

## ORIGINAL ARTICLES

## The Management of Renal Failure in Patients with Liver Disease. Experiences from a District General Hospital.

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## Abstract

## Aim

To compare the pre-existing management of patients with Hepatorenal Syndrome (HRS) in the gastroenterology unit of the Royal Alexandra Hospital, Renfrewshire, with the published evidence based studies.

## Method

A retrospective, 6-month, case record review of patients diagnosed with HRS was performed. An evidence-based protocol for the diagnosis and management of HRS was introduced into the unit, to aid patient treatment prospectively. After 6 months, both compliance with the protocol, and patient outcomes were analysed.

## Results

Eleven patients were identified in the first part of the audit cycle, all of whom died. Seven were identified in the second cycle. Two had their renal function successfully corrected and one was discharged from hospital. Renal impairment and staging of liver disease was equivalent in both groups. The second group received more appropriate and aggressive therapy. Alcohol was the causative aetiology of liver disease in all patients.

## Conclusions

Targetted therapy in patients with severe liver disease and HRS can improve renal parameters. Previous studies have shown this to be linked with improved patient outcomes.

## Introduction

The increased burden of alcohol related disease to the NHS is well-documented.<sup>1,2</sup> Complications of alcoholic liver damage occupy many NHS bed-days, and are often fatal. Although not the most common complication, hepatorenal syndrome (HRS) has possibly the highest mortality. HRS encompasses two different patterns of disease referred to as Type I and Type II. Type II HRS is an insidious, chronic form of HRS, occurring in the presence of well-established cirrhosis and often diuretic resistant ascites. It has a median survival of 1 year and the prognosis is very poor without the intervention of a transplant. Type I is the rapidly progressive form of the condition. It occurs in patients with decompensated liver disease and acute relapses of chronic liver disease. Death results from a combination of hepatic and renal failure. If untreated, mortality is 80% within 2 weeks.<sup>3</sup>

HRS is not an intrinsic disease of the kidney.<sup>4</sup> The kidney is compromised because of hormonal changes. Plasma renin levels can increase by as much as 8-fold. Aldosterone and norepinephrine levels are also greatly increased which cause renal vasoconstriction in the presence of both peripheral and splanchnic vasodilatation.<sup>5</sup> With a potential for rapid deterioration, close observation of these patients is paramount, particularly if there is an intervention that can alter the natural pathophysiology. Until recently there was scant published evidence on the management of HRS. Treatment varied from a supportive 'wait and see' policy, to the use of dopamine and dobutamine, either alone or in combination.

Treatment for acute alcoholic hepatitis has also changed slightly, with more authors advocating the use of oral steroids or pentoxifylline.<sup>6</sup> The Maddrey Discriminant Function (DF) is one of the original hepatic prognostic indicators, using a calculation involving both the prothrombin time and serum bilirubin, to determine those patients suitable for treatment (advocated if DF >32) (see Table I for formula). This applies to the prescription of both steroids and pentoxifylline. A recent analysis of alcoholic hepatitis management from Glasgow, has accounted for patient age, prothrombin time ratio, bilirubin, white cell count and urea (Table II). Scores  $\geq 9$  can be considered for such treated providing no contraindications exist.<sup>7</sup>

Table I: Calculation of the Maddrey Discriminant Function (DF).

A score &gt;32 qualifies for treatment.

$$4.6 \times (\text{Prothrombin time} - \text{Control}) + \text{Bilirubin} = \text{DF Score}$$

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Units: Prothrombin time : seconds

Bilirubin :  $\mu\text{mol/l}$ 

Table II: Calculation of the Glasgow Alcoholic Hepatitis Score.

| Score value                     | 1    | 2         | 3    |
|---------------------------------|------|-----------|------|
| Age                             | <50  | $\geq 50$ |      |
| WCC ( $10^9/\text{l}$ )         | <15  | $\geq 15$ |      |
| Urea ( $\text{mmol/l}$ )        | <5   | $\geq 5$  |      |
| Bilirubin ( $\mu\text{mol/l}$ ) | <125 | 125-250   | >250 |
| PT (ratio)/INR                  | <1.5 | 1.5-2.0   | >2.0 |

Cumulative scores  $\geq 9$  have a poor prognosis without corticosteroids or if corticosteroids are contra-indicated.

## Diagnostic criteria for hepatorenal syndrome

These were initially set out by the International Ascites Club. There are several major criteria that must be fulfilled to confirm the diagnosis of HRS – see Table III.

**Table III:** Major Criteria to be fulfilled for a diagnosis of HRS.



Liver disease must be present with a picture of advanced hepatic failure. Biochemical markers include serum creatinine above  $225\mu\text{mol/l}$  or creatinine clearance dropping below  $40\text{ml/min}$ . Pre-existent renal disease must be excluded, partly by ultrasound, and by ruling out significant proteinuria ( $>0.5\text{g/24 hours}$ ). Hypovolaemia must be excluded as well as the concomitant use of nephrotoxic drugs (eg diuretics, non steroidal anti-inflammatory drugs and some antibiotics). Intravenous fluid support should be given, with intravenous albumin solution being the favoured product. This has been shown to be the best fluid for support and resuscitation in both spontaneous bacterial peritonitis and HRS.<sup>8,9</sup>

Finally, sepsis from any source has to be excluded. Indolent infection on the background of immunocompromise is common in these patients. Infection must be looked for in the chest, urine, blood and ascitic fluid. Culture and staining techniques are preferred, as low-grade pyrexia, raised white cell count and C-reactive protein are common features of hepatic inflammation, and are not reliable indicators of sepsis. There are other minor criteria that augment but are not essential for the diagnosis including, oliguria ( $<500\text{ml/24 hrs}$ ), urinary sodium  $<10\text{mmol/litre}$ , urinary osmolality  $>\text{plasma osmolality}$ , and serum sodium  $<130\text{mmol/litre}$ .<sup>10</sup> Therefore, HRS is mainly a diagnosis of exclusion. Most patients presenting with acute renal failure and liver failure will not actually have HRS. Studies by Uriz et al, Moreau et al and Ortega et al have all shown that intravenous albumin and terlipressin used in combination, is a safe and effective therapy in hepatorenal syndrome.<sup>9,11,12</sup> Reversal of renal dysfunction was achieved in approximately 80% of their patients with a 40% 1-month survival.

## Methods

In the current study, an audit cycle was started to examine the current clinical practice of patients with HRS I, under the care of two consultant gastroenterologists whose ward is situated in a district general hospital, serving a patient population of 220,000. The pattern of alcohol-related admissions to both the medical unit of this hospital and the gastroenterology ward has already been outlined in a previous article.<sup>13</sup>

Admissions to the acute medical receiving ward are triaged to the gastroenterology ward within 24 to 48 hours. Case records were obtained for patients admitted with liver disease.

Those with impaired renal function at any point during their hospital stay were examined. Entries into the ward death certificate book were also reviewed to see the causes of death given for any of these patients that died during this time.

Case records were reviewed from the 6-month period prior to the intended intervention. A record of patient name, hospital number, gender, age, and aetiology of the liver disease was made. Liver disease severity was assessed by Child-Pugh scoring.<sup>14</sup> Serum creatinine on admission was noted and the subsequent rise, as well as any response to treatment. Vital sign charts were studied looking for hypotension, and if any action was taken: eg intra venous fluids/albumin or central venous pressure (CVP) monitoring. Prescription of vasoactive agents such as dopamine, dobutamine and terlipressin were assessed, and particularly the dose of the latter. Confirmation of renal tract structure by ultrasound was noted, and finally survival in days from the time renal failure was noted.

Evidence of sepsis was looked for from urine, blood, sputum (chest x-ray if no sputum production) and ascitic tap. Of the 4 possible systems a point was given for each if checked, with a maximum possible score of 4 out of 4. Positive culture results were reviewed to see if the correct action was taken. Drug prescribing charts indicated the pattern of antibiotic and diuretic use.

## Intervention

The intervention made after the 6-month review period was to design a management flow chart for HRS using the available published evidence. It would help to confirm the diagnosis and outline the management of HRS. It would also alert staff to look for alternative causes of renal impairment. A diagnostic algorithm for assessment and targeted therapy of HRS can be seen in Figure 1. This was implemented in the gastroenterology ward. The practice management and outcome of the patients was reviewed after a further 6-month period. Mortality from all causes was assessed and used as the study's endpoint. All patients were followed up until either death or discharge.

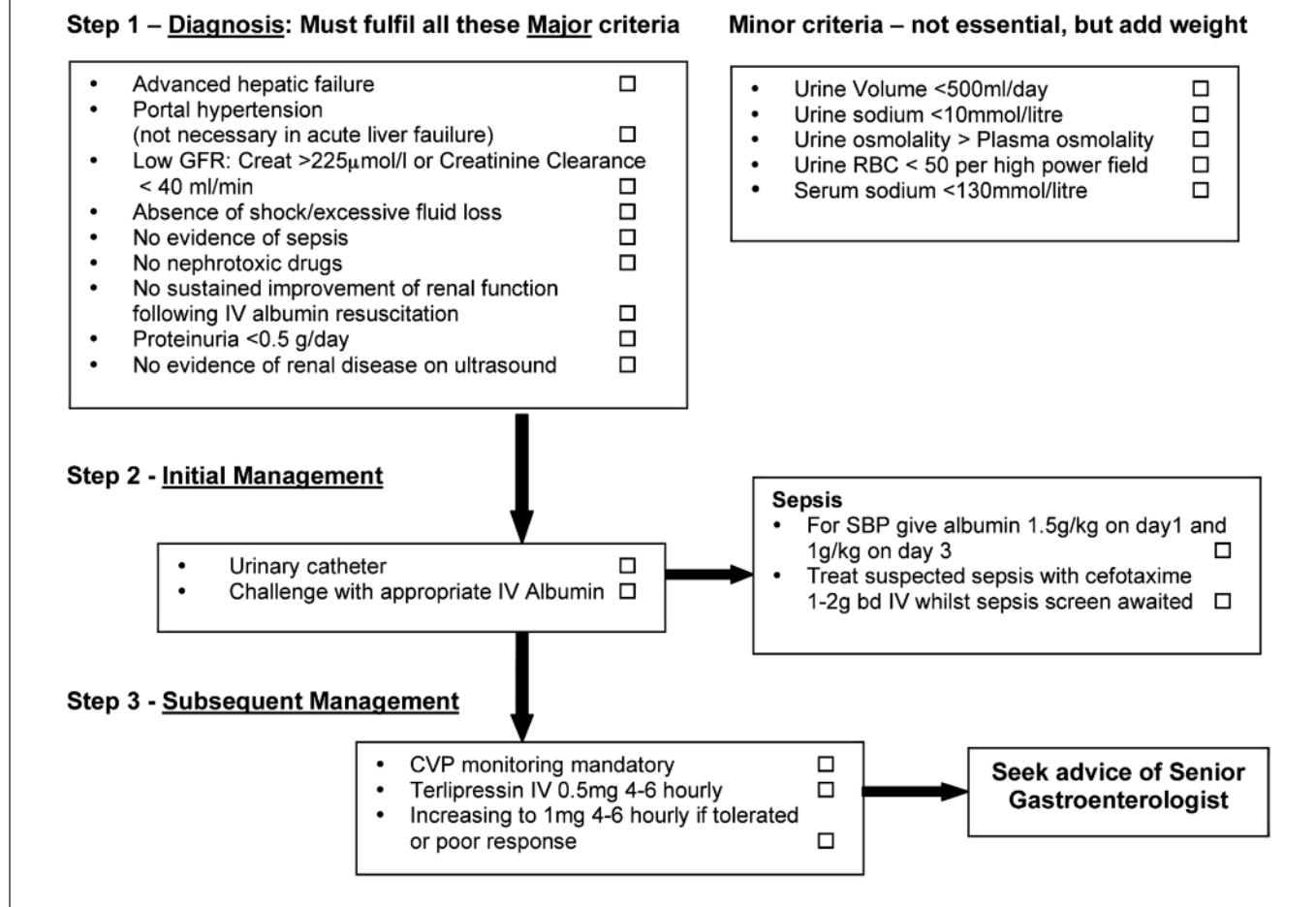
## Results

### Pre-intervention group

From the first arm of the audit cycle 12 patients were identified (10 male, 2 female). Eleven had liver failure with a diagnosis of HRS Type I. One female had end stage liver disease secondary to primary biliary cirrhosis, and was considered not to be a transplant candidate. She was diagnosed as having Type II HRS, and for this reason her data was excluded from the analysis of this study group.

For the HRS I group, the average age of the 11 patients was 51 years (range: male 33-70, female 62). All were Childs-Pugh grade C and the aetiology of liver disease was alcohol in all cases, although a liver screen was incomplete in 4 patients. Both ascites and coagulopathy were present in all 11 patients, contraindicating any attempt at transabdominal liver biopsy.<sup>15</sup> No transjugular biopsies were attempted. All 11 patients in the first arm of the audit cycle died, an average of 7.4 days (range 2 to 14) after developing renal impairment.

The average initial creatinine was  $156\mu\text{mol/l}$  (range 58-513) with subsequent rise to an average  $388\mu\text{mol/l}$  (range 231-842). Seven of 11 patients (64%) had suitable antibiotics prescribed and 10 of 11 (91%) had their diuretics stopped. Five (45%) had a renal ultrasound ruling out structural lesions. No single patient had a full sepsis screen. Five of 11 (45%) had no source examined, Three had one source, 2 had 2 sources, and 1 had

**Figure 1: Algorithm for Assessment/Diagnosis and Management of Hepatorenal Syndrome**

3 examined. This gave an average 0.9 out of 4 sources per patient. Two of the 8 patients (25%) on antibiotics had proven sepsis.

No patient had steroids or pentoxifylline prescribed as a therapy for alcoholic hepatitis. Ten of 11 (91%) would have qualified, providing no contraindications were present, using the DF, compared to 7 of 11 (64%) using the Glasgow Alcoholic Hepatitis Score (GAHS).<sup>7</sup> Two out of 11 (18%) were challenged with IV albumin, and only 1 of 11 (9%) had CVP line placement. Five patients (45%) were given dopamine, and 3 of these subsequently terlipressin. Three others were given terlipressin alone (6 total – 55%). Two of these had previously been given albumin. Only 2 of the 6 were given the correct starting dose with no increase in dose despite a poor renal response. Terlipressin was often reserved until the terminal stages, when the patient was usually anuric and had reached their ceiling creatinine, rather than earlier in the disease course.

One male did improve with treatment. After being given IV albumin and a combination of dopamine and dobutamine with little effect, therapy was changed to terlipressin 0.5mg qid with CVP measurement. Over a few days the creatinine fell from 355  $\mu$ mol/l to 75  $\mu$ mol/l, but the patient died 6 days later from a massive variceal bleed.

#### Post-intervention results

Seven patients were identified in the second arm of the audit

cycle. All 7 were male with an average age of 62 (range 49-77). All had alcoholic liver disease, HRS Type I and were Childs-Pugh grade C. The average initial creatinine was 122  $\mu$ mol/l (range 71-176) with an average subsequent maximum of 461  $\mu$ mol/l (range 240-850). Sepsis screen was complete in 2 patients. 3 of 4 sources were examined in 3 patients and 2 of 4 in the remaining 2. This gave an average sepsis screen of 3 out of 4. All 8 were given appropriate antibiotic cover. Renal ultrasound was performed in 6 out of 7 (86%), and CVP monitoring in 2 (29%); both lines were subsequently pulled out by the encephalopathic patients.

IV albumin was administered in 6 patients (86%). One had been given albumin during an earlier episode of spontaneous bacterial peritonitis, but not during his episode of HRS. 5 of the 7 patients would have qualified for steroid or pentoxifylline therapy under both the GAHS (scores 3x10, 2x9, 8, 6 – threshold 9), and the DF score (range 18 to 57 – threshold 32).

Terlipressin was used in 6 patients (86%), and dopamine in the remaining patient. The correct starting dose of terlipressin was used in 4 patients, however 2 of these did not receive an increased dose despite a poor clinical response. One patient was on the varices protocol (an initial 2mg intravenous bolus of Terlipressin, followed by 1mg qid) due to the presence of a GI bleed, and was also complicated by septicaemia. Another patient was on 1mg 4-hourly for their 11 days of treatment.

Two patients' renal function corrected whilst on therapy, requiring 8 and 10 days of treatment each. Their 'ceiling' creatinines were 520 and 850 accordingly. Both had their treatment commenced rapidly upon deterioration of their condition, thus, one would assume, aiding their subsequent renal recovery. The first patient unfortunately died later from a combination of pneumonia and left ventricular failure. Cardiac failure could possibly have been contributed to by terlipressin administration. The second patient was successfully discharged from hospital and still alive after 3 months of follow-up. In this second group, for the 5 patients that died from HRS Type I, the average survival from diagnosis of renal failure was 9 days. Significant proteinuria was not found in any patient from the two groups. Summary of patient results and therapies can be seen in Table IV.

## Discussion

### *Evidence based pathophysiology and management*

After consulting the literature it became apparent that some patients originally being diagnosed with HRS in our gastroenterology unit, did not fulfil all of the criteria for the condition and so were not included in the analysis. Despite renal failure in the presence of liver failure, there was either an alternative diagnosis, or strong signs that an alternative diagnosis was not sought thoroughly enough. The most commonly overlooked diagnosis was sepsis. At present there is no consensus whether treated sepsis with renal failure behaves as, or is an equivalent disease, to hepatorenal syndrome without infection. A large proportion of our patients presented with advanced renal impairment, which often caused medical staff to label them with HRS too early.

**Table IV: Summary of Audit Data**

|                                 | Pre-intervention | Post-intervention |
|---------------------------------|------------------|-------------------|
| Number of patients              | 11               | 7                 |
| Gender M:F                      | 10:1             | 7:0               |
| Av age (range)                  | 56 (33-70)       | 62 (49-77)        |
| Av age M:F                      | 49.9:62          | 62: -             |
| Childs Pugh                     | A:0,B:0,C:11     | A:0,B:0,C:7       |
| Mean initial creatinine (range) | 156 (58-513)     | 122 (71-176)      |
| Mean maximum creatinine (range) | 388 (231-842)    | 461 (240-850)     |
| Bilirubin $\mu\text{mol/l}$     |                  |                   |
| Mean (SD)                       | 370 (258)        | 241 (90)          |
| PT / secs                       |                  |                   |
| Mean (SD)                       | 26 (8.7)         | 19.4 (3.2)        |
| Serum Albumin g/l               |                  |                   |
| Mean (SD)                       | 24 (2.8)         | 24.9 (5.7)        |
| DF Score (SD)                   | 79.1 (50.0)      | 39.2 (1.5)        |
| GAHS Score (SD)                 | 9.4 (1.3)        | 8.9 (1.5)         |
| Renal US                        | (5/11) 45%       | (6/7) 86%         |
| Sepsis screen – mean score      | 0.9/4            | 3.0/4             |
| Antibiotics prescribed          | (7/11) 64%       | (7/7) 100%        |
| IV albumin                      | (2/11) 18%       | (6/7) 86%         |
| Dopamine                        | (5/11) 45%       | (1/7) 14%         |
| Central line                    | (1/11) 9%        | (2/7) 29%         |
| Terlipressin administered       | (6/11) 55%       | (6/7) 86%         |
| Steroids given                  | 0                | (2/7) 29%         |
| Survival of HRS / Renal Failure | (0/11) 0%        | (2/7) 29%         |

Once confirmed, the initial management should be to insert a urinary catheter and assess the intravascular status of the patient. Plasma volume expansion should be with intravenous albumin and an assessment of the response made. Prophylactic intravenous broad-spectrum antibiotics (often a cephalosporin), should be given until a sepsis screen is clear. Ideally the screen should be sent before any antibiotics have been administered. If HRS is confirmed then it is advised that CVP monitoring should be mandatory. This is partly required to assess the volume status of the patient. Urinalysis and renal tract imaging are early necessities. Following this, the vasopressin analogue terlipressin, should be given intravenously at a dose of 0.5mg/4-6 hours; titrated up to 2mg/4-6 hours if tolerated or if there is a poor renal response.<sup>7,9,12</sup>

The first arm of the audit cycle displayed a poor record when seeking a source of sepsis, prescribing antibiotic cover and performing renal ultrasounds. Also, IV albumin was seldom used as fluid support. When terlipressin was used for renal support it was often in advanced disease, and in an inappropriate dosage. All of these criteria were improved in the second audit cycle. The patients in the first group had higher DF scores than those in the second group. However, all were scored as Child's grade C, and the DF score has recently been shown to be less predictive of outcomes than the GAHS, which was similar in both groups. There was still a moderately poor adherence to the protocol in the second arm of the audit cycle. This was disappointing and probably reflects a need for re-education of junior staff in rotational posts. Placing a treatment algorithm in local junior doctor's handbooks would probably be beneficial.

Despite these improvements to supportive renal therapy we feel that further progress can still be made with the management of our patients with alcoholic hepatitis. Firstly it must be ensured that adequate nutritional support is in place. Secondly, the cautious use of corticosteroids or pentoxifylline has been shown to improve the outcomes of alcoholic hepatitis in selected cases. This could aid liver recovery as well as helping to correct the other physiological imbalances.

Points to the successful management of renal impairment in the presence of liver failure are anticipatory screening for HRS and early implementation of appropriate treatment. As the clinical presentation can vary between patients this should occur soon after admission. We consider, therefore, that with the potential delay of ward transfers this protocol should be implemented in the acute medical receiving unit. As this is both a condition and patient-type that requires a specialist team approach, there is an argument for direct admission to either a gastroenterology or high dependency unit.

Management of such patients is labour intensive for both medical and nursing staff. For this reason, whenever possible, a medical high dependency unit is often the best place to treat such patients. If not available, then such facilities should be established.

## Conclusion

Although this audit reviewed only a relatively small number of patients, it seems that with more rigorous assessment and aggressive treatment, it may be possible to support and correct renal function more effectively in selected patients with liver disease. Further studies in this area are essential.

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