Hepatitis E and Acute-on-Chronic Liver Failure

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Hepatitis E virus (HEV) is the most common cause of acute viral hepatitis (AVH) globally. It causes large scale epidemics of AVH across the low- and middle income countries in Asia and Africa, and also causes sporadic cases of AVH in the same geographical region. AVH due to HEV is usually an acute, self-limiting illness, similar in clinical presentation to AVH caused by hepatitis A virus (HAV). When HEV causes AVH in patients of chronic liver disease it may worsen rapidly to a syndrome called acute-on-chronic liver failure (ACLF) leading to very high mortality. Acute deterioration of liver function in a patient with compensated chronic liver disease is the characteristic feature of ACLF. The typical disease course of patients with ACLF is the appearance of organ failure, which progresses to multi-organ failure and death. Many publications have reported HEV as one of the leading causes for ACLF from Asia and Africa, where HEV is endemic. The mortality rate of HEV-related ACLF (HEV-ACLF) ranges from 0% to 67% with a median being 34%. These patients require admission in the intensive care unit and they benefit from a team approach of clinicians with expertise in both hepatology and critical care. The goals of treatment are to prevent further deterioration in liver function, reverse precipitating factors, and support failing organs. Liver transplantation is required in selected patients to improve survival and quality of life. One preliminary report suggests that ribavirin may be an effective and safe drug for treatment of HEV-ACLF however this requires validation in large trials. (J Clin Exp Hepatol 2013;3:225–230)

Hepatitis E virus (HEV) is a small non-enveloped virus with a size of 27–34 nm, and belongs to the genus Hepevirus in the Hepeviridae family.[1,2] It is primarily transmitted through the fecal–oral route, and is the most common cause of acute viral hepatitis (AVH) globally. It causes large scale epidemics of AVH across the low- and middle income countries in Asia and Africa, and also causes sporadic cases of AVH in the same geographical region.[3,4] AVH due to HEV is usually an acute, self-limiting illness, similar in clinical presentation to AVH caused by hepatitis A virus (HAV). However, in two situations HEV may cause serious disease leading to high mortality: when AVH occurs in pregnant women which may rapidly worsen as acute liver failure,[5] and when AVH occurs in patients of chronic liver disease which may worsen as acute-on-chronic liver failure (ACLF).

Keywords: hepatitis E virus, acute-on-chronic liver failure, liver failure, cirrhosis, ribavirin

Received: 26.8.2013; *Accepted:* 26.8.2013; *Available online:* 16.9.2013

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Abbreviations: HEV: hepatitis E virus; AVH: acute viral hepatitis; HAV: hepatitis A virus; ACLF: acute-on-chronic liver failure; HEV-ACLF: HEV-related ACLF; APASL: Asia–Pacific Association for the Study of Liver; HBV: hepatitis B virus; CHB: chronic hepatitis B; INR: international normalized ratio; MELD: model for end-stage liver disease; ICU: intensive care unit

http://dx.doi.org/10.1016/j.jceh.2013.08.013

The present review describes ACLF which is precipitated by HEV.

CONCEPT OF ACUTE-ON-CHRONIC LIVER FAILURE

ACLF is an increasingly recognized entity encompassing an acute deterioration of liver function in patients with cirrhosis, which is usually associated with a precipitating event and results in the failure of one or more organs and high short-term mortality.[6] Although, there is no universally agreed definition of this entity, two consensus working definitions for this syndrome exist: one put forward by the Asia–Pacific Association for the Study of Liver (APASL)[7] and the other based on an EASL-AASLD single topic symposium.[8] According to the APASL, ACLF is defined as 'Acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease'.[7] The EASL-AASLD defined ACLF as 'Acute deterioration of pre-existing, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure'.[8] Both these definitions address the essential feature of acute hepatic insult or acute deterioration in patients with pre-existing chronic liver disease.[9] Recently investigators from the EASL–CLIF Consortium collected data from 1343 hospitalized patients with cirrhosis and acute decompensation from 29 liver units in 8 European countries.[10] They used the organ

failure and mortality data to define ACLF grades, assess mortality, and identify differences between ACLF and acute decompensation. They also established diagnostic criteria for ACLF based on analyses of patients with organ failure (defined by the chronic liver failure–sequential organ failure assessment [CLIF-SOFA] score) and high 28-day mortality rate (>15%).[10]

ACLF differs from chronic hepatic decompensation in many aspects. First, the development of liver failure and end-organ dysfunction in ACLF is much faster than in chronic hepatic decompensation. Second, in ACLF, there is still a chance of recovery of liver function (i.e. there is reversibility component in ACLF). Third, there is usually a well defined precipitating event which precedes the liver failure. And lastly, the short-term (3-month) mortality is significantly higher than expected with chronic hepatic decompensation.[11,12]

ACLF is frequently accompanied by the development of severe inflammatory response syndrome associated with multi-organ failure leading to high in-hospital mortality despite costly intensive care therapy.[13,12] Basically all organ systems can be affected, particularly circulation, brain, kidneys and liver. A key role for the interaction of innate immune dysfunction, enhanced bacterial translocation from the gut, and circulatory dysfunction has been proposed. The characteristic circulatory dysfunction includes peripheral arterial vasodilatation, reduced renal blood flow, increased portosystemic shunting and high cardiac output (hyperdynamic circulation). These phenomena are thought to be secondary to a reduction in vascular responsiveness and down regulation of receptors leading to hyporesponsive vasoconstriction. Intense renal vasoconstriction may occur which may lead to the development of a hepatorenal syndrome.[13]

The onset of ACLF depends on the severity of underlying chronic liver disease and the severity of the acute event. A minor acute insult may be enough to cause the ACLF in a patient with severe underlying chronic liver disease, and a severe acute insult may be required in a patient who has mild underlying chronic liver disease.[7,14] Both hepatic and non-hepatic insults could occur as acute precipitating events leading to the syndrome of ACLF. The 'hepatic' precipitating events, that directly exaggerate the liver injury, are alcoholic hepatitis, drug-induced liver injury, superimposed viral hepatitis, portal vein thrombosis and ischemic hepatitis. The 'non-hepatic' insults precipitating ACLF are trauma, surgery, variceal bleeding or infection. In a proportion of patients, there may be no identifiable precipitating event.[6] Superimposed viral infections with hepatotropic viruses in patients with cirrhosis can have devastating consequences by direct hepatocellular damage. Perhaps, the best examples are HEVsuperinfection[15] and reactivation of hepatitis B virus (HBV) in patients on immunosuppression.[16]

ROLE OF HEPATITIS E VIRUS IN ACUTE-ON-CHRONIC LIVER FAILURE

The first report documenting HEV superinfection in patients of chronic liver disease leading to severe liver decompensation was published from Pakistan in 2002.[17] Subsequently, many publications have reported HEV as one of the leading causes for decompensation of cirrhosis from Asia and Africa, where HEV is endemic (Table 1).[14,15,17–33] Most of these studies have used the APASL definition of ACLF and in median21% of cases (range 4–72%) of ACLF, HEV was the precipitating cause for liver decompensation. This contrasts with the Western countries where HEV is rarely the precipitating cause of acute decompensation in ACLF.

The largest of these studies documenting HEV as the acute insult of ACLF was from China by Zhang et al published in 2010.[27] The authors compared the demographics, liver function, and prognosis of Chinese patients infected with chronic hepatitis B (CHB) and superinfected with HEV or hepatitis A virus (HAV). Among 188 patients with CHB, 136 had HEV superinfection and 52 had HAV superinfection. More patients in the HEV group had complications (94.9 vs. 61.5%, $P < 0.001$), and liver failure (39.7 vs. 11.5%, $P = 0.002$). Additionally, the mortality among the HEV group was significantly higher (33.8 vs. 1.9%, $P < 0.001$). The authors concluded that patients with CHB with HEV superinfection had more severe liver disease and poorer prognosis than those with HAV superinfection. The authors recommended that since there is no vaccine against HEV, patients with CHB should take appropriate precautions against superinfection with HEV, such as consumption of boiled water and well-cooked food, in regions where it is endemic.

The largest study from India on this aspect was published by Radha Krishna et al from Lucknow, India in 2009.[26] The authors aimed to evaluate the clinical profile and predictors of 3-month mortality in patients with ACLF. In 121 cases of ACLF, the precipitating cause was HEV in 80 (61%), HAV in 33 (27%) and both in 8 (6%). The underlying liver cirrhosis had varying etiologies such as HBV, alcohol, Wilson's disease, HCV, autoimmune, Budd–Chiari syndrome, hemochromatosis and cryptogenic. The three-month mortality was 45%. Multivariate analysis revealed grades 3 and 4 hepatic encephalopathy [odds ratio (OR 32.1)], hyponatremia (OR 9.2) and renal failure (OR 16.8) as significant predictors of 3-month mortality.[26]

CLINICAL FEATURES AND PROGNOSIS OF HEV-RELATED ACLF

Even though ACLF is a heterogenous disease in term of its varying acute and chronic etiologies, there is little evidence to suggest that its clinical presentation may differ depending on the etiology. In fact ACLF is defined by APASL to present *uniformly* as 'Acute hepatic insult manifesting as

Table 1 Summary of important studies on ACLF from countries where HEV is endemic.

Authors	Place	Year	Number (and %) of cases of ACLF due to HEV out of all ACLF cases	Short-term mortality
Hamid et al[17]	Karachi	2002	4	1/4 (25%)
Ramachandran et al[18]	Vellore	2004	9	6/9 (67%)
Kumar et al[19]	Lucknow	2004	14/32 (44%)	2/14 (14%)
Monga et al[20]	Delhi	2004	10	3/10 (30%)
Kc et al[21]	Kathmandu	2006	7	2/7 (28%)
Ke et al[22]	China	2006	80/107 (75%)	80/80 (100%)[a]
Acharya et al[15]	Delhi	2007	30/107 (28%)	13/30 (43%)
Kumar et al[23]	Delhi	2008	9/43 (21%)	0/9 (0%)
Kumar et al[24]	Delhi	2009	7/48 (15%)	–
Mahtab et al[25]	Dhaka	2009	15/69 (22%)	2/15 (13%)[b]
Radha Krishna et al[26]	Lucknow	2009	80/121 (66%)	35/80 (44%)
Duseja et al[14]	Chandigarh	2010	4/102 (4%)	2/4 (50%)[b]
Zhang et al[27]	China	2010	136/188 (72%)	46/136 (34%)
Lal et al[28]	Chandigarh	2011	3/31 (10%)	1/3 (33%)[b]
El Sayed Zaki et al[29]	Egypt	2011	13/100 (13%)	3/13 (23%)
Jagadisan et al[30]	Lucknow	2012	23/36 (64%)	8/23 (35%)[b]
Garg et al[31]	Delhi	2012	14/91 (15%)	9/14 (64%)
Jha et al[32]	Jaipur	2013	5/52 (10%)	3/5 (60%)[b]
Duseja et al[33]	Chandigarh	2013	8/100 (8%)	4/8 (50%)[b]
Total			471 (21% median)	220/464 (34% median)

[a]Only fatal cases included in the study.
[b]Exact HEV mortality data unclear, figure derived from overall mortality.

jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease'.[7] Thus the acute deterioration of liver function in a patient with compensated chronic liver disease mainly stable liver cirrhosis is the characteristic feature of ACLF. Multi-organ failure often ensues in the ACLF syndrome following the hepatic decompensation.[34] Liver insufficiency is typically associated with a decreased detoxification function as manifested by hyperbilirubinemia (with clinical jaundice), encephalopathy and reduction of synthetic function leading to hypoalbuminemia and a decrease in prothrombin time. In this specific setting, the lack of liver detoxification and metabolic and regulatory functions leads to life-threatening complications, which in the context of ACLF typically involve systemic hemodynamic dysfunction, renal insufficiency, cerebral failure (hepatic encephalopathy) and increased susceptibility to infections.[34]

In a large prospective study on ACLF, Garg et al have described the clinical, biochemical and etiological profiles of 91 ACLF patients.[31] The median ages of these patients was 36 years and most were males. Acute onset ascites with jaundice with or without hepatic encephalopathy was the presenting symptom in 92% of cases, and rest 8% presented with only hepatic encephalopathy with jaundice but no ascites (acute liver failure like presentation). Most patients had severe jaundice with median bilirubin of 23 mg/dL. Esophageal varices were present in 83% patients; however, only 2% presented with gastrointestinal bleeding. One-third of the patients had already hepatorenal syndrome at presentation. Most patients had leukocytosis with median white blood cell count of 12×10^3 cells/mm^3; however, infection could be documented in a few of these patients. Spontaneous bacterial peritonitis was present in 18% patients. Evidence of stigmata for chronic liver disease (splenomegaly, spider nevi, caput medusae and gynecomastia in males) were seen only <15% of patients. The most common etiology of chronic liver disease was hepatitis B followed by alcohol and cryptogenic. In 75% patients the acute and chronic insult had same etiology (alcohol or hepatitis B), whilst in 25% patients the etiology of chronic and acute insults were different from each other and in these patients, 61% had hepatitis E viral infection as acute insult.[31]

In the study by Radha Krishna et al[26] which had maximum patients of HEV-related ACLF (HEV-ACLF) from India (80 out of 121 [66%] patients of ACLF), the

clinical presentation was essentially the same as ACLF of any other etiology, with 100% having jaundice, 78% having ascites, 33% having grade III–IV encephalopathy, 12% having GI bleed, 34% having sepsis, 21% having SBP, and 36% having renal failure. The median values of serum bilirubin, serum albumin, and international normalized ratio (INR) were 16 mg/dL, 2.3 g/dL, and 2.3, respectively. The median model for end-stage liver disease (MELD) score was 27 and CTP score was 12.[26] Zhang et al[27] from China, compared the effects of HEV superinfection with HAV superinfection in their cohort of patients with chronic hepatitis B. In contrast to other smaller studies which could not discern any difference in presentation among ACLF of different etiologies, Zhang et al were able to show that HEV-ACLF was indeed a more severe illness than HAV-ACLF. The peak levels of serum bilirubin, serum albumin and prothrombin activity were significantly worse in the HEV-ACLF group than in HAV-ACLF group.

The hallmark of the disease course of patients with ACLF is the appearance of organ failure, which progresses to multi-organ failure and death. In the study by Garg et al,[31] at admission, all patients had severe liver failure with either ascites (66%) or hepatic encephalopathy (8%), or both (26%). Severe dysfunction of two or more organs besides liver failure (which constituted multi-organ failure) was present in 29% patients at admission. By one week, 13% patients had died and of the remaining 46% had developed multi-organ failure. At 2 weeks, 30% surviving patients had multi-organ failure. Thus the first 2 weeks determines the outcome in most patients with ACLF. The number of organ systems failed significantly correlates with hospital mortality; with rates ranging from 26% in patients with only one organ failure to >90% in patients with four or more organ system failures.[31]

Besides number of organs failed there are various other variables which help in determining prognosis. A recent systematic review aimed to identify prognostic indicators for patients with ACLF.[35] However, the ambiguity and variability in the definition of ACLF and in its predictive indicators hampered comparability among studies. Nevertheless, the authors suggested that age, hepatic encephalopathy, MELD score, total bilirubin and INR (prothrombin time) appear to be promising candidate factors for prognosis determination.[35]

Table 1 shows the mortality rate of HEV-ACLF. The mortality rate ranges from 0% to 67% with a median being 34%. In the Chinese study by Zhang et al,[27] 46 of 136 (34%) patients of HEV-ACLF had succumbed to liver failure. While in the two of the large studies from India the mortality rate was about 44%.[15,26] Multi-organ failure has been the main cause of death in all the studies.

TREATMENT OF HEV-RELATED ACLF

Patients with ACLF require admission in the intensive care unit (ICU) and these patients benefit from a team approach of clinicians with expertise in both hepatology and critical care.[36] The goals of treatment are to prevent further deterioration in liver function, reverse precipitating factors, and support failing organs. Liver transplantation is required in selected patients to improve survival and quality of life.[36]

Endotracheal intubation for airway control is mandatory in patients with a Glasgow coma scale score of <8 and/or in the presence of active upper gastrointestinal bleeding.[36] Management of respiratory failure and acute lung injury mandates the use of lung protective ventilation strategies; low tidal volume ~6 mL/kg of predicted body weight, positive end-expiratory pressure to maintain satisfactory oxygenation, and plateau pressures <30 cm/H_2O to prevent further lung injury. Sedatives delay extubation and prolong altered consciousness, hence they should be avoided.[36] All patients, whether ventilated or not, should undergo early mobilization and early initiation of physical therapy to prevent weakness associated with immobility and critical illness.

Patients may be hypotensive despite presence of a hyperdynamic state and being unresponsive to volume challenge. Vasopressors such as norepinephrine are titrated to achieve a mean arterial pressure of 65–70 mmHg. Vasopressin (or terlipressin) is norepinephrine-sparing in sepsis and appears to have a similar effect in patients with cirrhosis.[36]

The current recommendation for treatment of hepatorenal syndrome includes volume expansion with albumin (1 g/kg maximum 100 g/day initial dose then followed by20–40 g/day) and vasoconstrictors with the goal of treatment to decrease the serum creatinine to <1.2 mg/dL. The choice of vasoconstrictor depends on availability. Acceptable regimens include terlipressin, recommended at a dose of 0.5–1 mg given every 4–6 h, increasing to 2 mg every 4–6 h for up to14 days. Alternative regimens include norepinephrine at a dose of 0.5–3 mg/h as a continuous infusion; midodrine at a dose of 7.5–12 mg orally three times daily with octreotide at a dose of 100–200 μg subcutaneously three times daily.[36,37] Elevated intra abdominal pressure due to tense ascites may also result in the abdominal compartment syndrome which leads to renal, cardiovascular, and respiratory dysfunction.[36,38] Large-volume paracentesis with concomitant albumin replacement at 6–8 g albumin per liter of ascites removed may be essential to reduce intra abdominal pressure.

The mainstay of treatment of hepatic encephalopathy is use of lactulose and nonabsorbableantibiotics.[36,39] The optimal dose of lactulose is not well established; however, titration to two to three semiformed stools per day is recommended. Avoidance of profuse diarrhea and its associated electrolyte abnormalities is essential.[36]

Routine correction of coagulation abnormalities in the absence of active bleeding is rarely indicated. Correction may be associated with significant complications including

transfusion-associated lung injury, transfusion-associated circulatory overload, and transfusion reactions.[36,40] When correction of bleeding abnormalities is required in the presence of active bleeding, thromboelastography, prothrombin time, complete blood count, and activated partial thromboplastin time are used to guide therapy.

The current recommendation is to provide a diet that contains a normal amount of protein (0.8–1.2 g/kg/day). In the critically ill patient with cirrhosis, the protein requirement may be modified up or down on the basis of degree of catabolism and presence of renal failure.[36] A "tight" glucose control is not desirable. Thus, in patients with cirrhosis, we recommend maintaining blood sugars in the range of 140–180 mg/dL.[36,41]

Because overt signs of infection may be absent, a high index of suspicion is necessary for diagnosis. In patients in whom infection is suspected, early use of broad spectrum antibiotics is often used, preferably within1 hour of admission, is highly recommended as is adherence to early goal-directed therapy guidelines.[36,42]

All patients of ACLF admitted to the ICU deserve a consultation with a transplant center to determine candidacy for liver transplantation. Perceived contraindication to transplant should never preclude this consultation because patients with cirrhosis admitted to the ICU have a mortality rate of 50%. Established communication between the primary provider and the referral center will provide guidance on the optimal timing for referral and/or transfer.[36]

Liver support devices are intended to support liver function until such time as native liver function recovers, or until liver transplantation. Liver support devices are categorized into two main types: artificial livers, being acellular devices such as albumin dialysis and plasma-exchange/diafiltration, and bioartificial devices that contain cells from human, animal, or transformed sources. Early studies with both types of devices demonstrated biological effects (e.g., attenuation of systemic inflammatory response and improved biochemical profiles) but have failed to show a survival benefit. The liver support devices may improve quality of life and perhaps provide an economic benefit by reducing length of hospitalization. The determination of which patient benefits from liver support devices, or should be referred to early liver transplantation, and in which patient all treatment is futile awaits the results of future studies.[36]

There has been no established treatment for acute HEV infection.[43] Pegylated IFN-α-2a has been successfully used for treating chronic hepatitis E in transplant recipients.[44] Further, ribavirin is also shown to inhibit the viral RNA replication and induce a sustained virological response in chronically infected patients.[45,46] One preliminary report from India suggests that ribavirin may be an effective and safe drug for treatment of HEV-ACLF.[47] The investigators Goyal et al treated four patients of HEV-ACLF by ribavirin in the dose of 200–600 mg/d for a median duration of 12 (range 3–24) weeks. The diagnosis of HEV as the cause of ACLF was confirmed by detection of HEV RNA by reverse transcriptase PCR. All four patients had undetectable HEV in 3–8 weeks. All of them survived and tolerated ribavirin well without any adverse effects.[47]

CONCLUSIONS

In summary, HEV when causes AVH in patients of chronic liver disease it may worsen to ACLF leading to high mortality. This is one of the leading causes for decompensation of cirrhosis in endemic countries. The hallmark of the disease course of patients with ACLF is the appearance of organ failure, which progresses to multi-organ failure and death. The mortality rate of HEV-ACLF ranges from 0% to 67% with a median being 34%. These patients require admission in the ICU and thy benefit from a team approach of clinicians with expertise in both Hepatology and critical care. The goals of treatment are to prevent further deterioration in liver function, reverse precipitating factors, and support failing organs. Liver transplantation is required in selected patients to improve survival and quality of life. One preliminary report suggests that ribavirin may be an effective and safe drug for treatment of HEV-ACLF however this requires validation in large trials.

CONFLICTS OF INTEREST

All authors have none to declare.

REFERENCES

1. Panda SK, Varma SP. Hepatitis E: molecular virology and pathogenesis. *J Clin Exp Hepatol*. 2013;3:114–124.
2. Kamar N, Bendall R, Legrand-Abravanel F, et al. Hepatitis E. *Lancet*. 2012;379:2477–2488.
3. Aggarwal R. Hepatitis E: epidemiology and natural history. *J Clin Exp Hepatol*. 2013;3:125–133.
4. Kmush B, Wierzba T, Krain L, Nelson K, Labrique AB. Epidemiology of hepatitis E in low- and middle-income countries of Asia and Africa. *Semin Liver Dis*. 2013;33:15–29.
5. Shalimar, Acharya SK. Hepatitis E and acute liver failure in pregnancy. *J Clin Exp Hepatol*. 2013;3, in this issue.
6. Jalan R, Gines P, Olson JC, et al. Acute-on chronic liver failure. *J Hepatol*. 2012;57:1336–1348.
7. Sarin SK, Kumar A, Almeida JA, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). *Hepatol Int*. 2009;3:269–282.
8. Olson JC, Kamath PS. Acute-on-chronic liver failure: concept, natural history, and prognosis. *Curr Opin Crit Care*. 2011;17:165–169.
9. Wlodzimirow K, Abu-Hanna A, Chamuleau RAFM. Acute-on-chronic liver failure – its definition remains unclear. *J Hepatol*. 2013;59:190–191.
10. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013;144:1426–1437, 1437.e1–9.
11. Olson JC, Kamath PS. Acute-on-chronic liver failure: what are the implications? *Curr Gastroenterol Rep*. 2012;14:63–66.

12. Verbeke L, Nevens F, Laleman W. Bench-to-beside review: acute-on-chronic liver failure – linking the gut, liver and systemic circulation. *Crit Care Lond Engl*. 2011;15:233.
13. Graziadei IW. The clinical challenges of acute on chronic liver failure. Off J Int Assoc Study Liver. *Liver Int*. 2011;31(suppl 3):24–26.
14. Duseja A, Chawla YK, Dhiman RK, Kumar A, Choudhary N, Taneja S. Non-hepatic insults are common acute precipitants in patients with acute on chronic liver failure (ACLF). *Dig Dis Sci*. 2010;55:3188–3192.
15. Acharya SK, Kumar Sharma P, Singh R, et al. Hepatitis E virus (HEV) infection in patients with cirrhosis is associated with rapid decompensation and death. *J Hepatol*. 2007;46:387–394.
16. Shouval D, Shibolet O. Immunosuppression and HBV reactivation. *Semin Liver Dis*. 2013;33:167–177.
17. Hamid SS, Atiq M, Shehzad F, et al. Hepatitis E virus superinfection in patients with chronic liver disease. *Hepatol Baltim Md*. 2002;36:474–478.
18. Ramachandran J, Eapen CE, Kang G, et al. Hepatitis E superinfection produces severe decompensation in patients with chronic liver disease. *J Gastroenterol Hepatol*. 2004;19:134–138.
19. Kumar A, Aggarwal R, Naik SR, Saraswat V, Ghoshal UC, Naik S. Hepatitis E virus is responsible for decompensation of chronic liver disease in an endemic region. Off J Indian Soc Gastroenterol. *Indian J Gastroenterol*. 2004;23:59–62.
20. Monga R, Garg S, Tyagi P, Kumar N. Superimposed acute hepatitis E infection in patients with chronic liver disease. *Indian J Gastroenterol*. 2004;23:50–52.
21. Kc S, Mishra AK, Shrestha R. Hepatitis E virus infection in chronic liver disease causes rapid decompensation. *JNMA J Nepal Med Assoc*. 2006;45:212–215.
22. Ke WM, Li XJ, Yu LN, et al. Etiological investigation of fatal liver failure during the course of chronic hepatitis B in southeast China. *J Gastroenterol*. 2006;41:347–351.
23. Kumar M, Sharma BC, Sarin SK. Hepatitis E virus as an etiology of acute exacerbation of previously unrecognized asymptomatic patients with hepatitis B virus-related chronic liver disease. *J Gastroenterol Hepatol*. 2008;23:883–887.
24. Kumar A, Das K, Sharma P, Mehta V, Sharma BC, Sarin SK. Hemodynamic studies in acute-on-chronic liver failure. *Dig Dis Sci*. 2009;54:869–878.
25. Mahtab MA, Rahman S, Khan M, Karim MF. Hepatitis E virus is a leading cause of acute-on-chronic liver disease: experience from a tertiary centre in Bangladesh. *Hepatobiliary Pancreat Dis Int*. 2009;8:50–52.
26. Radha Krishna Y, Saraswat VA, Das K, et al. Clinical features and predictors of outcome in acute hepatitis A and hepatitis E virus hepatitis on cirrhosis. Off J Int Assoc Study Liver. *Liver Int*. 2009;29:392–398.
27. Zhang X, Ke W, Xie J, Zhao Z, Xie D, Gao Z. Comparison of effects of hepatitis E or A viral superinfection in patients with chronic hepatitis B. *Hepatol Int*. 2010;4:615–620.
28. Lal J, Thapa BR, Rawal P, Ratho RK, Singh K. Predictors of outcome in acute-on-chronic liver failure in children. *Hepatol Int*. 2011;5:693–697.
29. El Sayed Zaki M, Othman W. Role of hepatitis E infection in acute on chronic liver failure in Egyptian patients. *Liver Int*. 2011;31:1001–1005.
30. Jagadisan B, Srivastava A, Yachha SK, Poddar U. Acute on chronic liver disease in children from the developing world: recognition and prognosis. *J Pediatr Gastroenterol Nutr*. 2012;54:77–82.
31. Garg H, Kumar A, Garg V, Sharma P, Sharma BC, Sarin SK. Clinical profile and predictors of mortality in patients of acute-on-chronic liver failure. *Dig Liver Dis*. 2012;44:166–171.
32. Jha AK, Nijhawan S, Rai RR, Nepalia S, Jain P, Suchismita A. Etiology, clinical profile, and inhospital mortality of acute-on-chronic liver failure: a prospective study. *Indian J Gastroenterol*. 2013;32:108–114.
33. Duseja A, Choudhary NS, Gupta S, Dhiman RK, Chawla Y. APACHE II score is superior to SOFA, CTP and MELD in predicting the short-term mortality in patients with acute-on-chronic liver failure (ACLF). *J Dig Dis*. 2013;14:484–490.
34. Laleman W, Verbeke L, Meersseman P, et al. Acute-on-chronic liver failure: current concepts on definition, pathogenesis, clinical manifestations and potential therapeutic interventions. *Expert Rev Gastroenterol Hepatol*. 2011;5:523–537.
35. Wlodzimirow KA, Eslami S, Abu-Hanna A, Nieuwoudt M, Chamuleau RAFM. A systematic review on prognostic indicators of acute on chronic liver failure and their predictive value for mortality. *Liver Int*. 2013;33:40–52.
36. Olson JC, Wendon JA, Kramer DJ, et al. Intensive care of the patient with cirrhosis. *Hepatol Baltim Md*. 2011;54:1864–1872.
37. Ginès P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med*. 2009;361:1279–1290.
38. Aspesi M, Gamberoni C, Severgnini P, et al. The abdominal compartment syndrome. Clinical relevance. *Minerva Anestesiol*. 2002;68:138–146.
39. Khungar V, Poordad F. Hepatic encephalopathy. *Clin Liver Dis*. 2012;16:301–320.
40. Kor DJ, Gajic O. Blood product transfusion in the critical care setting. *Curr Opin Crit Care*. 2010;16:309–316.
41. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283–1297.
42. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345:1368–1377.
43. Parvez MK. Chronic hepatitis E infection: risks and controls. *Intervirology*. 2013;56:213–216.
44. Kamar N, Abravanel F, Garrouste C, et al. Three-month pegylated interferon-alpha-2a therapy for chronic hepatitis E virus infection in a haemodialysis patient. *Nephrol Dial Transplant*. 2010;25:2792–2795.
45. Kamar N, Rostaing L, Abravanel F, et al. Ribavirin therapy inhibits viral replication on patients with chronic hepatitis E virus infection. *Gastroenterology*. 2010;139:1612–1618.
46. Kamar N, Izopet J, Dalton HR. Chronic hepatitis E virus infection and treatment. *J Clin Exp Hepatol*. 2013;3:134–140.
47. Goyal R, Kumar A, Panda SK, Paul SB, Acharya SK. Ribavirin therapy for hepatitis E virus-induced acute on chronic liver failure: a preliminary report. *Antivir Ther*. 2012;17:1091–1096.

