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Alcoholic hepatitis – current concepts and management

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ABSTRACT

Alcoholic hepatitis is a form of acute injury to liver tissue that is also a precursor of cirrhosis, and carries significant morbidity and mortality. Severe alcoholic hepatitis in particular causes a high short-term mortality, and also places an enormous burden on healthcare resources.

The treatment of alcoholic hepatitis remains one of the most debated topics in medicine and a field of continued research. In this review, we discuss the clinical point of view (evolution of scoring systems), the current solutions on management, and the perspectives of new drugs.

Nutritional support, medical therapy with glucocorticoids, pentoxifylline, infliximab, s-adenosyl-methionine, colchicine and other drugs are reviewed, as well as the role othotopic liver transplantation (OLT). Glucocorticoids currently remain the mainstay of treatment for severe alcoholic hepatitis.

INTRODUCTION

Alcoholic liver disease is one of the top ten leading causes of death in developed countries, responsible for 3% of all deaths (1). Age adjusted death rate from alcohol induced liver disease accounts for 40% of deaths from cirrhosis or 28% of all deaths from liver disease (2).

The syndrome of alcoholic hepatitis develops in only a minority of chronic alcohol abusers (3), with a clinical spectrum ranging from an asymptomatic histological diagnosis to a life-threatening clinical illness that may include jaundice, ascites, gastrointestinal bleeding or encephalopathy.

While alcoholic hepatitis is common, its pathogenesis, predictors for survival, and treatment remain debated. The prevalence of the disease, its high fatality rate, and the elusiveness of cure keeps this disease in the forefront of topic reviews and scientific investigations. ❑

EPIDEMIOLOGY AND CLINICAL DATA

Alcohol intake – how much is "too much"?

This topic is of major importance in current medical practice, as many people confuse the term for "alcohol use" with "alcohol abuse", and other people believe that they do not actually drink if they use low alcohol concentration beverages. It has to be said from the beginning that, regarding the hepatic toxicity, it is not the type of drink that matters, but only the amount of pure alcohol that is used.

According to epidemiological data, a man who drinks more than 4 units/day or 14 units/week, respectively a woman who drinks 3 units/day or 7 units/week are exposed to the risk of developing chronic liver disease (1 unit equivalent to 14 grams of absolute alcohol) (4).

Although, we must not forget that, in the presence of additional factors (age over 65 (5), co-morbidities – HCV (6), hemochromatosis, diabetes mellitus (7), drug use (8) even intake below this doses may cause liver injury (9). Also, during pregnancy, abstinence must be recommended in order not to affect the mother and the child (10).

Population-based studies show that in USA, as in Western Europe, 68% of the population drinks alcohol at least once a month. About 10% of the population drinks at least 2 units/day. From these alcohol abusers, in time 80-100% will

develop liver steatosis, 13-35% alcoholic hepatitis and 10-20% liver cirrhosis (11).

Alcoholic hepatitis – clinical and laboratory data

This entity covers a large clinical spectrum, from subclinical, asymptomatic forms (consisting of biochemical and histological changes) to the acute fulminant hepatic failure.

This large clinical variability is the main cause for the underdiagnose of this entity. On the other hand, the occurrence of steatohepatitis is an important prognostic factor in the evolution of chronic liver disease (12).

Severe forms present fever, anorexia, painful liver enlargement (90%), splenomegaly (50%), jaundice, ascites (40-50%), encephalopathy. In a severe evolution, renal failure occurs and the general condition is worsening. The patients who need hospitalization for this reason have a short-term mortality (one month) of 40-50% (13).

Lab results show leukocytosis with neutrophilia (correlated to the severity of liver injury) and high levels of aminotrasferases (usually below 400 IU/l) (14). The increased seric levels of bilirubin and prothrombin time are correlated to the degree of liver involvement, being included in the scores for the stratification of the severity of the disease (15).

Scoring systems

Patients stratification for therapy allocation and prognostic evaluation is important in current medical practice. There are several scoring systems that may be used in alcohol-induced liver disease (Child-Pugh, Maddrey, MELD, or recently published Lille model).

1. The Child-Pugh score is the most frequently used score in cirrhotic patients, irrespective of etiology, with an uncontestable prognostic value (16). There is although evidence that in alcoholic hepatitis other scoring systems have a better prognostic value.

2. The Maddrey score takes into account the prothrombin time and bilirubin, two parameters that proved to be independent mortality factors in patients with ethanolic hepatitis (17). A Maddrey score > 35 shows a severe alcoholic hepatitis with bad prognosis and the addition of encephalopathy predicts a mortality rate > 50% (18). The value of this score is diminished by some interfering elements such as the large variability of prothrombin time among different centers(19). For this reason, some authors recommend other scoring systems.

3. The MELD score (Mayo Endstage Liver Disease) was developed for patients with terminal liver cirrhosis and include parameters that also appear in the Madrrey score. In addition, it also includes parameters that have a prognostic role, such as creatinin levels, which predicts an eventual development of the hepato-renal syndrome. There is evidence that the MELD score may also be used in patients with alcoholic cirrhosis, having a predictive value similar to the Maddrey score (20). Although, there are also some restraints in using this score in the current clinical practice, mainly concerning the lack of a well defined cut-off value and the fact that the MELD on day 7 after admission would be more useful than the score at admission (21).

4. The GAHS score (Glasgow Alcoholic Hepatitis Score) was especially created for alcoholic hepatitis, taking into account the variables that are independently associated to mortality by this disease (22). Patients with a GAHS greater than or equal to 9 have an extremely poor prognosis if they are not treated with corticosteroids, or if such treatment is contraindicated (23). The superiority of this score compared to those formerly presented is still uncertain, further studies being needed to reach this conclusion.

5. The Lille model is the last proposed scoring system for evaluating the prognosis of alcoholic hepatitis (24), and of course is not yet validated A specific prognostic model was generated by logistic regression in order to identify candidates early on for alternative therapies. The model combining six reproducible variables (age, renal insufficiency, albumin, prothrombin time, bilirubin, and evolution of bilirubin at day 7) was highly predictive of death at 6 months. Patients above an ideal cutoff of 0.45 showed a marked decrease in 6-month survival as compared with others (25% versus 85%). This cutoff was able to identify approximately 75% of the observed deaths, showing a better prognostic value than MELD and GASH.

Liver biopsy

Liver biopsy is the only one able to distinguish an alcoholic hepatitis from liver cirrhosis. Moreover, alcoholic hepatitis lesions may overlap in a patient with preexistent ethanolic cirrhosis. Since it was reported first (25), the morphology of alcoholic liver disease has been well described (26).

Moreover, several histological characteristics as the presence of perivenular fibrosis, steatosis and giant mitochondria in a known alcoholic may

herald the transition from alcoholic hepatitis to cirrhosis (27).

While histologic changes from steatosis and steatohepatitis to cirrhosis are known, correlating degree of steatosis with liver function and survival is currently under investigation. Few studies finds a correlation between low grade steatosis and advanced liver failure as well as lowered sensitivity to steroid treatment (28). However, patients with low grade steatosis had higher Maddrey discriminant function scores, which can also predict poor survivals. That's why liver biopsy for staging and predicting survival has been replaced by the discussed scoring systems.

It is generally accepted to perform a liver biopsy if the diagnosis of alcoholic hepatitis is either in question or a concomitant pathology, such as hepatitis C, is suspected (29).

Another important indication for the liver biopsy is the distinction between alcoholic hepatitis alone and the concomitance of liver cirrhosis in patients with severe disease (30). In clinical practice, transjugular liver biopsy is recommended in these cases (given the presence of coagulopathy and/or ascites) if leukocytosis, fever and hepatic bruit are absent (31).

In conclusion, the role of liver biopsy in defining prognosis and treatment of alcoholic hepatitis in the clinical setting remains unclear, in the absence of the above recommendations. ❑

THERAPY OF ALCOHOLIC HEPATITIS

1. Abstinence

It is the key point in the management of every clinical form of alcohol-induced liver disease, being even able to reverse the lesions of hepatic steatosis or alcoholic hepatitis. The persistence of alcohol intake is an independent risk factor with a bad prognosis in patients with alcoholic hepatitis, liver cirrhosis and after liver transplantation (32.). Liver steatosis may be completely reversible in case of abstinence in a few weeks. Alcoholic hepatitis may be partially reversible after stopping the alcohol intake (33).

Reaching this goal is not easy in alcohol-addicted patients and therefore a therapeutic plan is needed, which has to involve a psychological component and a pharmaceutical one. The psychological intervention involves strategies for educating and informing the patients about the problems related to chronic consumption and alcohol addiction and also for recommending behavioral changes (34).

In addition to psychotherapy, alcohol addicted patients could benefit from a pharmacologic therapy (35). Acamprosate proved itself useful in reducing the number of intake days and increasing the abstinence ratio (36), with also a good tolerability (except for cirrhotic Child C patients). Naltrexone had similar effects, but a lower tolerability. Disulphiram (inhibitor of the acetaldehyde dehydrogenase) is being used for many years in alcohol addicted patients, although the results are uncertain and the adverse events are significant (37).

Not to forget the "other side of the coin" in abstinent patients – the alcohol withdrawal syndrome. Symptoms usually start within a few hours (tremors, sweating, elevated pulse and blood pressure, nausea, insomnia, anxiety. The delirium may follow after 1-3 days (altered sensorium, disorientation, hallucinations, poor shot-term memory, altered sleep-wake cycle). Mild withdrawal can be managed in an outcare setting, while severe cases require hospitalization and intensive treatment (thiamines, benzodiazepines, anticonvulsivants, beta-adrenergic blockers, or antipsychotics) (38).

2. Nutrition

Malnutrition is found in a significant number of patients, having various etiology and important consequences in amplifying the toxicity of the ethanol (39). Prognostic studies showed benefits for nutritional therapy similar to corticotherapy and their association might result in a synergic therapeutic effect (40). One-year mortality was lower in patients with nutritional therapy (41).

Thus, supportive nutritional therapy still represents a therapeutic alternative in the management of these patients although some authors consider it's efficacy "unproven" (42). It is necessary to supplement proteins (1g/kg/day), calories (2000-3000 kcal/day) and vitamins (mainly thiamine). Vitamin K is routinely administered in patients with prolonged prothrombin time, although this is not completely benefic because liver failure causes complex abnormalities of the coagulation.

Conventional amino acids may be used in enteral or parenteral administration, branched-chain amino acids being reserved for patients with encephalopathy. Medium-chain triglycerides may also be used.

If oral nutrition is not possible (severe disease, encephalopathy, dynamic ileus), total parenteral nutrition must be started. In the other situations one may choose oral or parenteral catheter nutrition.

Hyperhydration must be avoided in parenteral nutrition, because it could increase the

ascites, cause a dilutional hyponatremia or favor a variceal bleeding by increasing the pressure in the portal vein.

3. Medical therapy

Corticoids

They have been used for treating alcoholic hepatitis starting from the '60s and represent the main discussed drugs in this disease. Although, their use is still controversial to date, even if every author agrees that they are the most efficient available therapy at this moment (43).

The mechanism of action is centered on blocking the pathogenic inflammatory and cytotoxic routes, by decreasing the level of pro-inflammatory cytokines such as TNF-alpha and reducing the expression of ICAM-1 (44).

The therapeutic indication is the severe alcoholic hepatitis (Maddrey score > 35) (43).

Although in variable proportions, therapeutic trials showed a benefic result of steroid therapy, demonstrating decrease of mortality, clinical and biological improvement and even histological improvement.

Thus, response ratio ranged between 67% and 87%, with an NNT (number of treated patients to obtain a therapeutic response) between 2 and 6. In the absence of infection or upper digestive bleeding, the presence of encephalopathy is an additional reason to administer corticoids (31). Overall mortality after one month of corticoid therapy decreased from 35% to 15%.

The duration of administration is one month. A number of studies showed that the best marker to evaluate the benefits of corticoid therapy is the early decreasing of total bilirubin level (after 7 days of therapy) (45). If total bilirubin level after 7 days of therapy is lower than its level at admittance, then there is a therapeutic response; if not, corticoids can be stopped. 6 month survival was 84% if there had been an early decreasing of bilirubin level and only 23% if bilirubin levels had not changed in 7 days. Though, regarding 2 years survival, no significant difference was found in patients with corticotherapy compared to the other patients.

On the other hand, we must not omit the adverse events of corticotherapy, especially the infectious ones, which may cause mortality by themselves (46). Therefore, corticoids should not be administered with mild and moderate disease, while overall survival in this category exceeds 90% anyway.

In conclusion, in selected cases, corticotherapy is benefic in patients with severe alcoholic hepatitis, resulting in a significant decrease in mortality.

Pentoxifylline

This is a phosphodiesterase inhibitor, whose mechanism of action is related to the inhibition of TNF-alpha (47). The recommended dose is 3 x 400 mg/day for 4 weeks. Relatively recently added to the therapeutic arsenal, pentoxifylline proved useful in severe alcoholic hepatitis (48), increasing overall survival by 20% (49). It must be stated that the improvement in survival was related to the decrease in number of deaths due to hepatorenal syndrome, the benefit of the pentoxifylline being strictly related to the decrease of this complication (50).

Anti TNF-alpha therapy

This therapy is based on the premise that cytotoxic effect of TNF alpha is a key element in the etiopathogeny of alcohol-induced liver injury. The administration of these drugs was proposed for the therapy of severe alcoholic hepatitis (Madrey score > 35), in association with corticosteroids, but to date, this category of drugs cannot be recommended in current medical practice, further efficacy and safety trials being needed for the usage of etanercept and infliximab.

a) Infliximab

It was used in a 5mg/kg or 10 mg/kg i.v. dose; a single or multiple administration (weeks 0, 2, 4) has been proposed. If the 5 mg/kg dose in single administration proved itself useful (51), the therapy with 10mg/kg in 3 doses was inferior to corticotherapy, resulting in a higher mortality by infectious complications (52). Moreover, except the increased risk of infection, infliximab was associated with cases of acute liver failure in patients with Crohn's disease and rheumatoid arthritis. And this risk may preclude its use in patients with underlying severe liver injury who are less capable of withstanding an additional insult to the liver.

b) Etanercept

This drug is a soluble TNF p75 receptor, which neutralizes the soluble TNF. The usage of this drug in patients with severe and moderate alcoholic hepatitis (score >15) showed a possible improvement in 30-days survival (92%), but also a high ratio of adverse events (infections, renal failure, digestive hemorrhage) which led therapy discontinuation in 23% of patients (53).

c) Thalidomide

The proposed mechanism of action is the reduction in the synthesis of TNF-alpha and the

inhibition of the Kupffer cells response to bacterial endotoxins. Experimental studies showed a decrease of necro-inflammatory processes, respectively of hepatic steatosis after the administration of alcohol in association with thalidomide during 8 weeks (54). Moreover, this drug has been shown to reduce the hepatic venous pressure gradient in stable alcoholic cirrhotics (55). On the other hand, major side effects result in not using this drug in medical practice for alcoholic hepatitis. To date, researches are ongoing for synthesizing thalidomide analogues with no teratogenic effect.

d) Pioglitazone

It is a PPAR-g (peroxisome proliferator-activated receptor-gamma) agonist, which inhibits the production of TNF-alpha by Kupffer cells in response to endotoxinemia. Animal studies showed that pioglitazone prevents alcohol-induced hepatic lesions (56). There are no studies on humans to date, but in the future this drug could be useful for patients with severe alcoholic hepatitis.

Antioxidant therapy

This therapeutic alternative is based on the concept that oxidative stress is in a high degree responsible for the development of alcohol-induced liver injury. Moreover, chronic alcohol abusers have a low intake of antioxidants (selenium, vitamin A, vitamin C, coenzyme Q).

a) Antioxidant coktails

Relatively recent studies compared corticosteroids to a cocktail containing beta-caroten, vitamin A and C, selenium, methionine, allopurinol, desferoxamine and N-acetylcysteine (57). Corticotherapy was superior to this therapy after one month, but after one year, the mortality rates were similar. Other studies that associated antioxidant therapy to corticotherapy showed no additive benefit, suggesting the lack of efficacy of this kind of therapy (58).

b) Vitamin E

Studies performed in patients with mild and moderate ethanolic hepatitis, who received vit. E 1000 IU/day for 3 months, showed a decrease in the seric level of hialuronic acid (serologic marker of liver fibrogenesis), but had no effect concerning the improvement of hepatic function or mortality after the firs year of therapy (59). Thus, this therapy remains a subject of controversy.

c) Silymarin

This is an antioxidant compound widely used in patients with liver cirrhosis, irrespective of the etiology. The mechanisms of action are numerous, including regulation of membrane permeability, inhibition of 5-lipooxygenase, decrease of oxygen-centered free radicals, suppression of the nuclear factor NF-kappaB (60).

The recommended dosage is 150 mg x 3/day orally. While experimental studies showed that silymarin delays the development of alcohol-induced liver fibrosis, therapeutic trials showed discordant results, some of those showing a decrease by 20% of 4-years mortality, while the others showed no significant difference to placebo (61).

Counting currently available data, we could state that silymarin might have a favorable therapeutic effect in some groups of patients with alcoholic cirrhosis, but this effect might not be superior to that resulting from abstinence. Though, considering that these drugs have a good tolerability and a low cost, silymarin may be recommended in current practice.

Propylthiouracil

The mechanism of action is related to the inhibition of the hypermetabolic status and reduction of oxygen consumption (62). The therapeutic indication is moderate and severe alcoholic hepatitis. While initial studies revealed a benefit in terms of decreasing the complications and mortality rates, a meta-analysis of data in the literature did not show any benefit regarding histological improvement, complications, liver injury related mortality or overall mortality (63). Under these circumstances, this drug cannot be to date recommended in current medical practice.

Anabolic steroids (oxandrolone)

There is a measurable and clinically apparent decline in gonadal function in patients with alcoholic liver disease, but available data could not demonstrate a significant effect of anabolic-androgenic steroids on the symptoms improvement and mortality of patients with alcoholic liver disease (64). Currently, anabolic steroids are no longer recommended for the treatment of alcoholic hepatitis.

S-adenosyl-methionine

In the setting of alcoholic hepatitis, there is a measurable decrease in hepatic methionine, and glutathione levels The proposed mechanism of action for this drug concerns the reduction of liver alcoholic injury by diminishing the oxidative stress and raising the level of mitochondrial glutathione (65).

Administered in dose of 1200 mg/day for 1-2 years in cirrhotic patients, led to a decrease of mortality rate and number of liver transplants compared to placebo, but the differences were not statistically significant in different studies (66). Furthermore, currently there are no available trials studying the effect of the drug in acute alcoholic hepatitis. Therefore, this drug cannot be recommended in current clinical practice.

Colchicine

The mechanism of action is anti-inflammatory and antifibrotic. Its use in alcoholic hepatitis (1 mg/day, orally) did not prove efficacy (67), and long-term use in cirrhotic patients resulted in discordant data regarding the benefits (complications, liver transplant, death) and negative results concerning the adverse events (68). Therefore, this drug cannot be recommended to date in current medical practice.

Dilinoleoylphosphatidylcholine

The mechanism of action is antifibrotic by reducing the activity of stellate cells (Ito cells) and stimulating the activity of the colagenases, but also anti-inflammatory by reducing the activity of cytochrome P450-2EI and inhibiting TNF-alpha (69). There are few clinical trials, which makes it difficult to evaluate the efficacy of this drug. Current data show that a 2 year administration led to a decrease of the bilirubin and aminotransferases levels, but did not influence the progression of liver fibrosis (70).

Therapy of the hepatorenal syndrome

The occurrence of this complication represents a bad prognosis factor, while it is associated with a mortality rate of 90%. In liver cirrhosis, combination therapy with i.v. albumin and a splanchnic vasoconstrictor (terlipressin) has been successfully implemented (71). There are no studies in alcoholic hepatitis to date, but theoretically this kind of approach could be useful in reducing the mortality rate in patients with hepatorenal syndrome, in association with pentoxifylline.

Transplant for alcoholic hepatitis

Liver transplant is the only permanent therapeutic option in patients with terminal liver disease, including patients with alcohol-induced liver cirrhosis. But also severe forms of alcoholic hepatitis may evolve with fulminant liver failure, which could represent another indication for liver transplant, in the absence of a therapeutic response to medical treatment (72).

At this moment, there is no absolute recommendation for transplant in these patients, because there is no pre-transplant abstinence period, comorbidities are frequently found and there is no appropriate psychiatric evaluation (73). There are only isolated case reports concerning patients who survived the transplant. There is probably at least one subgroup of patients with severe alcoholic hepatitis who could benefit from transplant, but further studies are needed to asses this indication (if it does exist). ❑

CONCLUSION

Alcoholic hepatitis is still a "difficult to diagnose" entity because of its large variability in clinical presentation. Severe onsets represents a "difficult to treat" group, in which the actually recommended therapies are still modest, and short/long-term mortality is significant.

Despite the recent advances in understanding the pathways of ethanol liver injuries, attempts to link therapeutic options to the pathogenesis prove no major benefit for the moment. ❑

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