Part III: Gastroenterological Disorders

Chapter 31: Acute Gastrointestinal Bleeding

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Acute bleeding from the gastrointestinal tract is a serious and potentially lethal condition. The bleeding may be upper gastrointestinal (including variceal) or lower gastrointestinal. Bleeding from peptic ulceration is continuous or recurrent in 20% of patients, with a 10% mortality. The risk increases with advanced age or with associated cardiovascular or malignant disease. Variceal bleeding contributes to the death of over one-third of all patients with cirrhosis, half of whom die as a consequence of their first bleed. Continuous, massive colonic bleeding in the elderly has a mortality rate of over 15%.

Upper Gastrointestinal Bleeding

Clinical Presentation

Haematemesis, bloody gastric aspirate or melaena, usually indicate bleeding from the upper gastrointestinal tract. The absence of blood in gastric aspirate does not eliminate significant bleeding. Haematemesis without melaena may occur with oesophageal lesions. Melaena infrequently originates from right sided colonic bleeding. Massive upper gastrointestinal bleeding often gives "maroon" melaena. Rarely, bright blood alone may be passed.

The patient's history may suggest a possible source of bleeding (i.e. forceful vomiting in Mallory Weiss syndrome, or previous gastric surgery in stomal ulceration) but it is unreliable. Bleeding may occur without prior dyspepsia in 10% of patients with peptic ulceration. Salicylate ingestion is as likely to be associated with bleeding from chronic ulceration as from erosions. Upper gastrointestinal bleeding in cirrhotics has a non variceal origin in over 50% of cases.

Management - Non Variceal Bleeding

Once the history of bleeding is clearly established, the severity of hypovolaemia must be determined. This assessment and subsequent resuscitation have immediate priority.

1. Resuscitation

Blood is taken for cross-matching. Plasma expanders are given until whole blood is available. Vital signs (pulse, blood, pressure, respiration and temperature) are recorded together with hourly urine output. Baseline haematological and biochemical parameters are measured. Serial haematocrit may be useful in assessing blood requirements once haemodilution is complete.

Central venous pressure (CVP) measurements are a helpful guide to the rate and magnitude of volume replacement, particularly in the elderly. Pulmonary capillary wedge pressure measurements may be indicated.

Following adequate resuscitation, management is directed towards identifying the high risk patient and the high risk lesion, i.e. those most likely to benefit from early surgical or endoscopic control of bleeding.

2. The High Risk Patient

The mortality from gastrointestinal bleeding is significantly increased where the bleeding is massive or recurrent (usually indicative of an arterial or variceal source) or where the patient's ability to tolerate hypovolaemic shock or major surgery is severely compromised (Table 1).

Table 1. Poor Prognostic Factors in Gastrointestinal Bleeding

Age greater than 60 years.
Serious associated disease - i.e. ischaemic heart disease, respiratory or renal insufficiency, hepatic failure, malignancy, and coagulopathy.
Shock.
High transfusion requirement (greater than 5 units whole blood).
Recurrent haematemesis and melaena.

3. The High Risk Lesion

Diagnosis

(a) Endoscopy

Early endoscopic examination allows precise identification of the site and nature of the bleeding, and provides valuable prognostic information. It should not be carried out until the patient is adequately resuscitated. The use of an endoscope overtube facilitates the removal of gastric contents and minimizes the risk of aspiration. Massive bleeding infrequently prevents adequate examination and routine gastric lavage prior to endoscopy is unnecessary. The value of ised saline lavage in controlling bleeding is unproven.

Endoscopy performed within 24-48 hours of the bleeding episode reveals an actual or potential site of bleeding in the majority of patients - 15-30% of all lesions are actively bleeding at the time of endoscopy. Chronic ulcers may have signs of recent haemorrhage (overlying clot, an exposed artery or a solitary black spot). The endoscopic features indicate the likely outcome. Active arterial bleeding is frequently associated with continued or recurrent bleeding and, without intervention, has a high mortality. The rebleeding rates from ulcers with a visible vessel is 50-65%; with a black spot 8-10%; and without any signs of recent haemorrhage less than 2%. Ulcers on the posterior duodenal wall and high on the lesser curve of the stomach are almost twice as likely to rebleed as ulcers elsewhere.

Endoscopy may induce serious hypoxaemia in patients with significant cardiorespiratory disease. Continuous monitoring of oxygen saturation with a pulse oximeter, and administration of oxygen by nasal cannulae may be prudent.

(b) Radiology

(i) Barium meal

The standard barium meal examination is significantly less accurate than endoscopy in the diagnosis of upper gastrointestinal lesions. Superficial mucosal lesions (i.e. erosions) can be demonstrated by double contrast studies, but the exact site or nature of bleeding cannot be determined. Barium studies should not be carried out if early endoscopy or angiography are anticipated.

(ii) Angiography

Mesenteric angiography may be of value if the cause of bleeding has not been established by endoscopy. Selective catheterization of the coeliac axis and superior mesenteric artery are required. A bleeding point is identified by contrast extravasation. This occurs only when the bleeding rate exceed 0.5-1.0 mL/min. This technique is of value for arterial bleeding from solitary lesions such as chronic ulcers or mucosal tears. It does not exclude bleeding from diffuse mucosal lesions or varices.

4. Treatment

(a) H2 Antagonists

The H2 receptor antagonists (cimetidine, ranitidine, and famotidine) facilitate ulcer healing by reducing gastric acid output, and should be commenced once the diagnosis is established. They do not prevent early ulcer rebleeding. Oral administration is satisfactory in most patients. The intravenous route should be reserved for those patients with frequent vomiting, impaired gastric emptying (i.e. pyloric stenosis) or an ileus.

The suppression of gastric acid secretion in the critically ill patient by antacids or H2 receptor antagonists may prevent the development of subsequent bleeding from acute mucosal lesions (erosions or ulcers). Both should be given in a dose sufficient to maintain gastric pH above 4.0. If antacid is given by nasogastric tube, care must be taken to prevent mucosal suction trauma.

(b) Control of Bleeding

Bleeding from chronic ulcers ceases spontaneously in 80% of patients and does not recur. Early intervention for control of active bleeding or prevention of rebleeding is indicated in high risk lesions (i.e. arterial bleeding) or in the high risk patient with a visible vessel.

(i) Surgery

Surgical treatment is usually reserved for continued or recurrent bleeding from chronic lesions. With exsanguinating haemorrhage it should not be delayed by fruitless attempts at diagnostic endoscopy. Acute lesions sucha as a Mallory Weiss tear may bleed massively but only rarely require surgical intervention. The type of surgery (vagotomy and partial gastrectomy) depends on the nature and site of the lesion and the surgeon's preference.

Surgery based on the conventional indications - massive bleeding, recurrent bleeding in hospital or complications such as perforation, still has a substantial mortality rate, particularly in the elderly and frail. The decision to operate should be made early in the high risk patient with endoscopic evidence of a high risk lesion. Non-operative methods of haemostasis utilizing endoscopy are available and should be considered initially in the treatment of all high risk patients.

(ii) Endoscopic Haemostasis

1. Thermal Methods

Electrocoagulation: monopolar and bipolar diathermy (BICAP) with endoscopic probes can induce haemostasis in most cases. Control of brisk arterial bleeding is more difficult. Local tissue damage is unpredictable and perforation has been reported. The injection of water through the tip of the electrode prevents tissue adherence, and may limit the extent of coagulation.

Heater probe: an aluminium, non-stick, Teflon-coated probe, with the tip heated by an inner coil has been developed for endoscopic use. Early clinical experience indicates that it can control arterial bleeding from peptic ulceration with a significant reduction in rebleeding.

Laser photocoagulation: laser light can be transmitted endoscopically through a quartz fibre and directed at a bleeding lesion. Both argon-ion and neodymium YAG lasers are suitable for this purpose and will effectively stop ulcer bleeding in 80-90% of cases. Rebleeding does occur but the incidence of perforation is less than 1%. Controlled trials indicate that laser photocoagulation can significantly reduce the incidence of arterial rebleeding from ulcers and the need for emergency surgery.

2. Chemical Methods

The injection of sclerosants (adrenaline and alcohol) directly into the base of an ulcer adjacent to the visible vessel can control arterial bleeding in over 90% of cases. It significantly reduces the risk of rebleeding and the need for emergency surgery. It is a simple, safe and effective technique which is now widely available.

(iii) Angiographic Haemostasis

1. Vasoconstrictor Infusion

The selective infusion of vasopresin into a bleeding splanchnic artery reduces blood flow and promotes blood clot formation. Initial control of bleeding may be achieved in many cases. The hazards are minimal with short-term infusions but the rebleeding rate is high.

2. Embolization

A bleeding vessel may be occluded by embolization with gel foam or other materials through the angiographic catheter. Super-selective catheterization of the bleeding artery is

essential anhd there is a risk of tissue infarction. This procedure should be reserved for those patients who pose an unacceptably high surgical risk (i.e. blood dyscrasia, or recent myocardial infarction).

Management - Variceal Bleeding

The outcome of variceal bleeding depends on the severity of the haemorrhage and the degree of liver dysfunction. Adverse prognostic factors include active bleeding at endoscopy, a transfusion requirements of two litres or more, ascites, encephalopathy and impaired liver function tests (Child's grade C).

1. Resuscitation and Diagnosis

Resuscitation with whole blood should be initiated as soon as possible. The administration of fresh frozen plasma or prothrombin concentrates is indicated if a significant clotting abnormality is demonstrated. Measures to minimize encephalopathy (i.e. colonic lavage, oral neomycin and lactulose) are introduced once the bleeding has been controlled. Confirmation of the exact site of bleeding should be established by early upper gastrointestinal endoscopy. The bleeding is from fundal varices in 10% of cases. An alternative, non variceal source of bleeding (i.e. erosion or chronic ulceration) may be found in half the patients with oesophageal varices.

2. Treatment

(a) Variceal Sclerosis

At oesophagoscopy, a sclerosant such as ethanolamine or sodium tetradecyl sulphate, can be injected into the varix or the adjacent submucosa. This can be carried out under light sedation at the initial endoscopy. When the varix is actively bleeding, the technique is facilitated by simultaneous balloon compression of varices at the cardia (i.e. with a Linton-Nachlas tube). Control of bleeding is achieved in 90% of patients. Repeated sclerosant injections at fortnightly intervals leads to progressive variceal obliteration, with a significant reduction in rebleeding and improved long-term survival. Retrosternal pain and fever are common immediately after sclerosis. Early mucosal ulceration and late oesophageal strictures may occur after treatment.

(b) Vasopressin Infusion

The administration of vasopressin lowers portal venous pressure by splanchnic arterial constriction. An intravenous infusion of 0.2-04 units/min temporarily controls variceal bleeding in 60% of cases. Rebleeding is frequent and intra-arterial infusions confer no therapeutic advantage. Side effects include hypertension, colic and intestinal hurry. Severe ischaemic necrosis of skin, heart and intestine may occur. These effects may be significantly reduced by the simultaneous administration of nitroglycerine. Triglycyl-lysine vasopressin, a slow release depot form of vasopressin, may be just as effective and have fewer side effects.

Other drugs such as propranolol and somatostatin lower portal pressure, but a useful role in the emergency treatment of variceal bleeding has not been established.

(c) Balloon Tamponade

Variceal bleeding can be controlled by balloon compression either at the cardia or within the oesophageal lumen. A number of devices are available for this purpose. The Linton-Nachlas tube has a single balloon which is inflated in the gastric fundus. The Sengstaken-Blakemore tube incorporates an additional oesophageal balloon. A modification, the four lumen Minnesota tube allows aspiration of gastric and oesophageal contents.

Tamponade tubes are difficult to introduce and require meticulous supervision while inflated. The balloons are checked for patency and leaks before insertion. Use of a stiffening wire aids the passage of the tube into the stomach. The gastric balloon is inflated with 150-200 mL of air and is drawn up to the cardia by gentle traction. The tube is firmly secured by taping to the face, and the oesophageal balloon is inflated with air to 30-40 mmHg (4.5-5.4 kPa) using a sphygmomanometer. The lumen is clamped and the position of the balloon checked radiologically.

Balloon tamponade achieves initial control of bleeding in most cases, but rebleeding is common. The oesophageal balloon is deflated after 24 hours and variceal sclerosis may then be possible. Tamponade is poorly tolerated and should be reserved for bleeding not controlled by sclerosis or vasopressin. Complications are common and its use should be confined to Intensive Care areas. Oesophageal rupture can be avoided by careful monitoring of balloon position and pressure. Continuous oesophageal suction reduces the risk of pulmonary aspiration. Mucosal ulceration is minimized by limiting the duration of tamponade to 24 hours.

(d) Transhepatic Variceal Obliteration

Varices can be outlined by percutaneous transhepatic portography. Selective catheterization of the left and short gastric veins enables variceal embolization with a preparation such as gel foam, sclerosants or acrylate glue. Initial hemostasis is achieved in 80% of cases but early and late rebleeding is common. Complications such as portal vein thrombosis are potentially lethal.

(e) Surgery

Emergency surgical procedures can effectively control variceal bleeding. The two procedures most commonly used are trans-oesophageal ligation and a porto-caval shunt. Oesophageal trans-section (using a stapling gun) by the abdominal approach has a low operative morality (10-20%) and a low rebleeding rate. The incidence of portosystemic encephalopathy after emergency porto-caval shunt is high and long-term survival is not improved. Selective decompression procedures (i.e. Warren shunts) reduce the risk of encephalopathy but are technically more difficult and have a high operative mortality.

Lower Gastrointestinal Bleeding

Clinical Presentation

Massive haemorrhage from the colon invariably presents with bright rectal bleeding. Caecal and small intestinal bleeding may result in "maroon" melaena. If there is any doubt about the lower intestinal origin of bleeding (i.e. bright rectal bleeding and melaena), colonic investigation should be preceded by upper gastrointestinal endoscopy. Massive bleeding with a normal blood urea is unlikely to be from the upper gastrointestinal tract.

The commonest causes of massive colonic bleeding in the elderly, i.e. angiodysplasia, diverticular disease (both often occurring on the right side) and polyps, frequently have no preceding symptoms. Life-threatening haemorrhage is an uncommon event in the natural history of colonic carcinoma and inflammatory bowel disease.

Management

Initial management is again directed to resuscitation, followed by diagnosis of the source, and specific therapy, as indicated.

1. Diagnosis

(a) Endoscopy

Sigmoidoscopy following phosphate enemas is carried out initially to exclude a low colonic lesion. If this is unrevealing, fibreoptic colonoscopy to the caecun is often possible. The use of intestinal saline lavage, mannitol or "Golytely" allows rapid preparation of the bowel. Dilute blood in the lumen is easily aspirated and visualization is usually adequate. An actual or potential bleeding site can be identified in over 60% of cases. Bleeding from vascular anomalies (i.e. angiodysplasia), polyps, carcinoma or inflammatory bowel disease is easily recognized. An adherent clot or an exposed vessel may pinpoint diverticular bleeding.

(b) Isotope Scanning

If the source of bleeding is not demonstrated at colonoscopy, an abdominal scintiscan is carried out after the intravenous administration of radio-labelled technetium. Extravasated isotope can be recognized with a bleeding rate as low as 0.1 mL/min. A non-colonic site of bleeding may be suggested. Specific isotope uptake by parietal cells may outline a Meckel's diverticulum.

(c) Angiography

Selective mesenteric angiography is successful in identifying the source of massive lower gastrointestinal bleeding in up to 60% of cases. Bleeding can be detected at a rate of 0.5 mL/min or more. Failure is usually due to cessation of bleeding. Angiography is unlikely to be successful if the isotope scan is negative. Bleeding from a diverticulum gives rise to pooling of extravasated contrast. Angiodysplasia is recognized by an abnormal vascular pattern. If bleeding has ceased, investigation should start with colonoscopy, and be followed by a barium enema and small bowel series before considering angiography.

2. Treatment

Spontaneous cessation of bleeding from all sources is common. However, bleeding from angiodysplasic lesions tend to be recurrent.

Methods for controlling bleeding include:

(a) Endoscopy

Bleeding colonic polyps can be readily removed by polypectomy. Angiodysplasic lesions can be coagulated using diathermy, laser photocoagulation or alcohol sclerosis with a low risk of rebleeding.

(b) Angiography

Low dose infusion of vasopressin (0.1-0.2 units/min) into the inferior mesenteric artery will effectively stop both diverticular and angiodysplasic bleeding in over 7-% of cases.

(c) Surgery

Early surgery is the preferred treatment for massive lower gastrointestinal bleeding due to colonic carcinoma, colitis, Meckel's diverticulum, or small bowel tumours.

Emergency subtotal colectomy for bleeding diverticular disease or angiodysplasia has a significant mortality in the elderly. It should be reserved for continuing or recurrent haemorrhage not controlled by more conservative methods. Since bleeding is not uncommon from right-sided diverticula, the success of segmental colectomy depends on accurate endoscopic or angiographic diagnosis. Right hemicolectomy for angiodysplasic lesions can often be carried out as an elective procedure. Subtotal colectomy may be necessary when massive colonic bleeding continues in spite of normal mesenteric angiography.

Chapter 32: Acute Pancreatitis

J. Santamaria

Acute pancreatitis remains a relatively common disorder with a significant mortality. It may affect patients of all ages and often becomes a multi-system disorder requiring facilities within Intensive Care Units for optimal management.

Aetiology

Many conditions are known to cause acute pancreatitis (Table 1) but in most studies, these can be divided into four common categories:

1. biliary tract disease;

2. excessive alcohol ingestion over many years;

3. idiopathic; and

4. miscellaneous.

Biliary disease and alcohol count for 70% of cases. Although incidences vary from one location to another, biliary disease is more commonly reported in Britainj while alcohol predominates in American studies. Cases with no discernible cause (idiopathic) may account for up to 30% of some series. Several drugs are known to cause pancreatitis, and many others are implicated but without conclusive evidence.

Table 1. Aetiology of Acute Pancreatitis

A. Excess Alcohol Ingestion

B. Biliary Tract Disease

C. Idiopathic

D. Metabolic

1. Hyperlipaemia
2. Hyperparathyroidism
3. Diabetic ketoacidosis
4. Uraemia
5. Pregnancy
6. Post renal transplant

E. Mechanical Disorders

1. Post traumatis
2. Post operative
3. Post endoscopic retrograde cholangiopancreatography (ERCP)
4. Penetrating Peptic Ulcer
5. Duodenal Obstruction

F. Infections

1. Mumps, Epstein-Barr virus, mycoplasma, hepatitis, ascariasis

G. Vascular

1. Necrotizing vasculitis - Systemic lupus erythematosus (SLE), thrombotic thrombocytopenic purpura (TTP)
2. Atheroma, shock

H. Drugs

Definite

a. Azathioprine, thiazides, frusemide, tetracyclines, oestrogens, sulphonamides

2. Possible

b. Chlorthalidone, ethacrynic acid, procainamide, L-asparaginase, anticoagulants, propranolol, diazoxide, cimetidine, paracetamol, methyldopa

I. Toxins

1. Scorpion venom

J. Associations

1. Hypothermia, histocompatibility antigens, alpha 1 antitrypsin deficiency
2. Hereditary

Pathophysiology

As with many body systems, the pancreas reacts in a limited number of ways to an acute insult. The pancreas is rich in enzymes which have the potential to cause extensive tissue damage. Under normal circumstances, several mechanisms protect the pancreas from damage; they include containment within storage granules, potent enzyme inhibitors, and the production of enzymes in an inactive precursor form (zymogens). Inappropriate activation of these enzymes within the pancreas will lead to extensive damage by "autodigestion".

Although the proteolytic enzymes such as trypsin, chymotrypsin and elastase were initially considered to be the main destructive agents, there is increasing evidence that the lipolytic enzyme, phospholipase A2, may be more important. Furthermore, this enzyme has been implicated in extra-pancreatic complications.

Several mechanisms have been proposed to explain the initial processes by which autodigestion begins.

1. Duodenal Reflux

It is well established in animal models that reflux of duodenal contents into the pancreas will lead to acute pancreatitis but the evidence in humans is inconclusive.

2. Bile Reflux

Gallstones have been found in many patients with acute pancreatitis and reflux of biliary contents has been seen on cholangiography. However, impacted stones are rarely seen in autopsies of patients who die from acute pancreatitis.

3. Activation of the Complement System

4. Overstimulation of Secretions

This is an established initiating event in cases of scorpion stings (commonest cause of pancreatitis in the Caribbean) and in hyperparathyroidism.

The coincidental release of vasoactive substances such as bradykinin from the pancreas into the circulation, may explain the increased vascular permeability, hypotension, and organ dysfunction which accompany some episodes of acute pancreatitis.

Classification

The most commonly used classification relies upon a pathological description. Although the pancreas may exhibit a range of changes, two extreme patterns are described.

1. *Acute oedematous pancreatitis* results in a congested and swollen pancreas; this pathology is seen in patients with mild to moderate pancreatitis.

2. *Necrotizing pancreatitis*, on the other hand, causes severe inflammation with necrosis and haemorrhage. Fat necrosis may be seen in adjacent tissues and there is a tendency to suppuration. The whole gland is usually involved and mortality is increased.

Other classifications have attempted to differentiate acute pancreatitis from chronic relapsing pancreatitis. This separation is difficult and remains a retrospective classification with the documentation of chronic pancreatic insufficiency at least 4-6 weeks after the acute episode.

Investigations

1. Serum Amylase

A two or three fold elevation of serum amylase is usually diagnostic of acute pancreatitis but absolute levels do not correlate with severity or mortality. Levels rise within 2-3 hours and return to normal in 3-10 days. Quicker changes are seen in mild oedematous forms and severe necrotizing pancreatitis where enzyme levels diminish because of extensive damage to the gland. Unless levels are done early and frequently, rises in amylase may be missed. Serum levels may also rise in patients with perforated or infarcted bowel and in conditions affecting other organs which secrete amylase (i.e. salivary glands and ovaries). Although it is possible to separate the isoenzymes of amylase into pancreatic (P type) and other (S type), these tests are not routinely available.

2. Urinary Amylase

As 25% of the serum amylase is cleared by the kidney, elevated urinary levels are seen in pancreatitis. Such increases occur earlier and last longer than serum elevations. The ration of urinary amylase clearance to creatinine clearance (Cam/Ccr) is normally between 1-4%, but may be elevated in some patients with acute pancreatitis who exhibit normal serum amylase levels. However, the test is not sufficiently specific nor sensitive for routine usage.

3. Other Enzymes and Fluids

Serum lipase concentrations parallel those of serum amylase, but may remain higher for longer, and are not increased by extra-pancreatic disorders. Amylase levels within pleural

or ascitic fluid may be elevated in acute pancreatitis. Plasma trypsin-like immunoreactivity and phospholipase A2 increase, but are not routinely estimated.

4. Haematology

The white cell count is typically raised to 15-20 x 10^3 cells/microL with neutrophilia and left shift. Haemoglobin levels may increase if sufficient haemoconcentration occurs, or may decrease if there is bleeding from the gland.

5. Chemical Pathology

(i) Liver Function Tests

Transient elevations in serum bilirubin are seen in 10% of patients. Levels return to normal within 4 days. Concomitant increases in alkaline phosphatase and transaminases are also observed.

(ii) Glucose

Hyperglycaemia is observed with incidences varying from 25% to 75%. These rises have been attributed to decreased levels of circulating insulin and increased levels of glucagon, catecholamines and steroids.

(iii) Calcium and Magnesium

Serum calcium falls in 25% of patients. The change is usually due to concomitant hypoproteinaemia, although ionized levels of calcium may decrease possibly due to intraperitoneal saponification. Hypocalcaemia may occasionally require treatment. Hypomagnesaemia may also occur and is more common in alcohol induced pancreatitis.

(iv) Methaemalbumin

Methaemalbumin is formed when oxidized heme binds to albumin, and may be found with intraperitoneal haemorrhage, a feature of some patients with necrotizing pancreatitis. It is neither specific nor sensitive for pancreatitis.

6. Electrocardiography

Widespread ST-T wave changes may simulate acute myocardial ischaemia. Arrhythmias have been observed in pericarditis associated with pancreatitis.

7. Imaging

(i) Conventional Radiology

Many changes have been described but are not specific for pancreatitis. These include localized jejunal ileus, generalized small bowel ileus, colon cut-off sign or "sentinel loop" (from isolated peri-pancreatic dilatation) and duodenal distention. A swollen pancreas or

associated cyst/pseudocyst may displace the stomach anteriorly or widen the duodenal loop. These changes can be seen when a dye such as gastrografin is administered prior to plain erect and lateral abdominal radiographs.

(ii) Ultrasound

On abdominal ultrasonography, the pancreas is enlarged with decreased echogenicity. Definition of the gland is more difficult and it is not visualized in up to 40% of patients. Ultrasound is particularly useful in demonstrating collections such as abscesses, cysts or pseudocysts.

(iii) CT Scanning

In acute pancreatitis, the gland is often difficult to see and not visualized in 30%. However, this technique is most useful in demonstrating abscess or cyst formation.

(iv) Chest Radiography

Chest radiography may be abnormal in up to 40% of cases. An elevated left hemidiaphragm with pleural effusion, basal atelectasis or alveolar infiltrates may be noted.

Clinical Presentation

Symptoms

The patient may be any age. Alcoholic pancreatitis usually occurs in patients less than 40 years and males predominate. On the other hand, pancreatitis associated with biliary tract disorders occurs in middle to later life and a female to male ratio of 3:1 is usually described. There may be a history of heavy alcohol intake (usually more than 8 years duration) or previous biliary disorders. It is important to take a detailed drug history.

Pain comes on relatively quickly and is classically central in position radiating to the back and eased by sitting forward. Variations do occur with pain initially confined to the right upper quadrant or felt diffusely over the abdomen; isolated left upper quadrant pain is uncommon. Nausea and vomiting occur in 90% of cases.

Signs

On examination, the patient is usually agitated and restless with tenderness upon palpation of the epigastrium. A fever is often present but usually less than 39 °C. Occasionally, hypothermia may occur. Abnormal respiratory findings of basal wheezes or pleural effusions are seen in 10-20%. In the severe attack, the patient may be shocked with tachycardia and hypotension or in acute respiratory failure. Erythematous nodules from fat necrosis is evidenced by a gray discolouration in the flanks (Grey Turner sign) or in the umbilicus (Cullen's sign). The abdomen is usually distended due to an associated ileus or the presence of complications.

Acute pancreatitis may simulate other acute abdominal conditions and up to 20% of cases may be first diagnosed at laparotomy. Differential diagnoses include perforated viscus, cholecystis, bowel obstruction, vascular occlusions, renal colic, myocardial infarction, pneumonia and diabetic ketoacidosis.

Complications

Local

Local changes contribute to the mortality of pancreatitis. A phlegmon or swelling of the pancreas may be seen on ultrasound or CT in 30-50% of cases and is palpable in 15-20%. Pancreatic abscesses usually develop after the second week and may lead to septicaemia. Pseudocysts likewise occur after 2-3 weeks and are more commonly seen on scans (ultrasound, CT) than found on palpation. They may cause compression of adjacent structures and may lead to fistula formation, haemorrhage or infection. Spontaneous resolution of pseudocysts may occur. Pancreatic ascites has been described as has involvement of contiguous organs with massive intraperitoneal bleeding, vascular thrombosis and infarction of bowel.

Systemic

As noted above, respiratory complications are frequent and include effusions, atelectasis, pneumonitis and the adult respiratory distress syndrome. Cardiac abnormalities include hypotension, sudden death, ST-T wave changes and pericardial effusions. Renal function may be impaired with acute tubular necrosis progressing to acute renal failure requiring dialysis. Disseminated intravascular coagulation may be noted on coagulation studies. Metabolic complications are common - hyperglycaemia, hypertriglyceridaemia, hypocalcaemia and hypomagnesaemia. Gastrointestinal haemorrhage may be due to acute peptic ulceration, gastritis or erosion of adjacent blood vessels. Many psychic and neurological symptoms have been attributed to acute pancreatitis.

Prognosis

In the majority of cases, acute oedematous pancreatitis is a self-limited disease of 3-7 days duration and with 3-10% mortality. Necrotizing pancreatitis occurs in 20-30% with an estimated mortality of 50%. Abscesses are seen in 5-10% of patients but have a mortality approaching 100% without surgery. Chronic pancreatitis is a rare complication of an isolated episode of acute pancreatitis.

Several attempts have been made to define high risk patients upond admission and during hospital stay. Ranson et al in 100 patients, described 11 early objective findings (Table 2) which correlated with subsequent mortality and morbidity; prospective studies in a further 200 confirmed the initial findings. Additional factors which increase morbidity and mortality include pre-existing cardiovascular disease and diabetes. Failure of major organs (i.e. lungs, kidneys or circulation) reduces survival even further.

Table 2. Early Prognostic Signs of Morbidity and Mortality

At Admission

Age greater than 55 years
White cell count greater than 16000 cells/microL
Blood glucose greater than 11 mmol/L
Serum lactate dehydrogenase (LDH) more than twice normal
Serum aspartate transaminase (AST) more than six times normal

During initial 48 hours

Haematocrit (PCV) fall by more than 10%
Rise in urea more than 2.0 mmol/L
Serum calcium less than 2.0 mmol/L
PaO_2 < 7.9 kPa (60 mmHg)
Base deficit greater than 4 mmol/L
Estimated fluid seguestration over 6 litres.

Management

In general terms, acute management consists of medical therapies with surgical intervention reserved for complications. Patients with severe attacks of pancreatitis should be admitted to an ICU where major complications can be detected and treated with minimal delay.

Medical

1. Pain Relief

Adequate analgesia can be achieved by parenteral narcotics in most patients. Morphine should be avoided because it may contract the sphincter of Oddi and reduce drainage of pancreatic secretions. Epidural anaesthesia by intermittent or continuous infusion may be very helpful especially in patients with impaired respiratory function from pain and basal atelectasis.

2. Fluid Replacement

The inflammatory exudate around the pancreas resembles that of an internal burn and huge volumes of fluid may be sequestrated into the retroperitoneal spaces. Rapid fluid loss may occur with deficits of many litres recorded. Blood, plasma expanders and crystalloid should be administered to restore these deficits. The choice of solution is determined by the clinical signs, haemoglobin/PCV results and serum albumin. Volumes and rates of infusion must be adjusted according to central venous pressures, urine output and blood pressure. Pulmonary artery catheters arew very usefiul in patients with myocardial or respiratory disorders especially if the adult respiratory distress syndrome develops. Overzealous infusions of any fluid will increase the chance of pulmonary oedema especially when vascular permeability mau be abnormal. Low dose dopamine (2 microg/kg/min) may help to maintain or re-establish urine flow.

3. Suppression of Pancreatic Secretion

All patients should be fasted. A nasogastric tube is required if there is gastric distention, vomiting, paralytic ileus or when the patient requires endotracheal intubation. Various drugs (i.e. anti-cholinergics, cimetidine and glucagon) have not been shown to be helpful.

4. Metabolic and Electrolyte Balance

Hyperglycaemia usually requires insulin therapy. Under most conditions, insulin infusions provide rapid and better control, but a dextrose infusion should be administered concurrently to prevent inadvertent hypoglycaemia. Calcium gluconate is occasionally required to treat symptomatic hypocalcaemia. Magnesium and phosphate levels should be checked and major deficits corrected.

5. Nutrition

Total parenteral nutrition (TPN) is indicated for nutritional support. Although TPN may reduce pancreatic exocrine production and secretion, the amount of enzyme present in the gland is not reduced.

6. Antibiotics

Antibiotics should not be administered prophylactically. They may be required to treat complications such as abscess or initiating conditions such as cholangitis.

7. Other Therapeutics

Although initially used enthusiastically, aprotinin (Trasylol) is no longer recommended as results of trials have been disappointing. Endoscopic sphincterotomy may be necessary to provide emergency decompression of the biliary tree by an obstructing stone. Ranitidine/cimetidine may help reduce gastric stress erosions.

Surgical

1. Early Intervention

There are very few indications for early surgery in the course of acute pancreatitis. There are reports of increased and decreased mortality with early biliary surgery in patients with gall stone induced pancreatitis. In usual practice, cholecystectomy and/or exploration of the common bile duct are undertaken when the acute episode has settled. Early routine pancreatic resection or procedures to defunction the pancreas carry a mortality of around 25% and confer no clear benefits and are not recommended.

2. Peritoneal Lavage

Early peritoneal lavage using ordinary peritoneal dialysis catheters has been recommended for patients with moderate and severe pancreatitis. It does not treat the

underlying pathology, reduce the incidence of pancreatic collections, nor alter the eventual mortality. Nonetheless, it does result in better haemodynamic stability possibly by removing vasoactive substances within the peritoneal fluid. These substances include proteolytic enzymes, phospholipase A2 and kinins such as bradykinin. Other forms of dialysis such as haemodialysis do not show these benefits, supporting the concept that substances released from the pancreas in ascitic fluid may be absorbed into the bloodstream and contribute to the pathogenesis of the circulatory disturbances. Peritoneal lavage is not necessary in most patients with acute pancreatitis, and should be reserved for those with vascular instability or those at high risk of morbidity and mortality.

3. Management of Complications

Surgery is often necessary for complications which may develop days to weeks after the acute event. Extensive necrosis may require debridement and the placement of large drain tubes within the pancreatic bed. Patients with a pancreatic abscess (sometimes difficult to separate from necrotic tissue) must undergo surgery as mortality is 100% with antibiotics alone and 20-40% with surgery. Attempts to drain these collections by percutaneous catheters placed under CT control have only been moderately successful. Complications such as bleeding, vascular obstruction and fistulae require correction. Pseudocysts may also require drainage which can be undertaken many days after the acute changes have subsided, unless the cyst has become infected.

Chapter 33: Hepatic Failure

F. Hawker

Fulminant Hepatic Failure

Fulminant hepatic failure (FHF) is defined as liver failure complicated by encephalopathy occurring within 8 weeks of the onset of illness. Histologically, the liver shows massive necrosis of hepatocytes, often with preservation of the reticular framework. In broad terms, the clinical features of FHF are presumed to result from acute failure of the normal functions of the liver: synthesis, storage and detoxification.

Aetiology

1. Viral Hepatitis

Acute viral hepatitis accounts for approximately 70% of patients with FHF.

(a) *Acute hepatitis A (HAV)* is diagnosed by the presence of IgM antibody to hepatitis A virus. It accounts for 2-30% of patients with FHF.

(b) *Acute hepatitis B (HBV)* is diagnosed by the presence of the IgM antibody (HBcAb) to hepatitis B core antigen, with or without hepatitis B surface antigen (HBsAg). Up to 50% of patients with negative HBsAg are IgM anti-core antigen positive. It is the major cause of FHF and accounts for 25-75% of cases. Co-infection with hepatitis D (delta) virus, increases the risk of FHF in patients with acute HBV.

(c) *Acute non-A, non-B hepatitis* is diagnosed by the absence of serological evidence of recent infection with HAV, HBV, and other viruses, no history of exposure to drugs and toxins, and the absence of autoantibodies. There are three types of non-A, non-B hepatitis viruses; epidemic or enterally transmitted (A-type), post transfusion (B-type) and sporadic. Sporadic non-A, non-B hepatitis infection accounts for 23-44% patients with FHF. Characteristically, there is a long interval between the onset of jaundice and development of encephalopathy (more than 3 weeks) and a very high mortality (90%).

(d) *Other viruses*, such as herpes simplex 1 and 2, varicella zoster virus, cytomegalovirus (CMV) anbd Epstein Barr (EB) virus can produce severe liver cell necrosis.

2. Acute Drug-Induced Hepatitis

Drug-induced hepatitis is responsible for approximately 15% of cases of FHF. Many drugs have been implicated. However, isoniazid, sodium valproate, anti-depressants, nonsteroidal antiinflammatory drugs, and halothane have been reported most frequently. The risk of developing FHF in patients with drug-induced hepatitis and jaundice is 20%, whereas the risk is less than 1% with viral hepatitis and jaundice.

3. Acute Hepatitis due to Poisoning

(a) *Paracetamol overdose.* Since the mechanism of paracetamol hepatotoxicity is known, treatment of paracetamol overdose with N-acetylcysteine has decreased the incidence of subsequent FHF. In Britain, paracetamol poisoning is second only to viral hepatitis as a cause of FHF. However, in other countries, as few as 2% of FHF are due to paracetamol poisoning. FHF is also a complication of acute yellow phosphorus poisoning.

(b) *Amanita mushrooms,* particularly amanita phalloides, are toxic through heat stable amanatoxins, which cause hepatic necrosis. The lethal dose is 50 g.

(c) *Industrial solvents.* Carbon tetrachloride ingestion, chloroform inhalation and xylene (in glue sniffers) are very rare causes of FHF.

4. Miscellaneous

Miscellaneous causes account for approximately 10% of FHF. They include Wilson's disease, microvesicular steatosis (Reye's syndrome, acute fatty liver of pregnancy), ischaemic liver cell necrosis, hepatic venous obstruction, malignant infiltration of the liver, auto-immune chronic active hepatitis, reactivation of chronic hepatitis B, hyperthermia, complication of liver transplantation and partial hepatectomy.

Clinical Features

There may be a history suggestive of a cause. However, in many cases such a history may not be available. The disease typically evolves over several days, but deep coma can occur in hours or may develop over months in subacute or "late onset hepatic failure". Most patients become deeply jaundiced. A sickly sweetish breath (hepatic foetor) is characteristic of FHF. This is probably due to a mixture of volatile compounds, methethiol, dimethyl

sulphide and dimethyl disulphide (mercaptans) which are excreted in breath. The liver is usually small and impalpable. Abdominal pain may occur.

Signs of chronic liver disease, such as palmar erythema, spider naevi, ascites, splenomegaly and hypoalbuminaemia, are not usually present on admission. Acute portal hypertension commonly develops after 3 weeks and may result in bleeding from oesophageal varices.

1. Encephalopathy

By definition, encephalopathy is always present in FHF. It is classified, by severity, into 4 grades (Table 1). One of the earliest signs of encephalopathy in FHF is a generalized increase in muscle tone, which may progress to full decerebrate posturing with trismus and opisthotonus. Cerebral oedema is present in over 80% of patients with grade IV encephalopathy, and is the major cause of death. It is heralded by spontaneous hyperventilation, followed by dysconjugate eye movements and dilatation of the pupils which react only sluggishly to light. Papilloedema is unusual. Unless treatment is successful at this stage, respiratory arrest and brain stem coning ensue.

Table 1. Stages of Encephalopathy

O	Normal awareness
I	Mood change and confusion
II	Drowsiness, inappropriate behaviour
III	Stuporose but rousable
IV	Unrousable to minimal stimuli or no response to noxious stimuli

The cause of encephalopathy in FHF is unknown. It is generally attributed to accumulation of toxic substances in the circulation which damage the blood brain barrier (BBB), inhibit Na-K ATPase (the sodium pump) and impair neuronal function. Substances arising from the gut, such as ammonia, mercaptans, fatty acids and phenols can act alone or synergistically to produce coma. They have been shown experimentally to both increase BBB permeability and to inhibit Na-K ATPase.

Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in normal brain and may be important in hepatic encephalopathy. Most circulating GABA arises from the gut flora. In health, GABA is cleared from the portal circulation by the liver. Hepatic extraction is reduced in liver failure, and high circulating concentrations have been observed in animal models of acute hepatic encephalopathy. GABA normally penetrates BBB slowly, but in the presence of circulating toxins which increase BBB permeability, its neuroinhibitory effects might be facilitated. Other neurotransmitters such as octopamine, serotonin, histamine, phenylethanolamine and catecholamines are also implicated. Amino acids, such as glutamine (which, with alpha-ketoglutarate, interracts with ammonia in the brain), methionine (which is metabolized to mercaptans), and tryptophan all have neurotoxic potential.

The relative contributions of vasogenic oedema (in increasing BBB permeability) and cytotoxic oedema (in Na-Ka ATPase inhibition) to acute hepatic encephalopathy are even less

clear. Clinically, mannitol infusion can decrease intracranial pressure (ICP) in hepatic encephalopathy, suggesting that the BBB remains intact (at least) in some regions. An increase in cerebral blood flow of up to 3 times normal has been observed in Grade IV encephalopathy, contributing to raised ICP. Hypoglycaemia, electrolyte and acid-base disturbances, renal failure, sepsis and hypoxia may also contribute to cerebral dysfunction.

2. Bleeding Diathesis

Signs of bleeding may be present on admission or develop subsequently. Bleeding from the gastrointestinal tract (GIT), nasopharynx, respiratory tract or into the retroperitoneal space may occur. Intracerebral haemorrhage is unusual.

The prothrombine time (PT) is always prolonged and is used as a prognostic index and to chart the course of the disease. Liver synthesis of fibrinogen and factors V, VII, IX, X is impaired. The production of factors VIII, XI and XII may also be impaired.

Alterations in platelet count, morphology and function have all been described in FHF. About 2/3 patients have platelet counts less than 100,000 x 106 cells/L. The platelet count tends to decrease progressively during the course of FHF, and is lower in patients who die. There is increased platelet adhesion but decreased platelet aggregation. Low grade disseminated intravascular coagulation (DIC) may occur.

3. Respiratory Failure

The airway may be compromised because of the decreased level of consciousness. Hyperventilation leading to respiratory alkalosis is probably mediated by the central nervous system. Lactic acidosis may also be responsible for hyperventilation late in the course of FHF. Apart from centrally mediated abnormalities of respiratory control, hypoxia is commonly seen and is the indication for ventilation in approximately 1/3 of patients. This may represent intrapulmonary shunting and histological studies have confirmed diffuse dilatation of the pulmonary vascular bed, with pleural spider naevi in some cases. Complications of coma, such as bronchopneumonia, aspiration or atelectasis also contribute.

Around 30% patients have non cardiogenic pulmonary oedema confirmed by chest X-ray and lung water measurements. Pulmonary oedema is more common with extreme prolongation of the PT and therefore tends to occur in the sickest patients. No mechanism has been proven, but it is suggested that it may be either neurogenic, or the result of a common factor producing both cerebral and pulmonary oedema. This factor might possibly be an endogenous inhibitor of Na-K ATPase.

4. Cardiovascular Disturbances

In FHF there is a severe circulatory disturbance characterized by a low systemic vascular resistance with a compensatory increase in cardiac output. Hypotension is common, even in the absence of hemorrhage and sepsis, and carrier a poor prognosis. It has been suggested that, as in sepsis, there is maldistribution of blood flow in the microcirculation leading to covert tissue hypoxia. No mediator has been identified that can account for these circulatory changes.

5. Renal Failure

Renal insufficiency occurs in approximately 50% of patients with FHF, and usually indicates a poor prognosis. Renal failure may be due to acute tubular necrosis or more commonly, to *hepatic nephropathy*, also known as the *hepatorenal syndrome* or *functional renal failure*. In this condition there is a decline in the glomerular filtration rate but tubular function is preserved. The biochemical features are similar to prerenal renal failure with urinary sodium concentration < 10 mmol/L, urine osmolality > 1000 mOsm/kg and a urine to plasma creatinine ration of > 10. However, renal failure cannot be reversed by volume replacement. There are no morphological changes in the kidney to explain these observations, and such kidneys resume normal function when transplanted to recipients without liver disease. It is believed that hepatic nephropathy is due to intense renal vasoconstriction, but the exact mechanisms remain unknown.

6. Metabolic Disturbances

Fever develops in most patients with fulminant hepatitis. Hypothermia may develop in the late stages, and may indicate hypoglycaemia or progression of cerebral oedema with poor prognostic significance. Severe hypoglycaemia occurs in 25% of patients. Hypokalaemia is common early in disease. Hyponatraemia, oedema and ascites reflect sodium and water overload.

Respiratory alkalosis is common. Metabolic alkalosis may also occur, probably as a result of hypokalaemia and defective urea synthesis. In the later stages, over 50% of patients have high mixed venous lactate concentration associated with metabolic acidosis. Mortality is high in this group. Lactic acidosis is most likely related to underlying tissue hypoxia combined with a failure of lactate clearance by the liver.

7. Infective Complications

In 20-36% of patients, the course is further complicated by bacterial and sometimes fungal infections, especially septicaemia, pneumonia, urinary tract infections and infected ascites. This high incidence is probably related to low serum complement concentrations, impaired neutrophil function, and decreased humoral opsonizing activity in FHF.

8. Impaired Drug Metabolism

Patients with FHF are unduly sensitive to the depressant effects of sedative and analgesic drugs. This is chiefly due to impaired drug breakdown, but increased cerebral sensitivity and changes in plasma protein binding contribute.

9. Pancreatitis

Acute haemorrhagic pancreatitis is found at postmortem in 10% of patients dying from FHF. The aetiology is unknown.

10. Rare Complications

Rare complications of viral hepatitis include myocarditis, atypical pneumonia, aplastic anaemia, transverse myelitis and peripheral neuropathy.

Monitoring and Investigations

1. *Vital Observations* - Temperature, heart rate and rhythm and arterial blood pressure should be monitored continuously, and central venous pressure and urine output measured hourly.

2. *Pulmonary Artery Catheter* - Indications for insertion of a Swan-Ganz catheter are controversial. Optimization of oxygen delivery may benefit outcome, but coagulopathy and susceptibility to infection increase the risk of complications. It is prudent to reserve its use for situations where haemodynamic data are likely to lead to major management changes.

3. *Intracranial Pressure (ICP) Monitoring* - should allow early recognition and treatment of intracranial hypertension. However, experienced clinicians have been shown to be capable of detecting episodes of raised intracranial presureamd ICP monitoring is associated with an increased risk of intracerebral haemorrhage. At present, ICP monitoring should be reserved for the evaluation of new treatments or when cerebral oedema is likely to be prolonged as in Reye's syndrome.

4. *Laboratory Investigations* - should indicate serological investigations for hepatitis (hepatitis A and B, CMV, EB virus and herpes simplex) and a drug screen, specifically for paracetamol, to determine the cause of FHF. Plasma caeruloplasmin concentration and 24 hour urinary copper excretion exclude Wilson's disease.

5. *Coagulation Studies* - are a sensitive index of liver function and should be performed daily.

6. *Liver Functions Tests* - should also be performed daily. Both conjugated and unconjugated fractions are usually elevated. Bilirubin concentrations greater than 300 micromol/L and persistent are likely to be associated with severe disease. Plasma aminotransferase concentrations (alanine transferase (ALT) and aspartate aminotransferase (AST)) show variable increases in FHF, and peak levels vary from 400-4000 IU/L. Plasma concentrations of these enzymes do not correlate well with the degree of liver cell damage, and relatively normal levels in association with deep jaundice and a small liver, usually signify massive liver cell necrosis. Plasma alkaline phsophatase concentration (ALP) is rarely elevated above 3 times normal in the acute phase, but shows variable increases during recovery where there may be a cholestatic picture. Plasma alpha foetoprotein, pre-albumin and factor V concentrations have been used as prognostic indicators. Plasma albumin and globulin concentrations are usually normal on presentation.

7. *Other Investigations* - Blood glucose levels should be measured 4 hourly. Plasma electrolytes, urea, creatinine and albumine should be measured at least daily. Arterial blood gases should be measured daily or more frequently if indicated.

Specimens of sputum and urine should be cultured regularly, and blood taken for culture if there are signs of sepsis.

Chest X-rays and 12 lead ECG should be performed daily.

An electroencephalogram (EEG) may be helpful in the assessment of encephalopathy.

Liver biopsy may rarely be necessary to exclude underlying cirrhosis or malignancy. If indicated, the transjugular route is preferred, because of a decreased risk of haemorrhagic complications.

Managament

The mainstay of treatment in FHF is support, with accurate fluid balance, maintenance of the circulation and ventilation, control of bleeding, correction of hypoglycaemia and treatment of complications in anticipation of liver regeneration. As cerebral oedema is the major cause of death, treatment should be focused on preventing or minimizing this complication. Other major complications such as renal failure, haemorrhage and sepsis further compromise cerebral status. Where FHF is possibly due to drug administration, all medication should be ceased.

1. Management of Cerebral Oedema

Patients should be nursed with the head elevated to 30 degrees; with venous return from the head unimpeded by malpositioning or tapes.

The decision to intubate and ventilate is often difficult. The airway is often well maintained due to increased muscle tone associated with hepatic encephalopathy. A degree of spontaneous hyperventilation is common. Patients in stage III coma who appear unresponsive may become extremely irritable when an endotracheal tube is inserted. Sedative drugs should be avoided if possible, because of their unpredictably and prolonged effects, and neurological assessment is important to follow the course of the disease. Nevertheless, mechanical ventilation should be instituted when airway compromise, hypoxia, hypercarbia, or intracranial hypertension are present. Cerebral blood flow is increased in hepatic encephalopathy, and moderate hyperventilation can decrease intracranial pressure in the *short term* (although ineffective long term). Mechanical ventilation, however, decreases liver blood flow (see below), as does respiratory alkalosis.

The mainstay of treatment of cerebral oedema in FHF is mannitol. Infusion of 20% mannitol (1 g/kg) reversed clinical signs of cerebral oedema, reduced ICP by a mean of 22 mm Hg (2.9 kPa) and increased survival. In patients with renal failure, mannitol should only be used in conjunction with haemodialysis or haemofiltration, since fluid overload may exacerbate cerebral oedema.

Frusemide may be useful in FHF to maintain the initial osmotic gradient established by mannitol and normovolaemia during infusions of albumin and clotting factors, and to inhibit CSF secretion by the choroid plexus.

Perfect control of fluid balance is necessary. Hypervolaemia increases the risk of cerebral oedema, and hypovolaemia may result in hypotension, decreasing cerebral perfusion pressure. Hypertension is almost always secondary to increased ICP. If hypertension occurs, measures to decrease ICP (hyperventilation and mannitol infusion) should be instituted. Antihypertensive drugs may precipitate brainstem coning.

There is no evidence that lactulose administration will delay or prevent the development of grade III or IV encephalopathy. Nevertheless, it is widely used in a dose of 30 mL tds via nasogastric tube, to reduce ammonia production and to reduce the volume of colonic contents. Use of neomycin is not recommended because of its nephrotoxicity and ototoxicity.

Corticosteroids do not influence the incidence and severity of cerebral oedema. Barbiturates are not recommended because of cartiovascular depression.

Clinical and EEG improvement with a benzodiazepine antagonist (which acts as the GABA receptor) has been noted in a case report. However, therapeutic benefits are not proven.

2. Maintenance of Circulation

Relative hypovolaemia is common in FHF and has been observed in 76% of ICU admissions. It is likely due to inappropriate vasodilation and generalized capillary leak. If there is coexisting hypotension or oliguria, volume deficits should be corrected with blood or components depending on haematological parameters. Hypervolaemia must be avoided. A pulmonary artery catheter may be necessary to optimize fluid replacement.

Although inotrope infusion is indicated if hypotension persists despite normovolaemia, there is no evidence that any inotrope improves tissue perfusion or overall survival, and the requirement for vasopressor support is associated with increased mortality. However, rapid elevation of blood pressure with a noradrenaline infusion may be transiently lifesaving when a hypotensive patient develops signs of imminent brainstem coning.

3. Coagulopathy and Bleeding

Severe bleeding occurs in approximately 1/3 of patients. Prophylactic use of H_2-antagonists is recommended which may decrease the incidence and severity of GIT bleeding. Blood losses should be replaced by blood transfusion. Administration of fresh frozen plasma (FFP) is indicated to replace coagulation factors in the presence of bleeding, but its prophylactic use without bleeding does not influence morbidity or mortality. Vitamin K should be administered daily. Administration of Factor IX concentrates (eg, prothrombines) is contraindicated, as massive intravascular coagulation may result.

Platelet transfusions are indicated if the platelet count falls below 50.000×10^6 cells/L. Administration of FFP and platelets is indicated before surgical procedures and catheterisation of central veins.

4. Renal Management

The development of renal failure in FHF has mortality rates approaching 100%. Prevention of renal failure is therefore of prime importance. Hypotension and hypovolaemia should be treated promptly and potentially nephrotoxic drugs avoided. Low dose dopamine has not been shown to prevent acute renal failure. Despite the high mortality, recovery from FHF and renal failure may occur, particularly when both are due to paracetamol poisoning. Haemodialysis or continuous haemofiltration may be indicated if renal failure is due to nephrotoxic agents or ATN, but do not improve survival in the hepatorenal syndrome.

5. Nutrition

Most patients with FHF have normal nutritional status before their acute illness. Fluid restriction (for cerebral oedema) together with the requirement for blood components preclude giving large volumes of nutrient solutions. Consequently, nutritional support is neither necessary nor practical early in illness. Glucose 10% infusions to prevent hypoglycemia serve as a source of energy. If illness is prolonged, balanced feeding solutions, preferably enteral, should be administered. Branched chain amino acid (BCAA) solutions have not been demonstrated to improve encephalopathy or overall mortality. Hypoglycaemia is treated with 5 or 10% dextrose. However, if profound, 50% dextrose allows smaller volumes to be infused and has less effect on plasma sodium concentration.

6. Measures to Improve Liver Function

There are no drugs which reverse the effects of hepatic failure. Corticosteroid drugs have no place in treatment of FHF and their use has been associated with increased mortality. Beneficial effects of prostacyclin and fibronectin have not been demonstrated.

Maintenance of liver blood flow may theoretically prevent further damage and allow rapid recovery of hepatocytes, although effects are unproven. Hepatic blood flow is adversely affected by ventilation (flow is reduced by approximately 50%) and PEEP. Low dose dopamine increases splanchnic blood flow, although a benefit in FHF has not been investigated. Oxygen content should be maintained with an adequate Hb concentration and oxygen saturation.

7. Artificial Liver Support

Exchange transfusion, plasma exchange, human cross circulation, porcine liver cross perfusion, haemofiltration through large pore membranes and haemoperfusion have not improved survival.

8. Liver Transplantation

Recent results of liver transplantation in FHF have been encouraging, with survival rates of 60%. As survival with medical therapy alone is approximately 20%, liver transplantation is increasingly indicated in FHF. (See Chapter 34, Liver Transplantation.)

Prognosis

The strongest determinant of survival in FHF is the grade of coma. Survival is approximately 70%, 40% and 20% with grade II, III and IV encephalopathy respectively. If convulsions occur, survival is only 5%. Age also influences survival, and young patients have a better prognosis. When the time between onset of symptoms and encephalopathy is short, prognosis appears to be improved. With viral hepatitis, survival rates are poorest in non-A, non-B FHF, intermediate in hepatitis B, and best in hepatitis-A disease. The presence of alpha-foetoprotein in plasma suggests an improved prognosis, particularly in hepatitis B disease. Sex of the patient and duration of jaundice or coma have not been shown to be consistent prognostic indicators.

Extreme prolongation of the PT carries a bad prognosis, but plasma concentration of transaminases and ammonia do not discriminate survivors from nonsurvivors. The occurrence of complications, particularly renal failure, hypotension and haemorrhage adversely affects survival.

Precautions Against Hepatitis

All ICU staff should be vaccinated against HBV. AIDS cannot be spread by HBV vaccination. The majority of vaccinated individuals have circulating antibody for about 4 years, although protection is likely to be lifelong. There is no vaccine against either HAV or non-A, non-B hepatitis. All patients with FHF should be initially regarded as infectious. They should be barrier-nursed unless an alternative non-infectious diagnosis is proven. Vaccination should not lead to complacency. Disposable gloves and gowns should be worm and incinerated after use. Hands should be washed regularly and any spilt blood removed immediately. The bed area and related equipment are disinfected with glutaraldehyde, formadlehyde or hypochlorite. These have been shown to inactivate HBV, but their effect on non-A, non-B agents have yet to be conclusively demonstrated. Blood, urine, faeces and other biological samples should be handled carefully and labelled prominently. All precautions should be taken to avoid puncture by contaminated needles or other sharp instruments.

The procedure for needlestick or permucosal exposure to blood or high-risk body fluids depends on whether the exposed individual has antibodies (HBs-Ab) HBV surface antigen (HBs-Ag). These may be acquired by vaccinaton or by previous subclinical infection. If HBs-Ab is present no further action is necessary. If HBs-Ab status is unknwon, hepatitis B immune globulin (HBIG) (0.06 mL/kg) should be administered as early as possible within 7 days and the person tested for HBs-Ab. If HBs-Ab is negative, vaccination should also be started immediately, and the first dose of HBV vaccine (20 microg IM at a different site) should be given within 7 days of exposure and repeated 1 and 6 months later. Passively acquired HBs-Ab does not interfere with the immune response to the vaccine.

For HAV, immune globulin markedly reduced attack rate both pre- and post-exposure. A single IM dose of 0.02 mL/kg is advised within 2 weeks of exposure.

Hepatic Failure in Chronic Liver Disease

Chronic liver cell failure is usually the result of cirrhosis (alcoholic, chronic active hepatitis, postnecrotic, primary biliary, sclerosing cholangitis, metabolic disease) or infiltrative processes (neoplasia or metabolic). It is characterized by jaundice, ascites and encephalopathy,

which may be present singly or in combination. Spider angiomata and palmar erythema are usually present. Acute episodes of decompensation may be caused by additional insults, such as GIT bleeding, sepsis or large alcohol intake. It is therefore important to recognize and treat these precipitants if possible. Unlike FHF, patients with chronic liver disease have minimal potential for hepatic regeneration. ICU admission of these patients is dependent on a reversible component or consideration for liver transplantation. If these patients deteriorate sufficiently to need respiratory support, survival is unusual. In chronic liver failure, coagulopathy, cardiovascular and renal dysfunction are similar to those in FHF discussed above.

Encephalopathy

In chronic liver disease, the presumed mechanism of encephalopathy are similar to those described in FHF. However, the clinical picture typically develops more slowly and cerebral oedema is rare. Portal hypertension and the development of portal-systemic collaterals (shunts) are usual. Hence the failing liver cells are unable to metabolize circulating toxins from the GIT which gain access to the systemic circulation. Thus encephalopathy in chronic liver disease is often called portal-systemic encephalopathy (PSE). Surgical manoeuvres (eg, portacaval shunt) which decompress the portal venous system may precipitate PSE in this way.

The most usual precipitating factor is nitrogenous overload, particularly due to GIT haemorrhage. This results in excess ammonia and mercaptan production from blood protein breakdown in the gut, and is commonly associated with shock, which augments the predisposition to PSE. In addition, ammonia is present in transfused blood. Increased dietary protein, uraemia, constipation and hypokalaemia (by increasing renal veni ammonia output) also increase ammonia production. Sedative or analgesic drugs, fluid and electrolyte abnormalities, sepsis and surgery can also precipitate PSE.

The early stages of encephalopathy comprise personality changes with irritability, intellectual deterioration, slurred speech, reversal of sleep rhythm, confusion, drowsiness and later coma. There is characteristically a flapping tremor of the outstretched hand (asterixis). This disappears when coma supervenes. In coma, there is initially increased muscle tone with hyperreflexia, but later tendon reflexes are lost and the patient becomes flaccid.

Treatment of encephalopathy in chronic liver disease involves aggressive treatment of precipitating factors and full supportive care. Dietary protein should be ceased initially and calories provided as glucose (300-500 g/day). Lactulose should be given orally (30 mL tds) or by retention enema. Although the data are conflicting, it is unlikely that branched chain amino acids are useful.

Ascites

Ascites is a common complication and is almost invariably present in patients with bleeding varices or advanced encephalopathy. Portal hypertension, hypoalbuminaemia, excessive hepatic lymph formation and abnormalities of sodium and water balance all contribute to its pathogenesis.

Diagnostic paracentesis should be performed to exclude bacterial peritonitis (SBP), which occurs in 4-15% of cirrhotic patients with ascites. Treatment with parenteral broad spectrum antibiotics should be commenced if the ascitic fluid neutrophil count is > 250 x 10^6 cells/L, organisms are seen on Gram stain or subsequently cultured. Mortality from SBP approaches 70%.

Treatment of ascites includes salt restriction (40 mmol/day), fluid restriction (1500 mL/day) and diuretic therapy. However, these measures are not advised in cardiovascular instability. Up to 50% of cirrhotic patients develop complications with diuretic therapy. These include hypovolaemia, electrolyte disturbances, encephalopathy and renal failure. There is not evidence that paracentesis is an excellent adjunct to diuretic therapy and shortens hospital stay. However, if volume is not replaced similar complications may occur.

Oesophageal Varices

Portal hypertension, oesophageal varices and the treatment of variceal bleeding are discussed elsewhere. Variceal haemorrhage is the major cause of acute decompensation in chronic liver disease.

Liver Dysfunction in the ICU

Critically ill patients admitted to the ICU with primarily non-hepatic disease frequently develop liver dysfunction. There may be:

(a) direct hepatocellular damage (hepatitis-like pattern) with a marked rise in plasma ALT and AST, a prolonged PT, and variable elevations of both conjugated and unconjugated bilirubin, with only mild elevations of ALP; or

(b) intrahepatic cholestasis, where there is elevation of ALP and conjugated bilirubin, with relatively normal plasma ALT and AST.

Multiple aetiological factors may be present, and hepatocellular damage and intrahepatic cholestasis may coexist. It is likely that a decreased hepatic perfusion plays a role in many cases, as both hepatocytes and Kupffer cells are extremely sensitive to hypoxia. In patients with unexpeplained jaundice associated with a cholestatic picture, ultrasonography of the liver should be performed to exclude extrahepatic bile duct obstruction.

1. Circulatory Failure

Hepatic changes are common in shock due to acute heart failure, trauma, burns, haemorrhage or sepsis. Changes are due to cellular hypoxia and can be related to the duration of shock; if longer than 24 hours a degree of hepatic necrosis is almost always present, but unusual if less than 10 hours. Plasma ALT and AST rise rapidly to 8-10 times normal. This is known as ischaemic hepatitis. These may improve within 24 hours if shock is reversed. There may be mild jaundice and the PT frequently rises. In congestive heart failure, the increased pressure in the right atrium is transmitted to the hepatic veins. Mild jaundice is common and the elevation in plasma bilirubin is proportional to the degree of cardiac failure. The low cardiac output is probably a contributing factor. Plasma ALT, AST and ALP

concentrations are mildly elevated. There is tender hepatomegaly which may be associated with ascites and splenomegaly. The prognosis is that of the underlying heart disease.

2. Sepsis and Multiple Organ Failure

Hepatic dysfunction develops in a variable proportion of patients with sepsis and is associated with increased mortality. Jaundice develops 2-3 days after the onset of infection and is associated with hepatomegaly in 50% of patients. Plasma bilirubin is usually 100-200 micromol/L and ALP 2-3 times normal. Plasma ALT and AST are normal in 70% of patients. Occasionally, increased plasma bilirubin may be an isolated finding. Liver histology shows intrahepatic cholestasis with little hepatic necrosis, unless there is coexisting hypoperfusion.

Circulating endotoxin can produce cholestasis experimentally, but as hepatic dysfunction is similar in sepsis and in trauma, inflammatory mediators probably contribute. It is likely that metabolic dysfunction of hepatocytes mediates the characteristic changes of hypermetabolismmm and hypercatabolism observed in sepsis and multiple organ failure. Management is aggressive treatment of the precipitating infection. (See Chapter 63, Severe Sepsis.)

3. Drugs

Jaundice and liver dysfunction has been associated with many drugs (Table 2). Drugs may impair metabolism of bilirubin or may be hepatotoxic (directly or due to metabolites).

Table 2. Adverse Hepatic Drug Reactions

Type
    Examples
        Comments

Central (Zone III) Necrosis
    Carbon tetrachloride
    Paracetamol
    Halothane
        Dose dependent, multi-organ failure
Hepatitis-like
    Alpha methyldopa
        Chronic active hepatitis
    Nitrofurantoin
        Massive hepatic necrosis in severe cases
    Isoniazid, Halothane
Cholestatic hepatitis
    Chlorpromazine
    Tolbutamide, Chlorpropamide
    Erythromycin
Cholestasis without hepatitis
    Anabolic steroids
        Often some increase AST

Fibrosis
    Methotrexate
        Portal hypertension, cirrhosis
    Hypervitaminosis A
Vascular abnormalities
    Anabolic androgens
        Sinusoid dilation, veno-occlusive
    Oral contraceptives
Granulomatous reactions
    Hydrallazine
        Often some cholestasis, lobular hepatitis
    Allopurinol
Neoplasms
    Sex hormones
        Some benign.

Hypersensitivity reactions may also cause hepatocellular dysfunction, and occasionally, massive liver cell necrosis. In such cases there may be other allergic manifestations such as fever, arthralgia, urticaria and eosinophilia. Drugs may cause hepatocellular necrosis or intrahepatic cholestasis (Table 2).

4. Total Parenteral Nutrition (TPN)

Elevation of plasma AST, ALP and bilirubin concentration may occur with TPN, particularly if excessive calorie intake is prolonged (eg, over 17200 kL (4.000 kcal)/day for over 6 weeks). Histologically, there is fatty infiltration of the liver, associated with cholestasis and periportal inflammation. When energy intake is high, it is likely that fatty acid synthesis outstrips the ability of the liver to secrete lipid. Essential fatty acid deficiency is a rare cause of hepatomegaly with fatty infiltration.

5. Hepatitis

Exposure to viral or non-A, non-B hepatitis may have occurred. The clinical picture and management are as discussed above.

6. Benign Postoperative Intrahepatic Cholestasis

In this condition, jaundice typically appears on the first postoperative day, and both conjugated and unconjugated fractions are increased. Plasma ALT, AST and ALP concentrations are normal or only slightly elevated. Liver histology shows intrahepatic cholestasis, with dilated bile canaliculi and casts, with minimal liver cell damage. In most circumstances, there is an increased bilirubin load (from blood transfusion or resolving hematomas), and liver dysfunction may be due to a reduced ability to transport conjugated bilirubin. Although described as benign, mortality is 50%.

Chapter 34: Liver Transplantation

F. Hawker

Introduction

The first human liver transplant operation was performed in 1963 but extended survival (1.5 years) was not achieved until 1967. Since then, results have improved and liver transplantation has become accepted as a service rather than an experimental operation. Intensive care management of such patients is thus vital. Two forms of liver transplantation have been used clinically:

1. *Orthotopic* (OLT) - the recipient's diseased liver is replaced with a donor liver (homograft); and

2. *Heterotopic* - the diseased liver is left in situ with the new liver transplanted in an ectopic site.

OLT has been more successful and constitutes the vast majority of the total experience.

Recipient Selection

Liver transplantation is indicated in chronic, irreversible and progressive liver disease intractable to medical or alternative surgical therapy. It may also be indicagted when patients experience severe subjective symptoms, such as fatigue in primary biliary cirrhosis. Transplantation may be appropriate in the following diseases.

1. Biliary atresia.
2. Inborn error of metabolism, eg, alpha-1 antitrypsin deficiency, Wilson's disease and tyrosinaemia.
3. Chronic active hepatitis.
4. Primary biliary cirrhosis.
5. Sclerosing cholangitis.
6. Primary hepatic malignancy.
7. Subacute hepatic necrosis.

Major contraindications include extrahepatic malignancy and severe sepsis and active alcoholism. Portal vein thrombosis, severe cardiopulmonary or renal disease, age over 55 years, past multiple abdominal operations, psychological instability and positive hepatitis B e-antigen infection are relative contraindications. Fulminant hepatic failure (FHF) and advanced encephalopathy are by themselves, not outright contraindications.

Donor Selection

All necessary medical and legal formalities for organ harvesting are met beforehand. It is usual to obtain other organs at the same from the liver donor. The clinical criteria for postmortem liver donors are more restrictive than for renal donation (Table 1). The criteria for donor selection is less stringent when transplantation is urgent (eg, with FHF or retransplantation). Histocompatibility matching between donor and recipient is not undertaken because of the time involved and the small recipient pool. Lymphocytotoxic crossmatching

(testing recipient serum against donor lymphocytes) is controversial, but positive matches may predispose to humorally mediated rejection.

Table 1. *Clinical Criteria for Cadaveric Liver Donors*

1. Age less than 55 years.
2. No hepatobiliary disease or severe liver trauma.
3. Acceptable liver function tests and coagulation profile.
4. Size and ABO compatibility with available recipient.
5. No extracerebral malignancy.
6. No active systemic or hepatic infection.
7. Negative HIV and hepatitis B serology.
8. Negative cytomegalovirus (CMV) serology (if recipient is CMV negative).

Operation

There are three components to the entire procedure for liver transplantation.

1. Donor hepatectomy.

2. Recipient hepatectomy and establishment of veno-venous bypass during the anhepatic period. Routine use of bypass has resulted in improved haemodynamic stability, less blood loss and postoperative renal failure, and better survival.

3. Liver implantation by anastomoses of the liver vessels and biliary tract reconstruction. The recipient operation takes 6-16 hours. A recently developed University of Wisconsin perfusion solution, has increased liver preservation times from approximately 8 to 20 hours. This may allow transplantation to be undertaken on a more elective basis.

Blood loss can reach 1500 mL/min, and blood requirements may range from 10-100 units. In general, one unit each of fresh frozen plasma (FFP) and platelets are required for each unit of blood. The anhepatic phase (when metabolic acidosis may develop) and the revascularization phase (when disseminated intravascular coagulation (DIC) may occur) are critical times during the operation.

Postoperative Management

The postoperative care of liver tranplant recipients is potentially difficult and patients should be admitted to the ICU.

1. *Mechanical ventilatory support* is required for the first 12-48 hours.

2. *IV fluids and blood products* are administered as required. Excessive drainage of ascites will require increased fluid and protein volumes. This occurs mostly in those with gross ascites preoperatively, but may rarely signify development of an acute Budd-Chiari syndrome.

3. *Surgical drains* are monitored for volumes and presence of frank blood or bile which may be indications for reoperation.

4. *Routine medications* include a broad spectrum antibiotic (eg, cefotaxime) for 5 days, stress ulcer prophylaxis (eg, IV ranitidine 50 mg tds), vitamins and minerals, oral and nasogastric nystatin and immunosuppressive drugs (see below). If the patient has negative cytomegalovirus (CMV) serology, CMV hyperimmune globulin (10.000 units) is administered daily for at least one week. In some centres selective decontaminatino of the digestive tract is practised.

5. *Routine investigations* include regular arterial blood gas measurements, 6 hourly measurements (for the first 24 hours) of full blood count, coagulation profile, plasma electrolytes, glucose, creatinine, ionised calcium and liver function tests. Plasma concentrations of magnesium, phosphate, albumin and amylase are measured daily. Cyclosporin levels are measured daily and other drug levels are determined when indicated. A chestX-ray and 12-lead ECG are performed daily. Cultures of drains and body fluids are performed every second day. The function of the allograft is routinely monitored by radionucleide scanning on day 2 and day 5.

6. *Narcotic analgesics* are administered by infusion (eg, morphine 1-10 mg/h). Analgesic requirements usually decrease markedly after the first few postoperative days.

7. *Active chest physiotherapy* is required.

8. *Psychiatric and emotional support* for both the patient and relatives should be continued.

9. *Nutritional support* by enteral or parenteral (TPN) feeding should be given. Resting energy expenditure (REE) is increased in chronic liver disease. Hypercatabolism is present in the early period after OLT. Lipid and carbohydrate intolerance occur, and high caloric TPN should be avoided.

Immunosuppression

Methylprednisolone (1 g IV) is administered intraoperatively before revascularization of the liver. A further 500 mg IV is administered postoperatively. The dose is then tapered daily to give a maintenance dose of 0.5 mg/kg by the end of the first 2 weeks.

Cyclosporin 10 mg/kg is given orally preoperatively. If renal function is stable, 4 mg/kg/day is given IV in 2-3 divided doses from the first postoperative day. Once oral intake is established, 12 mg/kg/day is given orally in 2 divided doses. Cyclosporin absorption depends on enterohepatic circulation and requirements may decrease when the T-tube is clamped. Therapeutic levels are 400-800 ng/mL. Adverse effects of cyclosporin are shown in Table 2.

Table 2. *Adverse Effects of Cyclosporin*

1. Nephrotoxicity.
2. Neurotoxicity.
3. Hepatotoxicity.
4. Hypertension.
5. Hirsutism.
6. Gingival hyperplasia.
7. Flushing, nausea and abdominal discomfort.
8. Thromboembolism.
9. Lymphoproliferative disease.

Azathioprine or other immunosuppressive agents should be substituted if renal dysfunction is present, until cyclosporin can be introduced.

Postoperative Complications

Patients with endstage liver disease frequently have profound nutritional depletion, debility and multiple organ dysfunction preoperatively. Hence, 85% develop at least one postoperative complication.

1. Bleeding

Continuing postoperative bleeding is usually of surgical origin. Urgent re-exploration is often required. Bleeding associated with coagulopathy can usually be corrected with infusion of fresh frozen plasma and platelets. Inability to correct the coagulopathy is usually a sign of poor graft function. Thrombocytopenia is common in the first week. The aetiology is unclear but patients usually have a hyperplastic bone marrow. The allograft itself, with ischaemic damage, may be the major site of platelet sequestration.

2. Metabolic Complications

(a) *Hypothermia* occurs despite intraoperative use of warming blankets and requires continuing treatment.

(b) *Hypokalaemia* is probably secondary to preoperative potassium depletion and uptake into the allograft, following loss from the hepatic cells during the period of cold preservation. Controlled replacement is indicated. Persistent hyperkalaemia postoperatively is an ominous sign of poor liver function.

(c) *Metabolic alkalosis* is frequent during the early postoperative period and is probably due to the large amounts of citrate infused with stored blood as well as hypokalaemia.

(d) *Hypocalcaemia* is also due to the citrate load from massive transfusion. Calcium deficits should be replaced.

(e) *Hypomagnesaemia* is implicated in postoperative seizures. Postoperative magnesium deficits should be corrected.

(f) *Hyperglycaemia* occurs frequently and is probably secondary to steroid therapy. Insulin by infusion may be required. Persistent hypoglycaemia in the early postoperative period suggests poor liver function and a grave prognosis.

3. Pulmonary Complications

Patients are electively ventilated in the initial postoperative period. The most common pulmonary complications are infections including pneumonia, empyema and lung abscess, caused by bacteria, viruses, fungi, or *Pneumocystis carinii*. Pleural effusions, primarily right-sided, are common. The majority resolve spontaneously or respond to diuretic therapy. If the adult respiratory distress syndrome (ARDS) occurs after liver transplantation, an intra-abdominal catastrophe should be suspected. ARDS is associated with acute allograft rejection, hepatic artery thrombosis, and most commonly, sepsis.

4. Cardiovascular Dysfunction

Hypertension is a frequent complication when cyclosporin is used, and antihypertensive agents are required. When sustained and refractory, infusions of hydralazine or sodium nitroprusside may be indicated. Hypertension is thought to be due to effects of cyclosporin, although the mechanism is unknown. Other cardiovascular complications are rare.

5. Renal Dysfunction

Postoperative renal dysfunction occurs in up to 2/3 of liver transplant recipients. Preexisting renal failure is exacerbated. Raised plasma creatinine levels and the need for haemodialysis are poor prognostic indicators. Persistent renal failure may result from continuing bleeding, sepsis or poor allograft function (possibly further compromised by nephrotoxic drugs, especially cyclosporin, aminoglycosides and amphotericin). Preoperative renal failure due to the hepatorenal syndrome, usually resolves postoperatively. The use of venovenous bypass and low-dose dopamine infusion (2 microg/kg/min) have decreased the incidence of postoperative renal failure.

6. Neurological Complications

Neurological complications occur in 1/3 of liver transplantation patients. Fits are common, usually associated with cyclosporin toxicity or hypomagnesaemia. Clinical features of cyclosporin neurotoxicity range from minor neuropsychiatric syndromes through to the syndrome of encephalopathy, seizures and white matter oedema, sometimes associated with cortical blindness. Cyclosporin neurotoxicity occurs in 30% of liver transplantation patients, but in only 0.5% of other organ transplantation. If no cause can be demonstrated for neurological compilcations, cyclosporin dosage should be reduced. Other neurological complications include hypoxic encephalopathy, air embolism, intracerebral haemorrhage, central pontine myelinolysis, hepatic and metabolic encephalopathy, and opportunistic infection (with listeria, cryptococcus and viruses being most common).

7. Infection

Up to 80% of liver transplant patients have at least one infection postoperatively. The majority are bacterial infections and appropriate antibiotics should be given. Fungal infections (42%, with Candida and aspergillus being most common) should be treated with amphotericin B. The most common viral infections are of Herpses and CMV, and should be treated respectively with acyclovir 5 mg/kg tds and gancyclovir 5 mg/kg/day. Abdominal infection occurs in approximately 20%. Diffuse peritonitis has a mortality rate of 75%, due more to mixed infections than isolated bacterial infection. Localized intra-abdominal abscesses occur most commonly in the right subphrenic space. Immunosuppressive therapy should be reduced in significant infection.

8. Liver Dysfunction

Immediately after transplantation, plasma transaminases are elevated, due to unavoidable ischaemic injury. Concentrations are usually less than 1000 IU/mL. Levels above 3000 IU/mL usually indicate significant damage. Plasma bilirubin is often lower than preoperative levels due to "wash-out" from massive transfusion. Liver function usually returns towards normal relatively quickly but up to 2/3 patients have a degree of liver dysfunction after this initial ischaemic episode.

(a) *Ischaemic Injury* - A non-functioning graft is an extreme form of ischaemic injury. There is total hepatic failure with profound hypoglycaemia, coagulopathy and coma. Treatment is retransplantation, although only 20% of those retransplanted survive.

(b) *Technical Consultations* - Bleeding is the most frequent postoperative technical complication. Graft failure may result from occlusion of any of the four vascular anastomoses. Hepatic artery thrombosis occurs in approximately 3% of adults and 12% of children. It may present as massive liver necrosis, bile duct necrosis, or liver abscesses. Problems with the biliary anastomosis occur in 10-15%. These include biliary leaks, strictures, and obstruction. Biliary tract problems are diagnosed by a T-tube cholangiogram or by percutaneous cholangiography.

(c) *Rejection* - Rejection is the commonest cause of graft dysfunction and occurs to some extent in every patient in the 2nd and 3rd week. The clinical picture and severity are variable. There is frequently general malaise, fever and abdominal pain associated with firmness and tenderness of the graft. Rejection may develop slowly and progressively or acutely and rapidly, which is difficult to treat. The diagnosis is made by liver biopsy. In acute rejection there is infiltration of the portal tracts, particularly the bile ducts, with lymphoid cells and associated endothelitis. A common form of chronic rejection is the vanishing bile duct syndrome, which has been associated with a mismatch for class I HLA antigents. Treatment of rejection episodes consists of increasing steroid doses, antilymphocyte globulin (ALG) and/or a monoclonal antilymphocyte antibody such as OKT3. The latter has been shown to improve graft survival when steroid therapy is unsuccessful.

(d) *Hepatic Infection* - Infection of the transplanted liver with viruses may occur at any time but usually between 2 weeks and 3 months. Pathogens include Hepatitis B, CMV, Herpes simplex and zoster, adenovirus and Epstein Barr virus.

(e) *Drug Induced Injury* - Virtually all groups of drugs have been associated with liver injury. Cyclosporin, azathioprine, methyldopa, phenytoin and many antibiotics have been incriminated.

(f) *Cholestasis* - Cholestasis may occur in the first two weeks after srugery. The causes are multifactorial and similar to the "benign postoperative cholestatic syndrome" or "ICU jaundice", and it usually settles by the end of the third week. A schema for the diagnosis and treatment of postoperative liver dysfunction is shown in the figure.

1. Liver Dysfunction --> Sepsis Cholangitis Vascular
    a. No - Go to 2.
    b. Yes - Go to 3.
2. Liver Biopsy --> Rejection
    a. No - Go to 4.
    b. Yes - Go to 5.
3. Treat Appropriately
4. a. Drugs
    b. Surgical Cholestasis
    c. Viral
5. Anti-Rejecton Therapy.

Paediatric Considerations

The major indications for OLT in children are biliary atresia and genetic and metabolic disorders. Chronic liver disease, FHF and liver tumours are less common indications. The long term survival rate is higher than for adults, and as many as 80% survive for 2-3 years. Paediatric liver transplantation has been impeded by a shortage of paediatric donors. This has led to the technique of reduction hepatectomy of adult donor livers by performing an in-vivo or ex-vivo right hepatic lobectomy or trisegmentectomy. Complex vascular techniques are required to reduce adult major blood vessels to a size suitable for anastomosis. Technical complications, particularly hepatic artery thrombosis, are more common in children. Venovenous bypass is not always used in paediatric patients as they generally remain haemodynamically stable during the anhepatic phase. Most children exhibit normal or accelerated growth following a successful liver transplant, and the majority have an excellent quality of life.

Retransplantation

In the early postoperative period, retransplantation is indicated if the primary graft fails (up to 20% of cases). Survival rates approach 50% except those in coma. The most frequent indications are primary graft nonfunction, intractable rejection or complications arising from technical problems. Retransplantation may also be required some time after transplantation, usually because of intractable chronic rejection.

Liver Transplantation for Fulminant Hepatic Failure

Currently, worldwide survival rates for OLT in FHF (41 cases) is 61%, and hence transplantation is rapidly becoming a standard option in the treatment of FHF. The key issues are:

1. Rapid diagnosis and estimation of prognosis. The best clinical predictor of outcome is the degree and rate of deterioration of encephalopathy. Rising prothrombin time, renal impairment and hypoglycaemia are all ominous signs that influence the decision towards liver transplantation.

2. Meticulous medical support. (See Chapter 33, Hepatic Failure.)

3. Ready availability of donor.

Liver transplantation for FHF is technically less difficult because of the abscence of established porto-systemic collateral blood channels. Despite the coagulopathy, massive blood loss is not usually a major problem. Successful liver transplantation is followed by rapid return of consciousness within the first few days. Results have been poor with grade IV encephalopathy, severe renal failure and massive gastrointestinal bleeding. Improving survival rates suggest liver replacement may be justified in somewhat earlier stages of FHF. Viral hepatitis is the most common cause of FHF. Hepatitis B immunoglobulin, injected during the anhepatic phase, does not seem to be effective in preventing recurrent disease (and may be associated with fatal intraoperative thromboembolism).

Outcome

Early death is related to infection, multi-organ failure and uncontrollable rejection. One year survival can be as high as 80% and 5 year survival 60%, and the majority of patients experience a good quality of life. Most mortality occurs in the first 6 months after transplantation, and in patients who survive 1 year, the chance of dying each year afterwards, is < 3%. Deaths after the first year are due chiefly to recurrence of primary liver malignancy, graft rejection, lymphoproliferative disease, opportunistic infections or late bile duct complications. Recurrent tumour can be expected in up to 80% patients transplanted for primary hepatic malignancy.