the essence in this setting, and complete renal shutdown may occur within 12-24 hours of the precipitating event.
If complete renal failure occurs, then the patient must be maintained long enough to allow hepatic regeneration. This can be achieved using either hemo or peritoneal dialysis. Either is clearly a last-ditch effort in the patient with acute hepatic failure.

Cerebral Edema  Studies have shown that this is a common cause of death in acute hepatic failure [59]. Many pediatric intensive care units have gained sophistication in managing this problem in patients with Reye's syndrome. Intracranial or intracerebral monitoring is usually not part of the care of patients with acute hepatic failure but may be, provided it is not contraindicated by severe coagulopathy. Cerebral edema should not be precipitated by artificially raising the pCO₂ or by excessively volume-loading the patient.

Pancreatitis  Acute pancreatitis occurs frequently in acute hepatic failure [60]. Its cause is unknown. This complication should be suspected in any patient with protracted vomiting, ileus, or bloating, although it may be clinically inapparent as well. Serum amylase and lipase determinations should be done frequently if this complication is suspected. The treatment is identical to that of acute pancreatitis in other settings, specifically gut rest. It may be necessary to support the patient with parenteral nutrition while the pancreatitis resolves.

Miscellaneous Complications  The respiratory distress syndrome may accompany any acute major illness and is especially common as a complication of acute pancreatitis. Good respiratory toilet, early intubation, and monitoring of arterial blood gases should be part of the management of all patients with acute hepatic failure. Wide fluctuation in body temperature may occur in acute hepatic failure presumably because of a failure in central regulation. Either profound hypo- or hyperthermia is an ominous prognostic sign in acute hepatic failure.

Treatment for the Liver  

The actual mechanism by which most diseases cause hepatic injury is unknown. As a result, only in a minority of cases of acute hepatic failure is specific therapy available to stop or correct the hepatocellular destruction. Specific therapy depends, of course, on identifying the causative agent.

Stopping the Injury  

Drugs  The mechanism by which acetaminophen injures the liver has been well established—namely, one of its metabolites is detoxified in the liver by conjugation with the sulphydryl-containing compound glutathione. When an overdose is ingested, hepatic glutathione stores are rapidly depleted, and the toxic metabolite becomes free to covalently bind to structural elements in the hepatocyte, thereby causing injury. Therapy for acetaminophen poisoning is directed at replenishing hepatic glutathione stores. This is most easily accomplished by giving Mucomyst (n-acetyl cysteine). But this antidote must be given before the covalent binding occurs in order to prevent the injury—it is ineffective once necrosis occurs. The currently recommended regimen is as follows [33]:

1. Gastric aspiration and lavage
2. Acetylcysteine by mouth: 140 mg/kg as a loading dose, 70 mg/kg every four hours for a total of 17 doses

If the patient vomits persistently, then the acetylcysteine should be given by duodenal intubation.

Remember, in acetaminophen poisoning the injury is not immediate, but peaks three days after the ingestion. The antidote must be given as soon as possible after ingestion in order to prevent injury. Serial blood levels of acetaminophen obtained
early in the course can be used to calculate the plasma half-life, which correlates well with the degree of injury. As a rule, however, all patients who have ingested overdoses of acetaminophen should be treated early, as once the degree of liver damage becomes evident, it is too late.

If the cause of acute hepatic failure is a prescribed drug (e.g., diphenylhydantoin), the drug must be stopped. Surprisingly often the physician forgets to establish what medications the patient is taking or is unaware that the medication can cause liver disease. In general, all medications should be stopped in patients with acute hepatic failure. Also surprisingly, often the damage will progress and liver failure worsen, despite stopping the offending agent.

**Metabolic** Several of the genetic causes of acute hepatic failure can be treated by removing the substance whose metabolism is blocked. Specifically, the treatment for galactosemia or hereditary fructose intolerance is to remove the offending sugar from the diet. When Wilson's disease presents as acute hepatic failure, most clinicians will begin copper chelation with D-penacillamine, despite the fact that this therapy is ineffective in the pre-terminal patient, as a rule.

**Steroids** Corticosteroid therapy was advocated for years for the treatment of acute hepatic failure of viral or unknown etiology. This therapy is very effective in certain forms of chronic active hepatitis, but has been shown to be of no value in the treatment of fulminant hepatitis [61]. Some would still recommend the use of steroids in drug-induced fulminant hepatitis, although no data exist to suggest any benefit in this setting.

**Other Therapies: In the Future** Specific measures, such as interferon or antiviral agents, have been tested in limited situations already and, although not yet suitable for clinical use, may be successful in treating fulminant viral hepatitis. **In the Past** Outmoded therapies which have been discarded, for the most part, include attempts to remove unknown poisons using exchange transfusion, cross-circulation with another primate, dialysis, or hemoperfusion using a variety of exchange columns. A multicenter trial demonstrated that hepatitis B hyperimmune globulin was ineffective in the treatment of acute hepatitis B.

**Stimulating Regeneration** If we are usually unable to shut off the injury to the liver, perhaps we could be more successful in turning on regeneration of new, healthy liver. This organ is, after all, one of the few which can regenerate normal tissue. The field of stimulating hepatic regeneration remains in its infancy, however, as we know relatively little about the modulations of normal hepatic growth. Certain facts are known and will allow us to speculate about hepatic regeneration and its control [62].

Experiments in both rats and dogs have demonstrated a “hepatotrophic” effect of portal blood, as contrasted with blood originating in either the arterial or systemic venous systems [63]. Regeneration of the liver is enhanced in resected lobes receiving portal blood [64]. These observations suggest the existence in this blood of substances which enhance regeneration, so-called “portal vein goodies,” which may, perhaps, be insulin and/or glucagon. Both have been studied as possible stimulators of hepatic regeneration. In experimental fulminant hepatitis, infused insulin and glucagon have been demonstrated to promote hepatic recovery [65]. In addition, some substance within the regenerating liver seems to stimulate regeneration. This material, so-called hepatic regeneration stimulator substance, is also present in the livers of weaning rats and enhances regeneration when injected into animals which have undergone partial hepatectomy [66].

Clearly, amino acid building blocks are also required to repair liver damage. But
patients with acute hepatic failure have encephalopathy and protein intolerance. Given this background, it is clear that nutrition may play an important role in the management of patients with acute hepatic failure. Practically, the clinician should keep the blood sugar level high. Carbohydrates administered by mouth (thus reaching the liver via the portal vein) are the best stimulants to endogenous insulin and glucagon. If the PO route cannot be used because the patient refuses to eat, cannot tolerate a nasogastric tube, or because of pancreatitis and ileus, high concentrations of glucose should be administered via a central intravenous line, along with insulin if necessary. In addition, the patient with acute hepatic failure should be given as much protein as he can tolerate, again preferably by mouth. If standard food or protein mixtures exacerbate hyperammonemia, then special amino acid mixtures may be tried, although without proof of benefit. Again, if the oral route is contraindicated for one or another reason, then intravenous amino acids may be given, as long as care is taken to avoid worsening hepatic coma.

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