Recent Advances

Hepatology

A N B McNair, C J Tibbs, R Williams

In the past decade, molecular biological techniques have led to an explosion of information about the mechanisms underlying liver disease, particularly in the field of viral hepatitis, where at least five new viruses and a multitude of variants have been described since 1989. The impact of molecular biology on the treatment of liver disease has been less dramatic, although recombinant technology is allowing the production of some effective new treatments and vaccines. The single major factor that has transformed the clinical management and outcome of patients with acute or chronic liver failure has been the development of liver transplantation from a largely experimental technique to part of routine clinical practice.

Recent advances in hepatology

Viral hepatitis
- New viruses identified
- New antiviral agents
- Improved methods of screening and prevention

Liver transplantation
- Auxiliary liver transplantation in acute liver failure and some inherited metabolic diseases of the liver
- New immunosuppressive agents: licensing of tacrolimus

Acute liver failure
- New definition
- Improvements in supportive care, including use of intravenous *N*-acetyl cysteine
- Progress in development of artificial liver

Management of bleeding varices
- Banding ligation, octreotide infusions, and transjugular intrahepatic portosystemic shunting

Viral hepatitis

PREVENTION

Several options are now available for the prevention of viral hepatitis in patients at risk of infection. Immune globulin has been used for some time to prevent hepatitis A and B, and vaccines have now been developed against these viruses. Screening of blood products for evidence of exposure to hepatitis B and hepatitis C viruses has also had a substantial impact on the development of post-transfusion hepatitis.

Effective control of hepatitis B by vaccination in high prevalence areas will allow effective control of this infection and associated hepatocellular carcinoma. Viral escape mutants, in which alteration of a key viral antigen prevents neutralisation by vaccine induced antibodies in the host, do not substantially alter the effectiveness of vaccination programmes aimed at large populations; a field study in the Gambia has shown a clear reduction in the incidence of hepatitis B in a high prevalence area.[1]

For travellers to developing countries, the recently developed vaccine against hepatitis A offers an important means of protection against this infection, which affects 3/1000 to 20/1000 people per month's stay abroad.[2] This high incidence makes hepatitis A the most common infection in travellers that may be prevented by vaccination. The new inactivated hepatitis A vaccines induce protective immunity in over 95% of recipients and offer protection for at least 10 years, whereas protection by immune globulin lasts only three to five months. Although the prospects for vaccination against hepatitis C seem remote, screening for the virus has had a considerable impact on its spread. The testing of all blood products since 1991 has virtually eradicated post-transfusion hepatitis.[3,4]

HEPATITIS B AND C: ADVANCES IN UNDERSTANDING AND TREATMENT

Variants of hepatitis B virus were first described in 1989; since then it has become clear that these variants develop in a large proportion of chronic carriers in the virus's attempts to escape immune surveillance.[5] That the hepatitis C virus is a highly variable agent has been recognised from the outset. There are now six recognised genotypes, with numerous subtypes, many of which are grouped geographically. Type 4 has been shown to have high subtype diversity in Africa and type 3 in south east Asia, leading to speculation that in these regions the infection has diversified over many centuries.[6,7] In Europe and North America, where there is relatively little subtype diversity, the hepatitis C virus is thought to have been introduced only recently; it has spread rapidly through high risk populations, misusers of intravenous drugs, and patients receiving multiple blood transfusions owing to the high transmission rates that these practices offer.[8] Reassurance is now available to those infected regarding the risk of transmission to family members —infection does not arise from casual contact, and sexual transmission seems to be rare. Owing to the long clinical course of the disease, accurate prognostication remains difficult, but cirrhosis develops only rarely before 20 years of infection.

Institute of Liver Studies, King's College Hospital, London SE5 9PJ
A N B McNair, *lecturer in medicine*
R Williams, *director*

Queen Mary's Hospital, Roehampton, London SW15 5PN
C J Tibbs, *consultant gastroenterologist*

Correspondence to:
Dr McNair.

BMJ 1995;311:1351-5

Although the long term response rate to interferon alfa, the only licensed treatment for hepatitis B and C in the United Kingdom, has changed little since figures were first published in the late 1980s, some improvements have been achieved by more careful selection of patients. In chronic hepatitis B, those with low concentrations of hepatitis B virus DNA (<100 ng/l) are six times more likely to respond than those with high concentrations (>200 ng/l), yet even in the group with the most favourable indications for treatment only half respond. Many factors may predict responsiveness to interferon in chronic carriers of hepatitis C virus (box); of these, RNA measurement and genotype analysis bring the use of molecular biology techniques into routine laboratory practice. Higher doses or longer courses of interferon may improve the overall rate of response to treatment,[9] but long term response remains below 50% in most series.

Factors predicting response to treatment with interferon alfa in chronic hepatitis[9-11]

Predictors of long term response
- Duration of illness <60 years
- Age <45 years
- Total interferon dose >600 mU
- Genotypes 2 and 3
- Low level of viraemia (<350 000 hepatitis C virus RNA eq/ml)

Predictors of non-response
- Body weight >70 kg
- Cirrhosis
- Genotype 1
- Total interferon dose <250 mU

There are grounds for optimism as new antiviral agents are developed, particularly for hepatitis B. After the unfortunate experience with the nucleoside analogue FIAU, in which several patients developed liver failure due to the inhibition of mitochondrial enzymes, other compounds designed primarily to inhibit viral replication are currently under evaluation. Of these, lamivudine has particular promise; data now emerging show a rapid inhibition of viral replication[12] even in patients who are immunosuppressed after liver transplantation. This drug is also being used to prevent recurrence after transplantation.

Nucleoside analogues have also been used in chronic hepatitis C infection. Although its effect is limited if it is used alone, ribavirin in combination with interferon may induce long term remission in a higher proportion of patients than either compound on its own.[13]

NEW VIRUSES

Of great interest is the recent description of several new hepatitis viruses, including the GB viruses, GB-A, GB-B, and GB-C.[14,15] These agents were found as a result of an intensive, commercially driven research programme, and two other companies have also presented results on further novel flavivirus-like isolates from patients with chronic "non-A non-B" hepatitis. Whether all three research groups have isolated novel agents remains to be seen. The GB viruses, like hepatitis C virus, seem to be related to the flaviviruses. They were isolated from tamarins infected by the blood of a Chicago surgeon with non-A non-B hepatitis. Regions of the viral RNA have sequence similarities with hepatitis C, with overall sequence homologies of 34-45% in those regions examined. Serological evidence of infection with one or other of these agents has been found in patients from North and South America and Africa.

The clinical impact of these new agents is unlikely to be as dramatic as the isolation of hepatitis C in 1989. However, no agent can be identified in more than 50% of patients presenting in Britain with acute liver failure that is apparently virally induced.

Liver transplantation

PATIENT SELECTION

The success of transplantation depends on careful patient selection. Although broad agreement has been reached on the criteria for transplantation in those with end stage chronic liver disease,[16] the indications for and timing of transplantation in acute liver failure are more contentious: operating early may reduce postoperative morbidity and mortality, but at the expense of unnecessary transplantation in some patients whose livers might have regenerated with continued supportive care. Given the high mortality of acute liver failure, early identification of patients who would benefit from transplantation is essential. O'Grady *et al* analysed the outcome of a large cohort of patients with acute liver failure, showing that survival depended on the age, time taken for the development of hepatic encephalopathy, the prothrombin time and, most important of all, the aetiology.[17] Over 50% of patients with fulminant hepatitis A, but fewer than 10% of those with non-A non-B hepatitis, would be expected to survive. They proposed two sets of criteria, one for liver failure induced by paracetamol and one for other aetiologies which, although widely used, are by no means universally accepted. Concentrations of clotting factor V of less than 20%[18] and volume of liver determined by serial computed tomography have also been advocated as useful prognostic factors.[19]

NEW TECHNIQUES: AUXILIARY LIVER TRANSPLANTATION

Although orthotopic liver transplantation provides a means of rapidly restoring liver function in patients with acute liver failure, it carries with it two significant disadvantages: the need for lifelong immunosuppression and the elimination of the possibility that the native liver may spontaneously regenerate. These problems are circumvented by auxiliary liver transplantation, in which an additional segment of liver is implanted to provide temporary support. In theory, once the recipient's liver has recovered, immunosuppressive agents can be withdrawn and the transplanted liver either removed or left to atrophy.

Initially, auxiliary liver transplantation was carried out by placing the donor liver in the right upper quadrant, adjacent to the native liver (heterotopic transplantation). An alternative technique, now performed more commonly, is to replace part of the native liver with the equivalent section of donor organ; this is called auxiliary partial orthotopic liver transplantation (APOLT; fig 1). A series of nine such

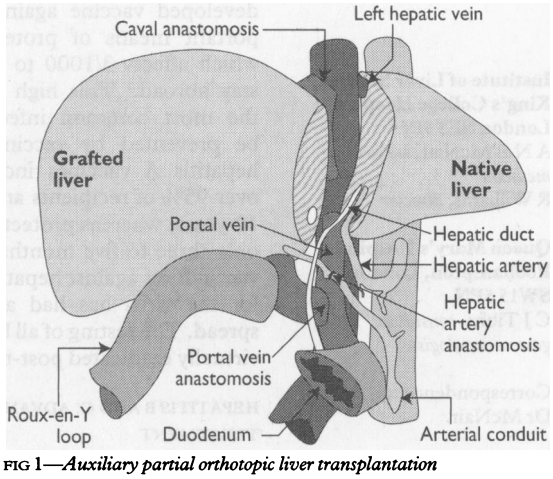

FIG 1—*Auxiliary partial orthotopic liver transplantation*

transplantations, performed in eight patients with acute liver failure, has recently been reported.[20] Although the complication rate was high—venous thrombosis occurred in two patients, and five required further surgery, one of whom had repeat auxiliary transplantation—the native liver regenerated rapidly in five of the patients, four of whom went on to discontinue permanently their immunosuppressive treatment. This technique may also prove useful in the management of patients with inherited defects of critical metabolic or synthetic processes which predominantly involve the liver but do not cause structural liver damage. A group in Chicago has recently described the use of auxiliary partial orthotopic liver transplantation to replace the defective enzyme in a patient with Crigler-Najjar syndrome; although the first graft failed, it was successfully replaced, resulting in a sustained reduction of bilirubin to near normal concentrations.[21]

NEW IMMUNOSUPPRESSIVE AGENTS

In 1994 the first new immunosuppressive agent since the advent of cyclosporin in 1980 was licensed. Immunosuppressive regimens based on cyclosporin have proved highly effective, with one year graft survival rates for elective operations in excess of 85%, but drug toxicity and graft rejection are still important causes of morbidity and mortality. Tacrolimus has a similar mode of action to cyclosporin, but weight for weight it is about 100 times more potent, and preliminary studies confirmed its efficacy both as a primary immunosuppressive agent and as a means of treating steroid resistant acute cellular rejection.

Two open randomised trials comparing immunosuppressive regimens based on tacrolimus and on cyclosporin have recently been published.[22,23] In total, 1074 patients were involved in these studies, and both found a lower incidence of acute, refractory acute, and chronic rejection in those receiving tacrolimus, though overall graft survival and patient survival were similar to the cyclosporin arm. Serious adverse events, including neurological complications and renal impairment, were more common in the tacrolimus group, but this may reflect the use of higher doses than are now regarded as necessary.

The value of tacrolimus in both the treatment and prevention of rejection will undoubtedly favour its use in patients who have had one or more episodes of steroid resistant acute rejection and in those who have had further transplantation for chronic rejection. Tacrolimus also requires less concurrent immunosuppression: prednisolone doses are usually lower than with cyclosporin based regimens and azathioprine is not required. This is advantageous in patients receiving transplants because of fulminant hepatic failure, who have a higher risk of postoperative infection and therefore benefit from lower doses of steroids.

A further advantage of tacrolimus over cyclosporin is that its oral absorption does not depend on the presence of bile salts. Cholestasis—caused, for example, by biliary obstruction or chronic rejection—leads to impaired absorption and lower blood concentrations of cyclosporin and may result in acute or worsening chronic rejection. However, a new microemulsion formulation of cyclosporin, whose absorption is independent of the presence of bile in the intestine, has recently been developed. Pharmacokinetic studies of this new agent have found that bioavailability is higher than for ordinary cyclosporin and is not affected by cholestasis.

Among other agents currently under evaluation, mycophenolate mofetil is shortly to receive a licence as an immunosuppressive agent in renal transplantation. Like azathioprine, this drug acts by inhibiting purine synthesis, but it has several theoretical advantages which suggest it will be useful in liver transplantation also.

STOPPING IMMUNOSUPPRESSION

Until recently, it was assumed that immunosuppression after organ transplantation had to be continued indefinitely. This view was supported by the observation that reducing or stopping immunosuppressive treatment commonly resulted in graft rejection and loss. A few of those patients who have discontinued their drugs, however, have done so without any adverse effects on the graft, suggesting a state of immunological tolerance. The mechanisms underlying this tolerance are uncertain, though clonal deletion, clonal anergy, or active immunosuppression by T cells have all been proposed. Starzl *et al* reported that donor specific hyporeactivity develops in recipients as a result of the exchange of migratory leucocytes between the graft and the recipient, with consequent cellular chimerism in both.[24] In support of this hypothesis, acute and chronic rejection have been significantly reduced in kidney recipients given an infusion of bone marrow after transplantation. This has now also been tested in the context of liver transplantation, but the initial results have been disappointing. In a randomised study, nine of 25 liver transplant recipients were given donor specific bone marrow after a 10 day course of antithymocyte globulin. There was no difference in the number of rejection episodes in the bone marrow and control groups, but unlike previous studies, donor cells were not identified in either peripheral blood or bone marrow of the recipient.[25]

Gradual withdrawal of immunosuppression in a group of patients at King's College Hospital who had undergone elective liver transplantation over five years previously led to 20% of patients permanently discontinuing treatment, with a significant reduction in treatment in most of the remainder.[26]

Acute liver failure

Extensive, acute liver damage, giving rise to hepatic encephalopathy within eight weeks of the appearance of the first symptoms, was originally termed fulminant hepatic failure. However, the recognition that patients with a more rapid onset of encephalopathy were more likely to recover spontaneously has led to a variety of other definitions. In an effort to standardise nomenclature, O'Grady *et al* have proposed a new terminology: hyperacute liver failure for cases in which encephalopathy occurs within seven days of the onset of jaundice; acute liver failure for those with an interval from jaundice to encephalopathy of 8-28 days; and subacute liver failure where the interval is 5-12 weeks.[27] Cerebral oedema is most common in patients with hyperacute liver failure, but survival is more likely in this group. The two other groups have a much poorer prognosis, the outlook being worst in patients with subacute hepatic failure.

TREATMENT OF ACUTE LIVER FAILURE

Recent advances in the understanding of the physiological changes which occur in acute liver failure have undoubtedly improved the quality of the supportive care that these patients receive. Cerebral oedema and sepsis are the commonest causes of death, and profound hypotension with multiorgan failure is frequently encountered. Rapid transfer to a specialist centre is essential to ensure optimal treatment. Early elective ventilation, prophylactic antibiotics and antifungal treatment, inotropic support, intracranial pressure monitoring, and technical advances in renal replacement therapy all play a role.[28-30] Specific treatments aimed at reversing the underlying physio-

logical abnormalities await development; antiviral treatments such as interferon have not proved beneficial, but agents that limit cell damage or promote hepatic regeneration seem more promising. Exogenously administered prostaglandins have been shown to protect the liver in animal models of hepatic failure,[31 32] though a randomised, double blind, controlled trial of prostaglandin E_2 therapy in 41 cases of virus induced and drug induced acute liver failure failed to show any benefit in terms of survival, with important side effects in those receiving active treatment.[33] The value of prostaglandins therefore remains in doubt, and their use will be restricted, for the present, to controlled trials.

The use of *N*-acetyl cysteine as a cytoprotective agent in cases of paracetamol toxicity is well established. The effects of *N*-acetyl cysteine are mediated in part through its ability to replenish intracellular stores of glutathione, and its use was initially restricted to the first 16 hours after overdose. Further studies have shown that the beneficial effects of *N*-acetyl cysteine extend beyond this period[34] and are not only mediated through its cytoprotective actions. *N*-Acetyl cysteine given by continuous intravenous infusion to 50 patients with paracetamol induced acute liver failure was associated with an increase in oxygen delivery and consumption,[35] possibly reflecting an effect on microcirculatory haemodynamics. *N*-Acetyl cysteine also seems to be beneficial in other types of acute liver failure and may be useful after liver transplantation in patients with early graft dysfunction,[36] but the results of controlled trials are awaited.

Bioartificial livers

Perhaps one of the most exciting areas in this field has been the research into the development of a hepatic support system or "bioartificial liver." Use of such a device in patients with acute liver failure could provide a bridge until the native liver regenerates or until a donor organ becomes available.

Recent efforts at hepatic replacement therapy have focused on systems, using cultured human hepatocytes, that would have the capacity to both remove toxins and provide synthetic functions. Animal models of acute liver failure provide evidence of a beneficial effect of such devices. As yet this has not been translated into clinical practice, but experiments in humans have begun. One such device, the extracorporeal liver assist device (ELAD), uses cultured human hepatoblastoma cells grown in the extracapillary space of a hollow fibre dialyser.[37] Venous blood is pumped through the fibres, leading to the ultrafiltration of plasma into the extracapillary space (fig 2). Return of the ultrafiltrate to the patient allows the delivery of high molecular weight products including clotting factors.

In one study of 11 patients with acute liver failure, no short term safety problems were encountered, and

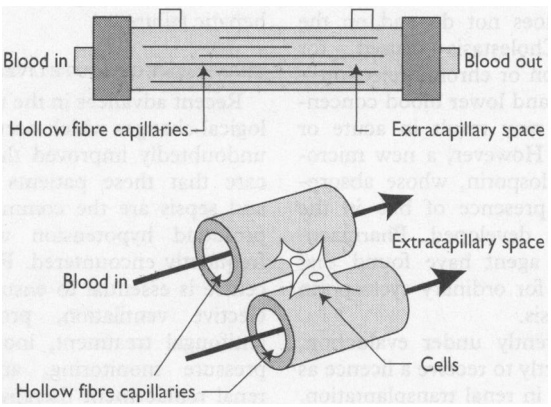

FIG 2—*Extracorporeal liver assist device*

Prevention and treatment of bleeding of oesophageal varices

Primary prophylaxis: β blockers
Secondary prophylaxis: β blockers, ?nitrates
Treatment of acute bleeding:
- Drugs: vasopressin, terlipressin, octreotide
- Endoscopic injection sclerotherapy: ethanolamine, thrombin, hystoacryl
- Endoscopic banding ligation
- Sengstaken-Blakemore tube
- Radiological: transjugular intrahepatic portosystemic shunt (TIPPS)
- Surgical: oesophageal transection, portosystemic shunts

10 patients were successfully weaned from the device or stabilised until the time of transplantation.[38] In another study of six patients treated as part of a randomised controlled trial, improvements in median international normalised ratio and concentrations of factor V were noted in five of the patients during continuous use of the device for periods ranging from one to six days, though treatment was discontinued in one patient due to an exacerbation of pre-existing disseminated intravascular coagulation.[39] Similar bioartificial livers, based on pig hepatocytes, have been used successfully in the treatment of animal models of acute liver failure.[40]

Chronic liver disease: advances in the management of varices

Although the use of immunomodulatory agents and liver transplantation has greatly improved the outlook for many patients with end stage liver disease, supportive measures still play a central role in the management of these individuals.

Variceal haemorrhage occurs in around 30% of patients with chronic liver disease, with a mortality as high as 50% for the first bleed. The list of therapeutic options for both preventing and treating bleeding varices has recently increased (box).

Endoscopic techniques remain the mainstay of treatment. Injection sclerotherapy controls bleeding in up to 95%, though rebleeding is common and adverse effects, including oesophageal ulceration and stricture formation, are common. More recently, variceal banding ligation has been shown in randomised trials to be at least as effective as sclerotherapy, and it requires fewer treatment sessions to eradicate varices.[41-43]

Increasing interest has been shown in pharmacological interventions, both as prophylactic treatment and as a means of controlling active bleeding. The use of β blockers to reduce portal pressure seems to be effective in preventing first bleed from varices and as secondary prophylaxis after variceal haemorrhage.[45] Several vasoactive agents, which cause splanchnic vasoconstriction, are also commonly used as an adjunct to endoscopic treatment in the management of bleeding varices. Vasopressin and its synthetic analogue terlipressin, given as intravenous boluses, are both widely used and control variceal haemorrhage in up to 80% of cases, but side effects, particularly with vasopressin, include myocardial ischaemia and infarction. More recently, infusions of somatostatin or its synthetic analogue octreotide have been shown to be highly effective at controlling haemorrhage from varices, with relatively few adverse effects. One randomised trial compared octreotide with injection sclerotherapy in treating acute variceal haemorrhage and found no significant difference in early (within 48 hours of randomisation) rebleeding, transfusion

requirement, or hospital mortality between the two groups.[46] The combination of octreotide and sclerotherapy has also been shown to be more effective than sclerotherapy alone in controlling acute variceal bleeding.[47] A Sengstaken-Blakemore tube is now needed only when all the above measures have failed and surgery or transfer to a specialist centre is being considered.

Patients with recurrent or intractable acute variceal haemorrhage may be considered for oesophageal transection, surgical portosystemic shunting, and, more recently, transjugular intrahepatic portosystemic shunting. This radiological technique involves creating a shunt within the liver between the portal and systemic circulations by a transjugular approach. The technique has the obvious advantage that it avoids the need for surgery, the operative mortality of which is around 10%. However, initial enthusiasm for this technique has been tempered by recent data suggesting that long term complication rates are higher than originally appreciated. Encephalopathy occurs in around 20% of cases after transjugular intrahepatic portosystemic shunting, with rebleeding rates of over 25% at one year.[48] Clearly, the exact role of this procedure in the management of patients with variceal haemorrhage remains to be established.

CONCLUSION

Though several important advances have recently been made in the management of acute and chronic liver disease, many problems remain. Lamivudine promises to be a highly useful agent against the hepatitis B virus, but antiviral agents effective in the treatment of hepatitis C resistant to interferon are still to be developed. In transplantation, immunosuppressive regimens are now much more effective with fewer side effects, but the ultimate aim of inducing immunological tolerance, allowing withdrawal of immunosuppressive treatment, remains an elusive goal.

We thank H Vilca-Melendez and N Heaton for the figure of auxiliary partial orthotopic liver transplantation and R Hughes for providing the figure of the ELAD bioartificial liver.

1 Whitle HC, Maine N, Pilkington J, Mendy M, Fortuin M, Bunn J, *et al.* Long term efficacy of continuing hepatitis B vaccination in infancy in two Gambian villages. *Lancet* 1995;**345**:1089-92.
2 Steffen R, Kane MA, Shapiro CN, Billo N, Schoellhorn KJ, van Damme P. Epidemiology and prevention of hepatitis A in travelers. *JAMA* 1994;**272**: 885-9.
3 Donohue JG, Munoz A, Ness PM, Brown DE, Yawn DH, McAllister HA, *et al.* The declining risk of post-transfusion hepatitis C virus infection. *N Engl J Med* 1992;**327**:369-73.
4 Gonzalez A, Esteban JI, Madoz P, Viladomiu L, Genesca J, Muniz E, *et al.* Efficacy of screening donors for antibodies to the hepatitis C virus to prevent transfusion-associated hepatitis: final report of a prospective trial. *Hepatology* 1995;**22**:439-45.
5 Hamasaki K, Nakata K, Nagayama Y, Ohtsuri A, Daikoru M, Taniguchi K, *et al.* Changes in the prevalence of HBeAg negative mutant hepatitis B virus during the course of chronic hepatitis B. *Hepatology* 1994;**20**:8-14.
6 Simmonds P, Alberti A, Alter HJ, Bonino F, Bradley OW, Brechot C, *et al.* A proposed system for the nomenclature of hepatitis C virus genotypes. *Hepatology* 1994;**19**:1321-4.
7 McOmish F, Yap P, Dow B, Follett E, Seed C. Geographical distribution of hepatitis C genotypes in blood donors: an international collaborative survey. *J Clin Microbiol* 1994;**32**:884-92.
8 Silini E, Bono FA, Cerino A, Maccabruni A, Tinelli C, Bruno S, *et al.* Molecular epidemiology of hepatitis C virus infection among intravenous drug users. *J Hepatol* 1994;**22**:691-5.
9 Poynard T, Bedossa P, Chevallier M. A comparison of three interferon alfa 2b regimens for the long term treatment of chronic non-A non-B hepatitis. *N Engl J Med* 1995;**332**:1457-62.
10 Chemello L, Cavalletto L, Noventa F. Predictors of response, relapse and non-response in patients with chronic hepatitis C treated with interferon-α. *J Viral Hep* 1995;**2**:91-6.
11 Yuki N, Hayashi N, Kasahara A, Hagiwara H, Takehara T, Oshita M, *et al.* Pre-treatment viral load and response to prolonged interferon-α course for chronic hepatitis C. *J Hepatol* 1995;**22**:457-63.
12 Deinstag J, Perrillo R, Schiff E. Double-blind, randomised controlled trial of lamivudine for chronic hepatitis B. *Hepatology* 1994;**20**:199A.
13 Brillianti S, Garson J, Foli M, Whitby K, Deaville R, Masci C, *et al.* A pilot study of combination therapy with ribavirin plus interferon alfa for interferon alfa-resistant chronic hepatitis C. *Gastroenterology* 1994;**107**:812-7.
14 Simons JN, Pilot-Matias TJ, Leary TP, Dawson GJ, Desai SM, Schlauder GG, *et al.* Identification of two flavivirus-like genomes in the GB hepatitis agent. *Proc Natl Acad Sci USA* 1995;**92**:3401-5.
15 Schaudler GG, Dawson GJ, Simons JN, Pilot-Matias TJ, Gutierrez RA. Molecular and serologic analysis in the transmission of the GB agents. *J Med Virol* 1995;**46**:81-90.
16 Consensus statement on indications for liver transplantation: Paris, June 22-23, 1993. *Hepatology* 1994;**20**:63-8S.
17 O'Grady JG, Alexander GJM, Hayllor KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989;**97**:439-45.
18 Bernuau J, Goudeau A, Poynard T, Dubois F, Lesage G, Yvonnet B, *et al.* Multivariate analysis of prognostic factors in fulminant hepatitis B. *Hepatology* 1986;**6**:648-51.
19 Sekiyama K, Yoshib M, Inoue K, Sugata F. Prognostic value of hepatic volumetry in fulminant hepatic failure. *Dig Dis Sci* 1994;**39**:240-4.
20 Boudjema K, Cherqui D, Jaeck D, Chenard-Neu M-P, Steib A, Freis G, *et al.* Auxiliary liver transplantation for fulminant and subfulminant hepatic failure. *Transplantation* 1995;**59**:218-23.
21 Whitington PF, Emond JC, Heffron T, Thistlethwaite JR. Orthotopic auxiliary liver transplantation for Crigler-Najjar syndrome type 1. *Lancet* 1993;**342**:779-81.
22 Group TUSMFLS. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression in liver transplantation. *N Engl J Med* 1994;**331**: 1110-5.
23 Group EFMLS. Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. *Lancet* 1994;**344**:423-8.
24 Starzl TE, Demetris AJ, Trucco M, Murase N, Ricordi C, Ildstad S, *et al.* Cell migration and chimerism after whole-organ transplantation. *Hepatology* 1993;**17**:1127-52.
25 Rolles K, Burroughs AK, Davidson BR, Karatapanis S, Prentice HG, Hamon MD. Donor-specific bone marrow infusion after orthotopic liver transplantation. *Lancet* 1994;**343**:263-6.
26 Devlin J, Slapak G, Portmann B, Williams R. Immunosuppression withdrawal in long-term recipients. *Hepatology* 1994;**20**:124A.
27 O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet* 1993;**342**:273-5.
28 Rolando N, Gimson A, Wack J, Phillop-Howard J, Casewell M, Williams R. Prospective controlled trial of selective and enteral antimicrobial regimen in fulminant liver failure. *Hepatology* 1993;**17**:196-201.
29 Salmeron JN, Tito L, Rimola A, Mas A, Navasa MA, Llach J, *et al.* Selective intestinal decontamination in the prevention of bacterial infection in patients with acute liver failure. *J Hepatol* 1992;**14**:280-5.
30 Blei AT, Olafsson S, Webster S, Levy R. Complications of intracranial pressure monitoring in fulminant hepatic failure. *Lancet* 1993;**341**:157-8.
31 Noda Y, Hughs RD, Williams R. Effect of prostacyclin (PGI2) and a prostacyclin analogue BW245C on galactosamine-induced hepatic necrosis. *J Hepatol* 1986;**2**:53-64.
32 Abecassis M, Falk JA, Makowka L, Dindzans VJ, Falk RE, Levy GA. 16,16-dimethyl prostaglandin E2 prevents the development of fulminant hepatitis and blocks the induction of monocyte/macrophage procoagulant activity after murine hepatitis virus strain 3 infection. *J Clin Invest* 1987;**80**:881-9.
33 Sheiner P, Sinclair S, Greig P, Logan A, Blendis LM, Levy G. A randomised controlled trial of prostaglandin E2 in the treatment of fulminant hepatic failure [abstract]. *Hepatology* 1992;**9**(suppl):S114.
34 Harrison PM, Keays R, Bray GP, Alexander GJM, Williams R. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. *Lancet* 1990;**335**:1572-4.
35 Harrison PM, Wendon JA, Gimson AES, Alexander GJM, Williams R. Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. *N Engl J Med* 1991;**324**:1852-7.
36 Devlin J, Ellis A, McPeake J, Wendon J, Williams R. N-acetylcysteine improves ICG clearance in addition to systemic hemodynamics during severe hepatic (graft) dysfunction. *Hepatology* 1994;**20**:123A.
37 Sussman NL, Chong MG, Koussayer T, He D-E, Shang TA, Whisennand HH, *et al.* Reversal of fulminant hepatic failure using an extracorporeal liver assist device. *Hepatology* 1992;**16**:60-5.
38 Sussman NL, Gislason GT, Conlin CA, Kelly JH. The Hepatix extracorporeal liver assist device: initial clinical experience. *Artificial Organs* 1994;**18**:390-6.
39 Ellis AJ, Wendon J, Hughes R, Langley P, Sussman NL, Kelly JH, *et al.* A controlled trial of the Hepatix extracorporeal liver assist device (ELAD) in acute liver failure. *Hepatology* 1994;**20**:140A.
40 Rozga J, Williams F, Ro M-S, Neuzil DF, Giorgio TD, Backfish G, *et al.* Development of a bioartificial liver: properties and function of a hollow-fiber module inoculated with liver cells. *Hepatology* 1993;**17**:258-65.
41 Stiegman GV, Goff JS, Michaletz-Onody PA, Korula J, Lieberman D, Saled ZA, *et al.* Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. *N Engl J Med* 1992;**326**:1527-32.
42 Gimson AES, Ramage JH, Panos MZ, Hayliar K, Harrison PM, Williams R, *et al.* Randomised trial of variceal banding ligation versus injection sclerotherapy for bleeding oesophageal varices. *Lancet* 1993;**342**:391-4.
43 Laine L, El-Newihi HM, Migikovski B, Sloane R, Garcia F. Endoscopic ligation compared to sclerotherapy for the treatment of bleeding esophageal varices. *Ann Intern Med* 1993;**119**:1-7.
44 Hayes PC, Davis JM, Lewis JA, Bouchier IAD. Meta-analysis of value of propranolol in prevention of varices haemorrhage. *Lancet* 1990;**336**:153-6.
45 Conn HO, Grace ND, Bosch J, Groszmann RJ, Rodes J, Wright SC, *et al.* Propranolol in the prevention of the first hemorrhage from esophagogastric varices: a multicenter randomized clinical trial. *Hepatology* 1991;**13**:902-12.
46 Sung JJY, Chung SCS, Lai C-W, Chan FKL, Leung JWC, Yung M-Y, *et al.* Octreotide infusion or emergency sclerotherapy for variceal haemorrhage. *Lancet* 1993;**342**:637-41.
47 Besson I, Ingrand P, Person B, Boutroux D, Heresbach D, Bernard P, *et al.* Sclerotherapy with or without octreotide for acute variceal bleeding. *N Engl J Med* 1995;**333**:555-60.
48 Laberge JM, Somberg KA, Lake JR, Gordon RL, Kerlan RK, Ascher NL, *et al.* Two-year outcome following transjugular intrahepatic portosystemic shunt for variceal bleeding: results in 90 patients. *Gastroenterology* 1995;**108**: 1143-51.