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Intensive Care Management of Acute Liver Failure

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Abstract: Acute liver failure represents one of the most challenging conditions in intensive care treatment. In most cases there is no causal medical therapy available for survive making the intensive care treatment as the most important management tool, as bridge to transplant or still the recovery of the liver! These patients frequently develop multi-organ failure, placing them at risk of hemodynamic disorder, cerebral edema, coagulopathy and various renal and metabolic complications.

Key words: liver failure; intensive care; coagulopathy; multi-organ failure; renal failure

Acute loss of liver function is a devastating disease with a high mortality rate. The clinical course of patients with acute liver failure (ALF) depends on potential and time course of the regeneration of the liver. If the liver does not recover, a progressing multiorgan failure with circulatory instability, renal failure and a systemic inflammatory response syndrome are common clinical features [5].

Furthermore, hepatic encephalopathy (HE) in ALF is often associated with the development of intracranial hypertension. A rise in intracranial pressure is a distinctive feature of ALF, which is not seen in multiorgan failure caused by sepsis, pancreatitis or severe burn. The pathophysiology of circulatory instability is due to an increased nitric oxide production in the splanchnic bed with blood pooling in this area, decrease of systemic vascular resistance and a high cardiac output [36]. The neurochemical mechanism responsible for HE is still controversial, but increased ICP is closely related to cerebral edema [8] and alterations in cerebral blood flow (CBF) [24].

ALF is rare and detailed experience of its management usually limited to specialist centres. In the following paper we will discuss recent developments in the treatment of this condition, and outline our current intensive care management (ICM) of patients with acute liver failure.

Definition

Acute liver failure is a broad term used to describe the development of severe hepatic dysfunction resulting in hypotension, encephalopathy, coagulopathy, jaundice and renal failure. Since its first recognition in 1940s, a number of attemps have been made to more precisely define this condition. The most recent refinement of these conditions was made by O'Grady et al. [30]. This classification also recognizes the markedly different clinical course and outcome that each category may follow. O'Grady distinguishes three divisions reflecting the marked different clinical course and outcome:

"Hyper-acute liver failure", in which encephalopathy occurs within 7 days of the onset of jaundice: this includes a significant proportion of patients likely to survive with ICU treatment.

"Acute liver failure" with an interval of between 8 days and 28 days from encephalopathy; also with cerebral edema like hyperacute liver failure, but with much worse prognosis without transplantation.

"In sub-acute liver failure the encephalopathy occurs within 5-12 weeks of the onset of jaundice. These patients are characterized by a low incidence of cerebral edema but with very poor prognosis.

The majority of patients with ALF resulting from acetaminophen intoxication develop the picture of hyper-acute liver failure as well as patients with an acute hepatitis A or B [30]. Drug reactions tend to follow an acute or sub-acute clinical course.

Etiology

It's estimated that there are about 2000 cases of ALF in the USA per year. In Germany 56 patients with ALF were transplanted in the year 2002 (personal communication with Eurotrasnplant, Leiden), in Denmark the rate of ALF is about 8/1.000.000. Acetaminophen intoxication accounts for approximately 50% of ALF in the United Kingdom [32]. Acetaminophen overdose is also the most common cause for ALF in the USA accounting about 20% of patients with ALF [37]. Acute hepatitis A or B is the predominant cause of ALF in central and southern Europe. Acute viral hepatitis E has been reported to be a frequent cause [1]. The role of hepatitis C in ALF in somewhat controversial; Japanese studies have found evidence of HCV RNA in tissue from ALF patients [46]. This fact is not reproduced in Europe studies [13]. Other causes of ALF may be mushroom intoxication, drug-induced hepatoxicity (ectasy, halothan, and valproate), autoimmune hepatitis, cardiac failure, Budd-Chiarie syndrome and inherited metabolic disorders [45].

Pathophysiology

Hemodynamic Alterations

Liver failure induces cardiovascular dysfunction. Using a dye-dilution technique in patients with liver disease, Kowalski and co-workers found that cardiac output was increased while mean arterial pressure was reduced [22]. They called it hyperdynamic circulation. Clinical trials with acute liver failure could confirm, that these patients suffers on the same hemodynamic deficiency [5, 40].

Trewby et al. [40] could show that in nearly 90 % (82 of 94 patients) of their examined patients with ALF systolic blood pressure was < 80 mmHg. The causes for this hypotension were low cardiac filling pressures and a low systemic vascular resistance (SVR) [5]. With volume replacement and norepinephrine support hypotension could be controlled.

Both, patients with cirrhosis as well with ALF develop portal hypertension. Leakage of the endotoxin from the gut to the lymph nodes may lead to elevated systemic endotoxin levels, because portal vein bypasses the liver via collaterals or the damaged liver is not able to clear the toxins due to impaired Kupffer Cell function (translocation) [14]. Endotoxins induce the release of various cytokines like tumor necrosis factor α (TNF α), interleukin 1 and interleukin 6 (IL 1; IL6), which are potent stimulators of the inducible nitric oxide synthetase (iNOS). The cause for the increased cardiac output and low SVR in ALF seems to be the excessive amounts of endotoxin and consecutive high serum levels of nitric oxide (NO) as Harrison et al. could show in 1996 [17]. Impaired tissue perfusion is due to an extensive peripheral shunting in most patients in the early stage of ALF [11]. NO plays a major role in the pathophysiology of tissue hypoperfusion. The King's College Group suggests that despite increased serum levels of NO, there may be a deficit of NO in the microcirculation [11].These findings are convinced with clinical observations that N-Acetylcystein (NAC) could reverse the hemodynamic changes in ALF even when used long term after ingestion of acetaminophen by increasing the cGMP levels [17]. It is assumed that NAC acts by increasing cGMP levels in the microcirculation. Therefore, the King's College Group suggests the use of NAC to all patients with ALF regardless of etiology [17].

The management of patients with ALF and hemodynamic disorder depends on multiple variables and is summarized in Table 1. Invasive hemodynamic monitoring is of outstanding importance. For a rapid volume replacement a large bore catheter (e.g. Shaldon catheter) is useful tool. Cardiac monitoring has to be done with a Swan-Ganz catheter and an arterial line. For volume replacement colloids like Gelatine or hydroxethyl starch and in face of coagulopathy fresh frozen plasma and red packed cells are recommended.

If the mean arterial pressure (MAP) remains < 70 mmHg, although the central venous pressure (CVP) = 10 mmHg or the pulmonary wedge pressure = 15 mmHg, cerebral perfusion, kidney and splanchnic perfusion may be compromised. An additional vasopressor like norepinephrine is required. If the hypotension is accompanied by a low cardiac index (CI) <2.5 l/min/m^2, dobutamine infusion or epinephrine <0.1 μg/kg/min may be considered.

Table 1. Management of hemodynamic instability in patients with ALV:

1. Target MAP > 70 mmHg
2. Invasive Monitoring: arterial line, central line, better; Swan.Ganz Catheter
2. Aggressive volume resuscitation till CVP = 10 mmHG or PCWP = 15 mmHG
3. If MAP < 70 mmHg then use Norepinephrine (NE)
4. If CI < 2.5 l/min/m2, use pos. inotrop agents e.g. dobutamine or epinephrine < 0.1 μg/kg/min
5. If NE > 0.5 μg/kg/min, use 1mg terlipressin

If patients with ALF develop a devastating hemodynamic requiring norepinephrine support >1μg/kg/min total hepatectomy may be considered to remove toxic substances released by the necrotic liver. This aggressive approach, however, is very controversial and can not be recommended in many patients. The time window of successful transplantation after total hepatectomy is limited to 24 – 36 hours [44].

Cerebral Edema

Cerebral edema can be detected in about 50 -60 % of patients with ALF and hepatic encephalopathy (H.E.) grade III or IV [27] .

Patients with a H.E. III and IV should be electively intubated to protect the airway. Patients who are listed for liver transplantation, intracranial pressure (ICP) monitoring is recommended for early detection of increased ICP. Unfortunately neither clinical signs nor findings in computed tomography correlate well with increased ICP until very late in the clinical course [27]. Subdural intracranial monitors may be associated with lower risk than intracranial monitors. However there is no prospective, randomized clinical trial that documents the benefit of an intracranial pressure monitoring [9, 20]. Cerebral blood flow is frequently reduced in patients with raised ICP [42] with the risk of cerebral ischemia. Mean arterial blood pressure should be kept above 70 mmHg. The approach to the management of increased ICP in ALF is summarized in Table 2.

Table 2. Management of increased intracranial pressure in patients with ALV

1. Keep the head of bed elevated 10-20°
2. Avoid unnecessary patient stimulation
3. Sedation
4. Endotracheal intubation, controlled ventilation
5. Maintain mean arterial pressure ≥ 70 mmHg

Adapted from Ellis and Wendon [7]

Signs of ischemia should be managed with 20 % mannitol at a dose of 0.5-1 g/kg by rapid bolus infusion to induce diuresis of at least twice the volume of mannitol administered. Mannitol should only be administered if the serum osmolality is < 320 mosm/l [11]. In patients with kidney failure, mannitol should be applied only in combination with a continuous veno-venous hemofiltration (CVVH) to prevent hyperosmolality.

Mechanical Ventilation

Intubation the trachea and mechanical ventilation is implemented for several reasons in ALF. But hypoxemia is rarely the primary cause for intubation [5]. As patients progress from H.E. Grade II to grade III, there is an increased risk for aspiration. Furthermore the grade III H.E. is characterized by agitation and aggressive behaviour and a need for sedation and intubation.

In the early clinical course the lungs of patients with ALF are relatively spared in comparison with other patients suffering from systemic inflammatory response syndrome from any other cause. Hepatopulmonary syndrome is not a feature of ALF.

The need for sedation varies from patient to patient and should be tailored individually. Many patients will tolerate intubation and ventilation with minimum amounts of opiate and perhaps little of hypnotics, e.g. Propofol.

Infection

Patients with ALF have an increased susceptibility to infections, principally as a result of impaired Kupffer cells, reduced complement levels, portosystemic shunting and the need for invasive procedure [35]. Bacteriological proven infections are reported in up to 80% of patients with ALF, with pneumonia as the leading cause for infection [33]. Clinical signs of infection like high white blood count (WBC) or high temperature are absent in 30 %. [33]. Identified risk factors for infection are high maximum aPTT, grade III or IV encephalopathy and intubation of the trachea [35].

Due to this high incidence of infection, there is an ongoing discussion about the prophylactic use of antibiotic agents.

Intravenous use of anti-microbial agents if given prophylactically will reduce the incidence of infection to 20% in patients with ALF, but it does not improve the outcome of patients with ALF or the length of stay in the intensive care [34].

The role of selective digestive decontamination (SDD) remains unclear. Rolando et al. [34] demonstrated no benefit of SDD over antibiotic treatment alone.

Regarding the emergency of multiply resistant organism within ICU and the blanket use of broad spectrum antimicrobial adds to this, thus antibiotics need to be prescribed appropriately if necessary.

Coagulopathy

Coagulopathy is common in patients with ALF, but less than 10 % of patients with ALF experience severe hemorrhage requiring blood transfusions [31].Common sites of hemorrhage include gastrointestinal tract, nasopharynx, lungs and skin puncture sites [43].

Prophylactic use of fresh frozen plasma (FFP) to patients with increased prothrombin time has not been shown to be beneficial [16]. In most cases a prothrombin concentration of 30% will be enough to avoid an active bleeding.

Thrombocytopenia and impaired platelet function are present in most cases of ALF. Among patients with ALF, a mean platelet count of 53/nl was found as a cause for a significant bleeding episode [31]. Prophylactic platelet transfusions are recommended for patients with a platelet count < 50/nl, if invasive procedure will be done.

Renal Failure

The incidence of renal failure in patients with ALF is more than 50 %. Relative hypovolemia and hypotension are important pre-renal factors. During the hyperdynamic circulatory failure in ALF the renal vascular autoregulation is in impaired. Thus the renal blood flow directly depends on blood pressure.

Direct renal toxicity in patients with ALF is described in acetaminophen and mushroom poisoning [28].

A number of treatments have been tried to maintain urine output and preserve the kidney function. In the early 70 and 80's the use of dopamine in doses <5 μg/kg/min (renal dose) was very popular to preserve the kidney function. But its use was increasingly questioned in the ICU. A Meta analyses by Holmes et al. [19] could show that the use of dopamine impairs the splanchnic perfusion. A recent review by Weigand et al. does not recommend dopamine infusion to protect the kidneys in face of a multi-organ failure (MOF) [41].

Actually the best approach to avoid a prerenal failure is an adequate volume load (CVP 10 -12 mmHg) and if necessary norepinephrine infusion to maintain the MAP > 70 mmHg.

Renal Replacement Therapy

Intermittent forms of renal replacement therapies are not recommended in ALF. Davenport et al. [10] have demonstrated increased hemodynamic instability and increased intracranial hypertension in patients who received an intermittent procedure for renal support in comparison to those with a continuous mode. However Gasparovic et al. [15] has demonstrated in a prospective randomized study in septic patients with multi-organ failure no benefit of continuous renal replacement therapy in comparison to intermittent hemodialysis. Although at present most intensive care physicians prefer a continuous procedure to provide a stable hemodynamic in septic patients with renal failure.

Anti-coagulation of renal replacement circuits can be problematic and the most units avoid systemic heparinization.

Mitchell et al. [25] could show that in patients with systemic inflammatory response syndrome (SIRS) with an increased risk of bleeding citrate is a safe anticoagulant for continuous veno-venous hemodialysis (CVVHD).

Due to this knowledge most liver transplant centers use citrate for patient with ALV or post liver transplant.

Extracorporeal Support of the Failing Liver

The first reported use of an extracorporeal system for treatment of hyperammonia dates from 1958 [21]. Since that time a number of different techniques like hemofiltration, whole blood or plasma exchange, hemoperfusion and plasmaperfusion over absorbents have been used for the treatment of acute liver failure. Despite very promising initial reports the clinical success was very limited. One of the best known examples is the treatment with charcoal hemoperfusion [28]. Improvement in hepatic encephalopathy was the most frequently observed benefit. However this improvement was not accompanied with an increased survival [39].

Many new approaches to extracorporeal liver support are under investigation.

In recent years a non-biologic liver support system called MARS (Molecular Adsorbent Recirculating System) has been used for treatment of patients with decompensated end stage liver disease (ESLD). MARS enables removal of water-soluble and of albumin-bound substances. Human serum albumin serves as a shuttle between a blood-sided dialysis membrane on one side and a remote set of absorbent columns (charcoal and anion exchanger) and a conventional dialysis unit on the other [38]. Since 1993, more than 1.000 patients were treated with MARS, but only two small prospective, randomized, controlled trials were performed. Mitzner et al. investigated patients with ESLD and HRS [26] (n = 13). He compared MARS versus standard medical treatment (SMT). Heemann et al. (n = 24) [18] examined decompensated ESLD with intrahepatic cholestasis. Both studies have demonstrated a better survival with MARS in comparison with SMT. Regarding to the small number of patients a general recommendation for MARS treatment cannot be ruled out.

Another liver detoxification device (FPSA-Prometheus) has reached the clinical setting. Kramer et al. [23] reports about a successful treatment of refractory cerebral edema in ecstasy and cocaine induced fulminate hepatic failure using this new liver detoxification device.

Bioreactors containing hepatocytes have been the basis for biological extracorporeal support systems. This remains experimental and confined to limited clinical trials [2].

Several large trials have to be completed in the next few years to increase our knowledge about liver assist devices.

Liver Transplantation in ALF

The selection of patients for liver transplantation is one of the most difficult problems for the physicians. Graft and 1 year survival in patients transplanted for ALF is usually lower than those undergoing hepatic transplantation for another reason. The 1 -year graft survival in a large group of patients undergoing transplantation was 20% lower in those transplanted for ALF (73 %) [12] compared to those with ESLD (80%)

However there is an organ shortage. A number of groups have developed criteria for selection of patients to undergo liver transplantation, identifying those who are unlikely to survive with medical treatment.

The most frequently used criteria are the King's College Criteria [29] (s. Table 3). The validation is based on prothrombin time, arterial pH, encephalopathy, serum creatinine in patients with acetaminophen-induced ALF, and age, duration of jaundice before encephalopathy, prothrombin time and bilirubin in those with ALF due to other causes.

Another commonly used criterion are coming from French. Bernuau assessed prognostic factors in

Table 3. King College Hospital Criteria for Nonsurvival Among Patients with Acute Liver Failure.

Acetaminophen:
- pH < 7.3 (irrespective of grade of encephalopathy)

or
- Prothrombin time > 100 seconds (INR > 6.5) and serum creatinine > 3.4 mg/dl in patients with grade III or IV encephalopathy

Nonacetaminophen patients:
- Prothrombin time > 100 seconds (INR > 6.5; irrespective of grade of encephalopathy)

or
- Any 3 of the following variables (irrespective of grade of encephalopathy)
  - ▷ Age < 10 or > 40 years
  - ▷ Cause: Non A Non B hepatitis, halothane hepatitis, idiosyncratic drug reactions
  - ▷ Duration of jaundice before onset of encephalopathy > 7 days
  - ▷ Prothrombin time > 50 seconds (INR > 3.5)
  - ▷ Serum Bilirubin > 17.5 mg/dl

Abbreviation: INR, international normalized ratio

115 patients with serologically proved hepatitis B. Multivariate analysis showed that the level of factor V, patient's age and absence of detectable HBsAg were independent predictors of survival [4].

Bismuth [6] used presence of confusion or coma and age corrected Factor V lever below 20 or 30 %of normal. 152 patients at that center fulfilled these criteria, all but one of the patients who were not transplanted died.

Numerous other studies have attempted to improve the accuracy of patient selection, but actually there is no general accepted system in use.

The 1-year survival rate in patients with ALF is between 50 and 75 % [7]. These data do not consider the number of patients who are listed for LTX but deteriorate such that their clinical course precludes transplantation.

Of 124 patients who fulfilled the acetaminophen criteria only 35% underwent transplantation [3].

A difficult balance must therefore be struck between the risks of delaying transplantation in the critically ill patient until an appropriate organ is available and the acceptance of sub-optimal grafts, like steatotic, reduce size or ABO-incompatible grafts which may be associated with a poorer outcome.

LITERATURE

1. Acharya SK, Dasarathy S, Kumer TL, et al. (1996) Fulminant hepatitis in a tropical population: clinical course, cause, and early predictors of outcome. Hepatology 23: 1448-55
2. Arkadopoulos N, Detry O, Rozga J, et al. (1998) Liver assist systems: state of the art. Int J Artif Organs 21: 781-7
3. Bernal W, Wendon J, Rela M, et al. (1998) Use and outcome of liver transplantation in acetaminophen-induced acute liver failure. Hepatology 27: 1050-5
4. Bernuau J, Goudeau A, Poynard T, et al. (1986) Multivariate analysis of prognostic factors in fulminant hepatitis B. Hepatology 6: 648-51
5. Bihari DJ, Gimson AE, Williams R (1986) Cardiovascular, pulmonary and renal complications of fulminant hepatic failure. Semin Liver Dis 6: 119-28
6. Bismuth H, Samuel D, Castaing D, et al. (1995) Orthotopic liver transplantation in fulminant and subfulminant hepatitis. The Paul Brousse experience. Ann Surg 222: 109-19
7. Bismuth H, Samuel D, Castaing D, et al. (1996) Liver transplantation in Europe for patients with acute liver failure. Semin Liver Dis 16: 415-25
8. Blei AT (1991) Cerebral edema and intracranial hypertension in acute liver failure: distinct aspects of the same problem. Hepatology 13: 376-9
9. Caraceni P, Van Thiel DH (1995) Acute liver failure. Lancet 345: 163-9
10. Davenport A, Will EJ, Davison AM, et al. (1989) Changes in intracranial pressure during haemofiltration in oliguric patients with grade IV hepatic encephalopathy. Nephron 53: 142-6
11. Ellis A, Wendon J (1996) Circulatory, respiratory, cerebral, and renal derangements in acute liver failure: pathophysiology and management. Semin Liver Dis 16: 379-88
12. Farmer DG, Anselmo DM, Ghobrial RM, et al. (2003) Liver transplantation for fulminant hepatic failure: experience with more than 200 patients over a 17-year period. Ann Surg 237: 666-75; discussion 675-6
13. Feray C, Gigou M, Samuel D, et al. (1993) Hepatitis C virus RNA and hepatitis B virus DNA in serum and liver of patients with fulminant hepatitis. Gastroenterology 104: 549-55
14. Garcia-Tsao G, Lee FY, Barden GE, et al. (1995) Bacterial translocation to mesenteric lymph nodes is increased in cirrhotic rats with ascites. Gastroenterology 108: 1835-41
15. Gasparovic V, Filipovic-Grcic I, Merkler M, et al. (2003) Continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IHD)--what is the procedure of choice in critically ill patients? Ren Fail 25: 855-62
16. Gazzard BG, Henderson JM, Williams R (1975) The use of fresh frozen plasma or a concentrate of factor IX as replacement therapy before liver biopsy. Gut 16: 621-5
17. Harrison P, Wendon J, Williams R (1996) Evidence of increased guanylate cyclase activation by acetylcysteine in fulminant hepatic failure. Hepatology 23: 1067-72
18. Heemann U, Treichel U, Loock J, et al. (2002) Albumin dialysis in cirrhosis with superimposed acute liver injury: a prospective, controlled study. Hepatology 36: 949-58
19. Holmes CL, Walley KR (2003) Bad medicine: low-dose dopamine in the ICU. Chest 123: 1266-75
20. Keays RT, Alexander GJ, Williams R (1993) The safety and value of extradural intracranial pressure monitors in fulminant hepatic failure. J Hepatol 18: 205-9
21. Kiley JE, Pender JC, Welch HF, et al. (1958) Ammonia intoxication treated by hemodialysis. N Engl J Med 259: 1156-61
22. Kowalski, et al. (1953) The cardiac output in Laennec's Cirrhosis. J Clin Invest 32: 1025 - 1033
23. Kramer L, Bauer E, Schenk P, et al. (2003) Successful treatment of refractory cerebral oedema in ecstasy/cocaine-induced fulminant hepatic failure using a new high-efficacy liver detoxification device (FPSA-Prometheus). Wien Klin Wochenschr 115: 599-603
24. Larsen FS, Ejlersen E, Hansen BA, et al. (1995) Functional loss of cerebral blood flow autoregulation in patients with fulminant hepatic failure. J Hepatol 23: 212-7
25. Mitchell A, Daul AE, Beiderlinden M, et al. (2003) A new system for regional citrate anticoagulation in continuous venovenous hemodialysis (CVVHD). Clin Nephrol 59: 106-14
26. Mitzner SR, Stange J, Klammt S, et al. (2000) Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled clinical trial. Liver Transpl 6: 277-86
27. Munoz SJ, Robinson M, Northrup B, et al. (1991) Elevated intracranial pressure and computed tomography of the brain in fulminant hepatocellular failure. Hepatology 13: 209-12
28. O'Grady JG, Gimson AE, O'Brien CJ, et al. (1988) Controlled trials of charcoal hemoperfusion and prognostic factors in fulminant hepatic failure. Gastroenterology 94: 1186-92
29. O'Grady JG, Alexander GJ, Hayllar KM, et al. (1989) Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 97: 439-45
30. O'Grady JG, Schalm SW, Williams R (1993) Acute liver failure: redefining the syndromes. Lancet 342: 273-5
31. Pereira SP, Langley PG, Williams R (1996) The management of abnormalities of hemostasis in acute liver failure. Semin Liver Dis 16: 403-14
32. Riordan SM, Williams R (1999) Cause and prognosis in acute liver failure. Liver Transpl Surg 5: 86-9
33. Rolando N, Harvey F, Brahm J, et al. (1990) Prospective study of bacterial infection in acute liver failure: an analysis of fifty patients. Hepatology 11: 49-53

34. Rolando N, Gimson A, Wade J, et al. (1993) Prospective controlled trial of selective parenteral and enteral antimicrobial regimen in fulminant liver failure. Hepatology 17: 196-201
35. Rolando N, Philpott-Howard J, Williams R (1996) Bacterial and fungal infection in acute liver failure. Semin Liver Dis 16: 389-402
36. Rolando N, Wade J, Davalos M, et al. (2000) The systemic inflammatory response syndrome in acute liver failure. Hepatology 32: 734-9
37. Schiodt FV, Atillasoy E, Shakil AO, et al. (1999) Etiology and outcome for 295 patients with acute liver failure in the United States. Liver Transpl Surg 5: 29-34
38. Stange J, Ramlow W, Mitzner S, et al. (1993) Dialysis against a recycled albumin solution enables the removal of albumin-bound toxins. Artif Organs 17: 809-13
39. Stockmann HB, Hiemstra CA, Marquet RL, et al. (2000) Extracorporeal perfusion for the treatment of acute liver failure. Ann Surg 231: 460-70
40. Trewby P N, Williams R (1977) Pathophysiology of hypotension in patients with fulminant hepatic failure. Gut 18: 1021-6
41. Weigand MA, Bardenheuer HJ, Bottiger BW (2003) (Clinical management of patients with sepsis). Anaesthesist 52: 3-22
42. Wendon JA, Harrison PM, Keays R, et al. (1994) Cerebral blood flow and metabolism in fulminant liver failure. Hepatology 19: 1407-13
43. Williams R, Gimson AE (1991) Intensive liver care and management of acute hepatic failure. Dig Dis Sci 36: 820-6
44. Williams R (1994) New directions in acute liver failure. J R Coll Physicians Lond 28: 552-9
45. Williams R (1996) Classification, etiology, and considerations of outcome in acute liver failure. Semin Liver Dis 16: 343-8
46. Yanagi M, Kaneko S, Unoura M, et al. (1991) Hepatitis C virus in fulminant hepatic failure. N Engl J Med 324: 1895-6

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