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EDITORIAL

Know When to Hold 'em, Know When to Treat 'em, Know When to Cut 'em: Why Severe Alcoholic Hepatitis Is Becoming a Surgical Disease

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A riff on the popular song *The Gambler*, written by Don Schlitz, sung by the late Kenny Rogers and many others, may have something to teach caregivers about the management of severe alcoholic hepatitis (SAH).

Excessive and binge drinking is increasing in most US counties, in particular among young women [1]. Those admitted to hospital for alcoholic liver disease have a greater median total cost, longer length of stay, greater blood product utilization, higher mortality, and a greater rate of discharge against medical advice than age- and gender-matched controls with other liver diseases [2].

SAH has defied concerted and intensive efforts to find a successful pharmacological treatment for more than a half-century. Limited knowledge about SAH pathophysiology limits the ability to find therapeutic targets. Prevalent features include disruption of gut barrier function, enhanced delivery of Gram-negative bacteria-derived lipopolysaccharide (LPS) to the portal vein, the interaction of LPS, other bacterial products, and damage-associated molecular patterns (DAMPS) with Toll-like receptors expressed on hepatic resident macrophages (Kupffer cells) and hepatocytes, and activation and secretion of Il-1β and other cytokines resulting in polymorphonuclear cell infiltration and other inflammation-associated changes. The systemic inflammatory response syndrome (SIRS) may supervene and, when present, portends a high risk for multi-organ failure and death [3, 4]. SAH treatment consists of alcohol cessation and adequate nutrition. To date, drugs intended to treat this disorder are of minimal benefit. Table 1 identifies current American Association for the Study of Liver Diseases (AASLD) guidance recommendations [5].

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After dozens of randomized controlled trials conducted over more than a half-century, it is now well known that corticosteroids benefit so infrequently that 13–15 patients need to be treated to see one additional survivor at day 28, with no survival benefit beyond [6]. Corticosteroid therapy is further limited by an impressive number of contraindications (uncontrolled infection, acute kidney injury, uncontrolled upper GI bleeding, concomitant hepatitis B or C, drug-induced liver injury) leaving many without viable treatment options.

If corticosteroids alone are unhelpful, what about a combination of drugs that work by different mechanisms? Pentoxifylline with or without prednisone is without value. *N*-acetyl cysteine (NAC) prevents or attenuates liver damage from acetaminophen overdose and is also used in severe acute liver failure of other causes. In SAH, NAC combined with prednisolone resulted in a one-month death rate 1/3 of that of patients given only prednisone (8% vs 24%, $P = 0.006$) [7]. No confirmatory RCT has been published, and a search of clinicaltrials.gov (February 12, 2020) reveals no ongoing therapeutic trials of NAC in SAH.

In this issue of *Digestive Diseases and Sciences*, Amjad et al. reported a single-center experience of NAC treatment of SAH. [8] Sixty-eight patients collected over 6 years received either prednisone or prednisone and NAC. The treatment choice was determined by the physician-in-charge. Overall short-term mortality (14.2% and 20.6% at day 30 and 90, for prednisone and prednisone + NAC, respectively) is similar to that reported by others. The authors conclude the use of NAC (given IV for 5 days) adds to the cost of care, without apparent benefit. The crude incidence of death was higher in those who received NAC. The groups were clinically similar in many ways except that renal failure was present more frequently in those who received prednisone and NAC, rendering this group sicker. Inclusion of many patients with sepsis or gastrointestinal bleeding may also impair interpretation. These negative results are not sufficiently robust to constitute the death knell for its use, but

Table 1 American Association for the Study of Liver Disease guidance for nonsurgical treatment of severe alcoholic hepatitis

Proven benefit	Likely benefit	Potential benefit	Unlikely benefit
Treatment recommendations for severe acute alcoholic hepatitis			
Alcohol abstinence	Corticosteroids	*N*-acetyl cysteine	Pentoxifylline
Enteral nutrition (> 21 kcal/kg daily		Granulocyte colony-stimulating factor	
			Data from Crabb et al. Hepatology 2020; 71; 306

mandate development of one or more adequately powered randomized controlled trials in order to better define the utility of this drug in SAH. Other agents, such as granulocyte colony-stimulating factor, require careful additional investigation.

The study also compared several of predictive models: The MELD score was slightly superior to the Maddrey discriminant function (MDF), with the Lille score somewhere in between. The MDF combined with a renal insufficiency component performed the best. Of these models, only the Lille score assesses change in liver performance over time. A major benefit of using this measure of dynamic response is the ability to promptly identify treatment futility. Why expose a patient to 28 days of corticosteroids if lack of responsiveness can be predicted earlier? It is important in this context to recognize that the Lille score using data collected at day 4 is as accurate as data collected on day 7 [9]. Corticosteroid treatment without clinical benefit beyond 4 or 7 days should be terminated.

Since liver transplantation provides an impressive survival benefit, a paradigm shift is brewing that includes more liberal application of liver transplantation for SAH. Nevertheless, despite one-year survival rates of 89–93%, < 10% of those with favorable psychosocial profiles are offered transplantation, representing < 3% of transplants [10]. Ethical considerations such as recidivism, social approbation about a self-induced disease, equity, and fairness constrain this approach as long as the donor organ supply remains limited. Each of these issues is being actively re-assessed with recent reports suggesting an expanding role for this treatment option. For example, the six-month period of abstinence formerly required before transplantation is no longer required. The AASLD recommends consideration of liver transplantation for carefully selected patients once they are confirmed to be nonresponsive to treatment, a practice that will require mobilization of substantial resources both to provide timely evaluation and to manage the social and psychiatric aspects of the patient with alcohol abuse disorders.

In summary, medical therapy of SAH is ineffective. Adding a second drug to corticosteroids is of uncertain (but unlikely) benefit. Pentoxifylline is ineffective. The jury remains out with regard to NAC and on granulocyte colony-stimulating factor, although each warrants further study. Barring finding a drug with substantial benefit, it seems likely that drug development will best be used to reduce the number of transplantable candidates rather than completely replace liver transplantation as the best available treatment. Even if started now, several years would go by before results of drug trials would be available. In the meantime, liver transplantation remains a proven but insufficiently employed option. Broadening the criteria for liver transplantation will save more lives than the development of new drugs for this condition. Those with SAH should be actively considered for liver transplantation if they fail the Lille score at day 4 or day 7.

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