Graft Dysfunction

Geoffrey H. Haydon

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Geoffrey H. Haydon, MRCP, MD
Liver Unit
Queen Elizabeth Hospital

The causes of graft dysfunction are classified either according to the time posttransplantation or to the etiology of graft dysfunction. Primary dysfunction can be due to massive hemorrhagic necrosis, ischemia/reperfusion injury, or hepatic artery thrombosis. Acute cellular rejection (ACR) occurs in 20% to 80% of grafts, usually 5 to 30 days posttransplant. ACR generally is asymptomatic. Chronic ductopenic rejection is defined histopathologically by obliterative vasculopathy and bile duct loss. CMV and EBV infections also diminish graft function. Malignancies occur in solid organ transplant recipients with a frequency 10-1000 times that of the normal population. Skin cancer and lymphoma are the most common types. Posttransplant lymphoproliferative disorders (PTLD) are associated with EBV infection. There are three types of PTLD: polyclonal B-cell hyperplasia, polymorphic B-cell lymphoma, and monoclonal polymorphic B-cell lymphoma. Graft ischemia is due to hepatic artery thrombosis (HAT), hepatic artery stenosis, and portal vein thrombosis. Biliary complications are the most frequent late complications of liver transplantation, with an incidence of 15% to 20%.

Keywords: liver transplantation; Banff criteria; cytomegalovirus; Epstein-Barr virus

Introduction

The causes of graft dysfunction occurring after liver transplantation may be classified either according to the time period posttransplantation (Table 1) or according to the etiology of the graft dysfunction. It should be emphasized that any of these conditions may become evident at any time after liver transplantation, and Table 1 lists the most common times for presentation.

Investigation of Graft Dysfunction

The general diagnostic approach is outlined in Table 2. Investigation of each of the complications above is considered under the appropriate heading.

Primary Graft Nonfunction

Primary graft nonfunction is defined as failure of the graft to function in the first postoperative week. It is manifested by

- Failure to regain consciousness
- Sustained elevations in transaminases
- Increasing coagulopathy
- Acidosis
- Poor bile production

Primary graft nonfunction may be due to

- Massive hemorrhagic necrosis
- Ischemia/reperfusion injury
- Hepatic artery thrombosis
- Idiopathic

It may be difficult to distinguish nonfunction, which will not recover, from early poor function, wherein graft function will return to normal after a period of systematic support. The value of agents such as prostaglandins and n-acetyl cysteine in these circumstances is uncertain.

Immunological Complications

Acute Cellular Rejection (ACR)

Definition:

- Inflammation of the allograft elicited by genetic disparity between the donor and recipi-

Geoffrey H. Haydon, MRCP, MD
Liver Unit
Queen Elizabeth Hospital
Birmingham, UK
e-mail: geoffhay@email.msn.com

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Table 1 | **Etiology of Graft Dysfunction More Than 1 Month Posttransplantation**

Time Period Post-OLT	Diagnosis
1-6 months	Acute cellular rejection
	Opportunistic infection -Viral: CMV, EBV (HSV, VZV less common)
	Vascular -Hepatic artery thrombosis
	Recurrent viral hepatitis
	Biliary tract abnormalities
6-12 months	Acute cellular rejection
	Recurrent viral hepatitis
	Biliary tract abnormalities
	Chronic ductopenic rejection
	Hepatic artery thrombosis
> 12 months	Recurrent viral hepatitis
	Biliary tract abnormalities
	Acute cellular rejection
	Chronic ductopenic rejection
	Recurrent autoimmune disease (PSC, PBC, AICAH)
	Hepatic artery thrombosis
	Steatohepatitis

Table 2 | **Graft Dysfunction According to Pathogenesis**

- Immunological complications: acute cellular rejection; chronic ductopenic rejection
- Primary viral infection: CMV, HSV, EBV
- Graft ischemia: hepatic artery thrombosis
- Biliary complications: biliary leaks, bile duct strictures, choledocholithiasis and cholangitis
- Recurrent disease: viral hepatitis (HCV, HBV), PBC, PSC, AICAH, NASH

Table 3 | **Banff Criteria Grade of Histologic Injury**

Subjective Grade	Criteria
Indeterminate	Portal inflammatory infiltrate that fails to meet criteria for the diagnosis of acute rejection
Mild	Rejection infiltrate in a minority of the triads, that is generally mild and confined within the portal spaces
Moderate	Rejection infiltrate expanding most or all of the triads
Severe	As above for moderate, with spillover into periportal areas and moderate to severe perivenular inflammation that extends into hepatic parenchyma and is associated with perivenular hepatocyte necrosis

Banff grading of acute liver allograft rejection. Global assessment of rejection grade made on review of the biopsy and after diagnosis of rejection has been established.

ent, primarily affecting interlobular bile ducts and vascular endothelia, including portal veins and hepatic venules, and occasionally the hepatic artery and its branches.

Incidence:

- Occurs in 20% to 80% of grafts.

Timing:

- First occurs between 5 and 30 days posttransplantation; 80% of ACR occurs in the first 10 weeks posttransplantation. ACR may still occur thereafter.

Clinical Findings:

- Usually asymptomatic, although in late or severe cases, fever and hepatomegaly occur. When bile is collected, it is noted to be pale and watery.

Investigations:

- Liver chemistry tests are usually abnormal (but nonspecific), and blood leukocytosis and

Table 4 | **Reported Risk Factors for Chronic Ductopenic Rejection**

Highly probable:
-Retransplantation for chronic rejection
-Late acute rejection episodes
-Steroid-nonresponsive acute cellular rejection
Controversial associations:
-Underlying liver disease
-AICAH
-PBC
-PSC
-Positive lymphocytotoxic cross-match
-CMV infection
-Recipient age
-Donor/recipient of different ethnic origins
-Male donor allograft into female recipient
-Cyclosporin-based immunosuppression (compared with tacrolimus regimes)

Table 5 | **Histological Features and Grading of Chronic Ductopenic Rejection**

Bile duct loss,* without centrilobular cholestasis, perivenular sclerosis, or hepatocyte ballooning, or necrosis and dropout
Bile duct loss,* with one of the following four findings:
-centrilobular cholestasis
-perivenular sclerosis
-hepatocellular ballooning
-hepatocyte necrosis and dropout
Bile duct loss,* with at least two of the four following findings:
-centrilobular cholestasis
-perivenular sclerosis
-hepatocellular ballooning
-centrilobular necrosis and dropout
*Bile duct loss: > 50% of triads.

BANFF CRITERIA

Grade of histologic rejection injury

CHRONIC DUCTOPENIC REJECTION

Involves obliterative vasculopathy and bile duct loss

eosinophilia are frequently present. The gold standard for diagnosis of acute cellular rejection remains liver histology. The histological features are mixed inflammatory infiltrate in the portal triads, bile duct damage, and vascular endothelial damage. The Banff criteria grade of the severity of histological injury (see Table 3).

The differential diagnosis of deteriorating graft function is infection, graft ischemia, and biliary obstruction. The gold standard for diagnosis of ACR remains liver histology.

Prognosis:

- A single episode of easily reversed acute cellular rejection confers a better patient and graft survival than observed in patients who never experience rejection. In contrast, acute cellular rejection that does not respond to increased immunosuppression (steroid-resistant rejection) is associated with graft loss.

Chronic Ductopenic Rejection

Definition:

- Chronic ductopenic rejection is defined by two histopathological features: obliterative vasculopathy and bile duct loss (Table 4). It is also called chronic rejection and chronic vanishing bile duct syndrome.

Incidence:

- Most programs report less than 5% of grafts develop chronic ductopenic rejection.

Table 6 | **Differential Diagnosis of Cholestatic Liver Disease in the Transplanted Liver**

Chronic ductopenic rejection
Biliary obstruction
Viral hepatitis (viral cholestatic hepatitis)
Sepsis
Drug hepatotoxicity
Recurrent primary biliary cirrhosis
Recurrent primary sclerosing cholangitis

CMV

Cytomegalovirus

Timing:

- Chronic ductopenic rejection may occur at any time after liver transplantation but is usually seen in the 1st postoperative year.

Clinical Findings:

- As with ACR, most patients are free of symptoms. Some have generalized systemic symptoms or complain of increasing jaundice and cholestatic symptoms.
- Risk factors for chronic ductopenic rejections are shown in Table 4.

Investigations:

- Liver chemistry tests usually demonstrate a relentless rise in markers of cholestasis. Liver biopsy is essential to make the diagnosis of chronic ductopenic rejection. Special cytokeratin stains to identify biliary epithelia are useful when assessing bile duct loss. Vascular lesions may be absent on needle biopsy specimens (Table 5).
- Hepatic angiography may show vascular injury.

Differential Diagnosis (see Table 6)

Treatment (this is described in this issue by Neuberger in "Immunosuppresion after Liver Transplantation").

Prognosis:

- Approximately 30% of patients with chronic ductopenic rejection respond to conventional additional immunosuppressive therapy. In those who do not respond to standard immunosuppression, re-grafting is the only other option.

De Novo Autoimmune Hepatitis

In a small number of liver transplant recipients, a syndrome resembling autoimmune hepatitis develops. It is characterized by biochemical hepatitis, autoantibodies, and histologic appearances of inflammatory hepatitis. The hepatitis usually responds to reintroduction or increased doses of corticosteroids.

Graft Infection

Infection is a major cause of morbidity and mortality posttransplantation; there is also a complex interplay between the immune system and infectious agents.

CMV Disease

Timing:

- Commonly within 2-3 months, and rarely within the first month of transplantation

Clinical Presentation:

- Triad: fever, leucopenia, thrombocytopenia
- May present as hepatitis, pneumonitis, GI tract infection (esophagitis, gastritis, duodenitis, and colitis)

Diagnosis of CMV Disease:

- Abnormal liver chemistry tests
- CMV PCR-positive when there is active viremia or shedding of virus (specificity 50%-60%)
- Typical CMV inclusion bodies demonstrated on liver biopsy. May also be seen in rectal or duodenal biopsies
- CMV PCR of liver biopsy

Risk Factors for CMV Infection:

Table 7 | **Clinical and Histological Features of EBV Related Graft Dysfunction**

Disease/Disorder	Clinical Features	Histology	Therapy	Outcome
Posttransplant infectious mononucleosis (IM)	Fatigue, fever, rash, sore throat, lymphadenopathy	Mild increase in portal infiltrates	Acyclovir	Self-limited disease/resolved
Polyclonal B-cell hyperplasia	Similar to acute IM with severe hepatitis, bone marrow failure, and ARDS	Prominent portal lymphocyte and (plasma cell) infiltrate	Decreased immunosuppression; treat with acyclovir or ganciclovir	Responds to antiviral treatment/ resolves
Polyclonal proliferation B-cell lymphoma	Nodal and extranodal lymphocytic proliferation in patients treated with immunosuppressive medication	Polymorphic lymphocytic infiltrate	Withdraw immunosuppression; treat with acyclovir, ganciclovir, or anti-B-cell monoclonal Ab	Most progress to lymphoma and have a low survival rate
Monoclonal polymorphic B-cell lymphoma	Nodal and extranodal lymphocytic proliferation in patients treated with immunosuppressive medication	Polymorphic to monomorphic lymphocytic proliferation depending on the stage of disease	Withdraw immunosuppression; treat with chemotherapy, radiotherapy, or surgical resection	Aggressive disease with survival rate of less than 1 year

- The respective serological status of the donor and recipient is most important and must be documented: seronegative recipients of a graft from a seropositive donor have the highest risk of infection
- Infection may be transmitted by the graft, blood products, reactivation of previous infection, or superinfection by a CMV variant
- Patients with septic biliary complications (including hepatic artery thrombosis)
- Patients transplanted for fulminant hepatic failure
- Recipients treated with muromab OKT3 or thymoglobulin. The risk of CMV in recipients of monoclonals directed against the IL-2 receptor remains uncertain

Prophylaxis against CMV Infection:

- Ganciclovir and acyclovir are highly effective against CMV reactivation, reinfection, or new disease
- Studies comparing the two drugs suggest that ganciclovir produces a more significant reduction in infection than acyclovir
- Individual programs determine policy regarding prophylactic regimes against CMV. Prophylaxis may be restricted to high-risk patients but are not essential for all recipients

Treatment of CMV Graft Infection:

- Immunosuppression should be reduced (azathioprine usually stopped)
- A 14-day course of intravenous ganciclovir (10 mg/kg/day IV in two doses) is most effective. Many programs follow this with 6 weeks oral ganciclovir
- Second-line therapy: Foscarnet 60 mg/kg every 8 hours for 14 days (avoid in renal failure); CMV Ig
- Third-line therapy: Cidofovir 5 mg/kg once weekly for 2 weeks, followed by 5 mg/kg every 2 weeks (also avoid in renal failure)

EBV Hepatitis (Table 7)

Timing:

- No specific timing after liver transplantation

Clinical Presentation:

- Infectious mononucleosis syndrome (fever, fatigue, lymphadenopathy, pharyngitis)

Diagnosis of EBV hepatitis:

- Abnormal liver chemistry tests
- Liver biopsy: well-differentiated mononuclear B lymphocytic portal infiltrate without bile duct damage. EBV does not infect hepato-

EBV

Epstein-Barr virus

Table 8 | **Presentation of Hepatic Artery Thrombosis (HAT)**

Clinical Presentation
Acute graft failure
Massive rise in liver enzymes (particularly transaminases). This is a feature of HAT presenting immediately after transplantation
Unexplained septicaemia
Biliary tract problems
-Leaks
-Abscess
-Breakdown of biliary anastomosis
Liver abscess (may be sterile, also called a biloma)

cytes, biliary epithelium, or vascular endothelium

- PCR for EBV DNA (serum and biopsy sample)

Prophylaxis against EBV Infection:

- None is necessary

Treatment of EBV hepatitis:

- A decrease in the immunosuppressive therapy will result in resolution of both symptoms and histopathological findings

Outcome of EBV infection after liver transplantation:

- Excellent prognosis

Posttransplant Lymphoproliferative Disorders (PTLD) (Table 7)

PTLD

Posttransplant lymphoproliferative disorder

Malignancies occur in solid organ transplant recipients with a frequency 10-1000 times that of the normal population. After skin cancer, lymphoma has the second highest incidence in the immunosuppressed patient. The association of EBV with posttransplant lymphoproliferative disorders has been well described, and the presence of EBV-specific proteins and fragments of EBV genome demonstrated consistently in PTLD. There are three clinical disorders of differing presentations and prognosis, which may involve graft dysfunction in PTLD.

Polyclonal B-cell Hyperplasia

Clinical Presentation:

- As for infectious mononucleosis

Subpopulation:

- Young patients in second to fourth decade, who are profoundly immunosuppressed

Histology:

- Polyclonal B-cell lymphoproliferation

Treatment:

- Acyclovir

Outcome:

- Usually excellent response to acyclovir

Polymorphic B-cell Lymphoma

Clinical Presentation:

- Patients present with infectious mononucleosis-like symptoms and then develop a rapidly disseminated lymphoproliferation involving the liver, spleen, and other visceral organs

Histology:

- Polymorphic B-cell lymphoproliferation

Treatment:

- Immediately withdraw immunosuppression and initiate antiviral therapy

Outcome:

- Usually fatal

Monoclonal Polymorphic B-cell Lymphoma

Clinical Presentation:

- Usually older patients more than 5 years posttransplant. Prominent extranodal masses de-

velop in the central nervous system, gastrointestinal tract, and liver

Histology:

- Non-Hodgkin's lymphoma with a monomorphic pattern and monoclonal immunoglobulin expression

Treatment:

- Withdraw immunosuppression. Surgical resection of masses with adjuvant radiotherapy and chemotherapy

Outcome:

- Aggressive disease with high mortality at 1 year

Graft Ischemia

HAT

Hepatic artery thrombosis

Hepatic Artery Thrombosis (HAT)

- Hepatic artery thrombosis is one of the principal causes of morbidity and graft loss following liver transplantation
- Presentation (see Table 8)

Incidence:

- This has been described as high as 10%; technical aspects of the arterial anastomosis are important particularly for early thrombosis, but with improvement in surgical technique, it is likely that the incidence is falling. It is a recognized component of the small-sized graft syndrome in recipients of adult-to-adult right-lobe grafts

Timing:

- It is most common within the first month after transplantation, but may occur at any time

Clinical Sequelae:

- Graft necrosis
- Intrahepatic abscesses. Also called "bilomas"
- Infarction of the bile ducts with bile leakage and gram-negative sepsis

Diagnosis of Hepatic Artery Thrombosis:

- Doppler sonography (sensitivity for diagnosis of hepatic artery thrombosis: 60%-92%)
- Confirmed by arteriography (CT, MR, or arteriograms)

Risk Factors:

- Technical aspects of the arterial anastomosis
- Raised hematocrit
- Low donor/recipient age ratio
- Procoagulant syndromes
- Smoking
- CMV infection (followed by rapid procoagulant response)
- Adult-to-adult right-lobe transplantation

Treatment:

- Early thrombosis is an indication for urgent regrafting
- Patients with late thrombosis may survive with conservative therapy and satisfactory graft function
- There are anecdotal reports of a good response to thrombectomy and thrombolytic therapy

Hepatic Artery Stenosis

Stenosis of the hepatic artery may present with unexplained elevated liver-chemistry tests. Doppler sonography and hepatic arteriography are required to confirm the diagnosis. Resection of the stenosed portion and angioplasty are the treatments of choice when graft function is well preserved. Hepatic artery stenosis presenting with severely compromised graft function may require urgent retransplantation.

Portal Vein Thrombosis

This can occur in up to 3% of recipients; the diagnosis is often suggested by the subsequent development of gastroesophageal varices or other signs of portal hypertension. Treatment is usually management of the complications of portal hypertension. Thrombectomy or angioplasty are rarely feasible.

Biliary Complications

Biliary tract complications are the most frequent late complication of liver transplantation, with an incidence of 15%-20%. Biliary leaks occur at T-tube withdrawal in up to 30% of patients who have

a biliary drainage tube placed at time of transplant. Among the important factors that have been implicated in the pathogenesis of biliary strictures or leaks are

- The arterial supply to the biliary tree: biliary epithelial cells are particularly susceptible to interruption of their arterial blood supply, so that if this is compromised by even relative ischemia, bile duct necrosis will follow
- Bile composition: the composition of bile is altered following transplantation, predisposing to supersaturation with cholesterol and stone formation
- Denervation of the liver may inhibit or alter the composition of bile

Biliary complications have been recorded in up to 20% of recipients of living donor adult-to-adult right-lobe grafts

Early Biliary Complications:

- These can be recognized by the appearance of bile in surgical drains and the measurement of drain fluid bilirubin, in patients without T-tubes

Late Biliary Complications:

- Biliary leak following withdrawal of preoperative biliary drainage tube (often referred to as a "T-tube")
- Biliary strictures (see below)
- Ascending cholangitis
- Increasing cholestasis
- The biliary cast syndrome

Investigations:

- When the patient is septic, a full sepsis screen is undertaken
- Increasing cholestasis is investigated by ultrasound (or CT) and collections drained under ultrasound guidance
- The integrity of the biliary tree can be assessed by T-tube cholangiography, endoscopic retrograde cholangiography, or magnetic resonance cholangiopancreatography. Biliary leaks may resolve if stented by ERC
- If these investigations are normal, a liver biopsy is necessary to exclude chronic ductopenic rejection

Biliary Leaks

These occur because of ischemic necrosis at the anastomosis or following removal of a T-tube.

Bile Duct Strictures

- These are usually classified as anastomotic or nonanastomotic, anastomotic being the most common. Nonanastomotic strictures may be caused by long warm ischemic times during transplant surgery or by thrombosis of hepatic artery radicals (ischemic cholangiopathy); they are associated with ABO mismatches and are a feature of recurrent PSC. Bile leaks that heal spontaneously may result in anastomotic stricturing.
- Biliary leaks following the removal of a T-tube are best stented via the endoscopic or percutaneous route. Anastomotic strictures usually require surgical reconstruction with excision of the stricture and reanastomosis to a Roux loop of jejunum. Stenting may be palliative in selected cases.

The Biliary Cast Syndrome

- Associated with biliary stricture formation and ischemic injury to the biliary tree. May be more common with non-heart-beating donors. In addition to strictures, the extrahepatic and ultimately the intrahepatic biliary trees are clogged with cast material/sludge. Cholesterol is the main component of biliary cast matter.
- Presents with intractable pruritus
- Managed by serial removal of biliary cast material/sludge by ERC or by percutaneous cholangiography
- May require retransplantation

Recurrence of Disease after Liver Transplantation

Recurrence of disease following liver transplantation remains a problem for the long-term survivor

in several indications and may affect graft function and survival. It does, however, provide useful information about the pathogenesis of the underlying disease process.

Suggested Reading

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