A clinical audit on the management of children with hepatorenal syndrome admitted to Assiut University Children Hospital

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Introduction
Hepatorenal syndrome (HRS) is defined as worsening kidney function in patients with advanced cirrhosis.

Aim
The study aimed to evaluate the management of children with HRS, who were admitted to the Pediatric Hepatology and Nephrology Units, Assiut University Children Hospital, according to published international guidelines, searching for defects, obstacles, or needs to improve the management of such cases.

Patients and methods
Medical records of children with advanced liver disease accompanied by renal manifestations during the period from the March 1, 2017 to the February 28, 2018 were collected and reviewed to choose the cases that fulfilled the inclusion criteria of the present study. A structured data collection form was designed according to the adopted published guidelines. The collected data were tabulated, statistically analyzed, and discussed.

Results
Out of 158 collected records, only 11 fulfilled the inclusion criteria of the present study. Their data revealed a severe defect in recording the admission and follow-up historical data, registered data about the clinical examination, important investigations, and management. Finally, the outcome data revealed that recovery with improvement of acute kidney injury had occurred in only two cases; they had early acute kidney injury diagnosis and proper management.

Conclusion
The study revealed that management of cases with HRS in the present study was not following any well-known published guidelines for management of such cases.

Recommendations
Management of children with HRS must follow the published international guidelines to improve both management and outcome of such cases.

Keywords:
acute kidney injury, hepatorenal syndrome, liver diseases

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Introduction

Hepatorenal syndrome (HRS) is defined as the development of renal impairment in patients with advanced liver disease (acute or chronic) in the absence of any other identifiable cause of renal pathological conditions [1]. A new definition and diagnostic criteria for HRS-acute kidney injury (AKI) are recently proposed by the International Club of Ascites (ICA) [2].

Renal vasoconstriction seems to be a hallmark of this disease [1]. Rapid progression of functional renal failure on top of acute or chronic liver disease occurs in type 1 HRS secondary to sepsis or bleeding over a course of 2 weeks [1,3,4]; slower progression in type-2 HRS is due to portal hypertension and diuretic-resistant ascites [1].

There are few data to guide effective treatment of such cases. Van Hoeve *et al.* [1] reported that treatment of HRS consists of improving renal blood flow by improving the effective intravascular volume by increasing the splanchnic arterial tone. Agents currently used include vasopressin analogs (terlipressin) and the alpha1-adrenoceptor agonist (midodrine). In 2012, Lata stated that albumin is an important adjunctive treatment in both the prevention and treatment of HRS [5]. On the other hand, Parsons *et al.* [4] and Kreuzer *et al.* [6] reported that 6–8% of children waiting for liver transplantation have severe HRS requiring renal replacement therapy (RRT). Liver transplantation remains the only curative treatment for HRS [7].

Table 1: Data collection form according to published guidelines

Evaluated Item	Asked Question	Asked	Not asked
Serial no.			
Name			
Age			
Sex: date of admission:			
Date of discharge:			
history		Asked	Not asked
	*Family history		
	-Liver disease		
	-Metabolic disease		
	-Autoimmune disease		
	-Malignancy		
	-Others		
	*Drug ingestion		
	-NSAIDs		
	-Aminoglycosides		
	-Iodinated contrast media		
	-Others		
	*Bleeding tendency, any blood disease (thromboembolic)		
	*History of travel, sick contacts		
Clinical symptoms	*Constitutional symptoms:		
	-Weakness		
	-Anorexia		
	*Pruritus		
	*Hematemesis, any bleeding form		
Clinical signs		Examined	Not examined
	*Hepatomegaly		
	*Cirrhosis		
	*Jaundice		
	*Clubbing		
	*Splenomegaly		
	*Stigmata of portal		
	hypertension:		
	-Ascites		
	-Any bleeding form		
	-Encephalopathy		
	*Signs of shock:		
	-Tachycardia		
	-Peripheral pulse		
	-Capillary refill time		
	*Signs of renal affection:		
	-Oliguria		
	-Edema		
	-Blood pressure measurement		
	-Convulsions		
	-Pallor		
Investigations	*Liver function tests	Done	Not done
	*Coagulation profile		
	*Complete specific investigations to diagnose chronic liver disease		
	-Hepatitis markers		
	-Autoantibodies		
	-Metabolic screen		
	-Biliary scan		
	-Ultrasound with Doppler		
	*Blood culture		
	*Urine culture		
	*Ascitic fluid culture and analysis		
	*Liver ultrasound		
	*Liver biopsy		

Contd...

Table 1: Contd...

Evaluated Item	Asked Question	Asked	Not asked
	*Kidney function test		
	*Baseline serum creatinine		
	*Serum electrolytes		
	*Glomerular filtration rate measurement		
	*Urine analysis		
	*Urinary biomarkers		
	-Fractional excretion of urea		
	-Serum cystatin C		
	-Serum neutrophil		
	Gelatinase-associated lipocalin		
	*Kidney ultrasound		
	*Renal biopsy		
The data collection form according to published guidelines:			
Management		Done	Not done
	General measures:		
	*Maintain intravascular volume		
	*Avoid nephrotoxic drugs		
	*Monitoring of:		
	-Urine output		
	-Vital signs		
	-Liver function test		
	-Kidney function test		
	*Screening for sepsis		
	-Blood culture		
	-Urine culture		
	-Ascitic fluid culture		
	Specific therapies		
	-Treatment with antibiotics		
	-Vasoconstrictors with albumin		
	-Albumin infusion alone		
	-Ascitic drainage		
	-RRT		
	-Transjugular intrahepatic portosystemic shunt		
	-Extracorporeal liver assist device		
	-Molecular adsorbent recirculating system		
	-Liver transplant		
Outcome			

RRT, renal replacement therapy.

Aim

The aim of the present study was to evaluate the management of children with HRS, who were admitted to the Pediatric Nephrology and Hepatology Units, Assiut University Children Hospital according to revised consensus recommendations of the ICA (2015), and European Journal of Gastroenterology and Hepatology (2018). These guidelines identify new AKI definition, early detection and management of HRS cases, searching for defects, obstacles, or needs to improve the management of such cases.

Patients and methods

Research methods

Medical records of children with advanced liver disease with renal affection, who were admitted during the period from the March 1, 2017 to the February 28, 2018 were collected and reviewed to choose the cases which fulfilled the inclusion criteria of the present study [8,9]. Reviewing the proposal was carried out before starting via the ethical committee of Assiut, Faculty of Medicine.

This audit was approved by the committee of medical ethics of the Faculty of Medicine Assiut University with IRB number: 17100067.

Inclusion criteria

(1) Diagnosis of cirrhosis and ascites (liver function tests, abdominal ultrasonography)
(2) Diagnosis of AKI according to ICA-AKI criteria.

Stage 1: increase in serum creatinine more than or equal to 0.3 mg/dl or an increase in serum creatinine

more than or equal to 1.5-fold to 2-fold from baseline.

Stage 2: increase in serum creatinine more than 2-fold to 3-fold from baseline.

Stage 3: increase in serum creatinine more than 3-fold from baseline or more than or equal to 4.0 mg/dl with an acute increase more than or equal to 0.3 mg/dl or initiation of RRT.

Exclusion criteria

(1) Presence of shock [AKI that is caused by prerenal azotemia (volume responsive state) is considered one of the functional causes of kidney injury other than that which is caused by hepatic origin (non-HRS-AKI vs. HRS-AKI)]
(2) Current or recent use of nephrotoxic drugs
(3) Macroscopic signs of structural kidney injury defined as:
    (a) Presence of proteinuria (>500 mg/day)
    (b) Presence of micro-hematuria (>50 red blood cells per high-power field)
    (c) Abnormal findings on renal ultrasonography (intrinsic renal disease: tubulointerstitial or glomerular origin) (Tables 1-3).

Results

The results of the study were:

(1) Out of 158 medical records for children with liver disease, only 11 (6.96%) cases fulfilled the inclusion criteria of HRS
(2) Age, sex, AKI staging, and duration of hospitalization distributions are detailed in Tables 4 and 5
(3) Rates of the registered clinical data: defective registration of the historical data [defective family history in three (27.3%) cases and defective history of travel and sick contacts in all the studied cases]
    (a) Rates of registered investigations: complete specific investigations to reach a diagnosis for the chronic liver disease were done only for five (45.5%) cases.
    (b) Blood culture was not done for four (36.4%) cases, urine culture was not done for eight (72.7%) cases, and ascitic fluid culture was not done for nine (81.8%) cases.
    (c) Liver biopsy was not done for 10 (90.9%) cases.

Rates of the registered data of HRS management:

(1) General measures:
    (a) Monitoring of the urine output was not recorded in seven (63.6%) cases and vital signs were not recorded in four (36.4%) cases.
(2) Screening for sepsis:
    (a) Blood, urine, and ascetic fluid cultures mentioned above; treatment with antibiotics was done for all the studied cases.
(3) Specific therapies:
    (a) Only one (9.1%) case received vasoconstrictors with albumin, also, only one (9.1%) case had received treatment with RRT.
    (b) Other specific therapies (Table 1) were not recorded to be received by all the studied cases.

Table 2 Rates of recorded early predictors of acute kidney injury among the studied cases

Early predictors	Frequency (*n*=11)	Rate (%)
(I) Symptoms and signs:		
Decreased urine output		
Asked	5	45.5
Not asked	6	54.5
Edema		
Examined	11	100
Not examined	0	0
Follow up of blood pressure measurement		
Done	7	63.6
Not done	4	36.4
(II) Investigations		
KFT follow-up (serum urea and creatinine)		
Done	11	100
Not done	0	0
Baseline serum creatinine measurement		
Measured	7	63.6
Not measured	4	36.4
Glomerular filtration rate evaluation		
Done	0	0
Not done	11	100
Urinary biomarker detection		
Detected	0	0
Not detected	11	100
Urine analysis		
Done	9	81.8
Not done	2	18.2
Urine output monitoring		
Done	4	36.4
Not done	7	63.6
Urine culture		
Done	3	27.3
Not done	8	72.7
Renal ultrasound		
Done	11	100
Not done	0	0
Renal biopsy		
Done	0	0
Not done	11	100

N.B.: The percentages in between () are out of the studied cases (11 cases).

Discussion

HRS is defined as worsening kidney function in patients with advanced cirrhosis [2]. In our study, HRS

Table 3 Individual outcome of the studied cases in relation to acute kidney injury staging and the received therapy

Patient no.	Received treatment			Outcome	Time from AKI to death
	General	Specific	AKI staging		
1	Antibiotics-liver supportive measures-diuretic - fresh frozen plasma (FFP)	_	3	Death	2 days
2	Antibiotics-liver supportive measures-IV fluid- blood transfusion	Norepinephrine, dobutamine, RRT (hemodialysis)	3	Recovery within 11 days	_
3	Antibiotics-liver supportive measures-IV fluids-blood transfusion - twice FFP	_	3	Death	3 days
4	Antibiotics-liver supportive measures-IV fluids-diuretic-blood transfusion-5 times FFP	_	3	Death	4 days
5	Antibiotics-liver supportive measures-FFP	_	2	Death	2 days
6	Antibiotics-liver supportive measures-IV fluids-twice FFP	Dopamine-albumin infusion	3	Death	1 week
7	Antibiotics-liver supportive measures-IV fluids-FFP	_	Not known	Death	Not known
8	Antibiotics-liver supportive measures-FFP	_	Not known	Death	Not known
9	Antibiotics-liver supportive measures-IV fluids	Norepinephrine	1	Recovery within 2 weeks	_
10	Antibiotics-liver supportive measures-3 times FFP	_	Not known	Death	Not known
11	Antibiotics-liver supportive measures-twice FFP	Albumin infusion	Not known	Death	Not known

AKI, acute kidney injury; RRT, renal replacement therapy.

incidence (6.96%) was in approximately in accordance with Deep *et al.* (5%) [10].

There is a defective registration of the family history and history of travel and sick contacts; those questions are important as they may identify metabolic or autoimmune diseases or bleeding tendencies [11], and exclusion of hepatotropic viruses by asking about history of travel and sick contacts [12].

The present data showed a defect in asking about decreased urine output, registration of blood pressure measurement, and urine output monitoring. Intravascular volume assessment is important in patients with acute liver failure to document fluid overload or dehydration [13] secondary to bleeding or diuretics [10], urinary catheter is inserted, urgent treatment for hypotension, and early nephrology consultation are needed to detect AKI early [11].

Our study showed a defect in some important investigations that needed to diagnose the underlying liver disease, as hepatitis markers and serum immunoglobulins for different hepatitis types, ultrasound with Doppler or endoscopic investigations to show bile ducts or other investigations that diagnose some metabolic liver disease such as galactosemia, tyrosinemia and Gaucher's disease [11,14], and liver biopsy if needed.

According to Van Hoeve *et al.* [1], the treatment of liver disease is largely dependent on its underlying pathological condition, so, good history and complete investigations should be taken into account.

Also a defect is noted in other investigations such as urine analysis, blood culture, urine culture, and ascitic fluid culture, which are needed for early screening for sepsis and early treatment with antibiotics [3]. Pearson and Thomson [15] reported that patients with cirrhosis show a greater systemic response to infection, so, incidence of septic shock, multiorgan failure, and death are increased, so, early treatment is a must.

Serum creatinine was done for all the studied cases but baseline serum creatinine was not done for four (36.4%) cases. According to Francoz *et al* [16]., serum creatinine is affected by many factors, so, following the new definition of AKI by the AKI network [17] using the baseline serum creatinine is important; so that early AKI diagnosis is not missed.

Serum electrolytes were evaluated in all the studied cases while measurement of glomerular filtration rate (GFR) was not done for any of the studied cases. It is important to follow up serum electrolytes and GFR as they are disturbed in such HRS patients; presence of hyponatremia is associated with many complications [18].

Also estimation of urinary biomarkers and renal biopsy were defective in our study; their role is to help differentiate HRS-AKI from non-HRS-AKI [2,19].

As regards the therapeutic lines of management which is defective in our study, European Association for the Study of the Liver (2010) emphasizes the importance of albumin infusion [3] in combination with vasoconstrictors to counteract splanchnic arterial vasodilatation [20,21]; paracentesis with albumin infusion is sometimes needed for symptomatic relief [22]; RRT is helpful for ammonia and lactate removal, so as to keep the fluid and electrolyte balance [10]. TIPS may delay the need for dialysis,

Table 4 Clinical and therapeutic profile and the outcome of the studied cases with hepatorenal syndrome

	Age	Sex	Cirrhosis/ ascitis	Baseline S.cr	Peak S.cr	Underlying chronic liver disease	Duration of hospitalization	AKI at admission	AKI grade	Resolution of AKI (days)	Outcome	Time from AKI diagnosis to death	Vasoconstrictors	Albumin	RRT	TIPS	LT	Others
1	3 months	M	Yes	0.1	1.1	Not diagnosed	17 days	No	3	NO	Death	2 days	No	No	No	No	No	No
2	10 months	M	Yes	0.3	3.9	Diagnosed	20 days	No	3	11 days	Recovery	–	Norepinephrine-dobutamine	No	Yes	No	No	No
3	11 years	F	Yes	0.3	3.6	Diagnosed	16 days	No	3	No	Death	3 days	No	No	No	No	No	No
4	2 years	M	Yes	0.26	3	Not diagnosed	30 days	NO	3	NO	Death	4 days	No	No	No	No	No	No
5	8 years	M	Yes	0.5	1.31	Diagnosed	5 days	No	2	No	Death	2 days	No	No	No	No	No	No
6	7 months	F	Yes	0.23	2.2	Diagnosed	9 days	No	3	No	Death	1 week	Dopamine	Yes	No	No	No	No
7	2 years	M	Yes	Not known	3	Diagnosed	10 days	Yes	Not known	No	Death	Not known	No	No	No	No	No	No
8	4 years	M	Yes	Not known	3	Not diagnosed	10 days	Yes	not known	No	Death	Not known	No	No	No	No	No	No
9	16 years	F	Yes	0.9	1.8	Not diagnosed	22 days	No	1	2 weeks	Recovery	–	Norepinephrine	No	No	No	No	No
10	12 years	M	Yes	Not known	2.5	Not diagnosed	5 days	Yes	Not known	NO	Death	Not known	No	No	No	No	No	No
11	2 years	M	Yes	Not known	3.2	Not diagnosed	4 days	Yes	Not known	NO	Death	Not known	No	Yes	No	No	No	No

AKI, acute kidney injury; RRT, renal replacement therapy.

acting as a bridge to liver transplant [23,24]. Others as extracorporeal liver assist devices are now being increasingly used in clinical practice [25,26] to help toxin removal, finally liver transplant is considered the only option for HRS patients who do not respond to other treatment modalities [10].

And according to the outcome, O'Riordan [13] reported that for those with AKI with cirrhosis, mortality rates are very high, up to 80% of patients dying within 2 weeks, using albumin and vasoconstrictors as a bridge to transplantation, thereby improving patient survival by 30–40%.

Presence of all these defects may be due to absence of a well-known systematic and organized base to follow a patient with liver disease and possible renal complications.

Conclusion

Data of the present study revealed a severe defect in recording the admission and the follow-up historical data, data about the clinical examination and data of important diagnostic investigations of the studied cases. Also, the therapeutic regimens that were used for the treatment of almost all the studied cases were random, and had not followed any well-known published guidelines for treatment of such cases. It is noteworthy that the two cases that were managed more or less according to the adopted guidelines in the present study were recovered completely.

Recommendations

The recommendations of the study are:

(1) Meticulous history taking including family history and history of travel and sick contacts.
(2) Improve registration of the admission and follow-up data.
(3) Complete specific investigations to diagnose the liver disease must be done.
(4) Early detection of AKI in patients with advanced liver disease:
    (a) Evaluation of the baseline serum creatinine.
    (b) Monitoring of blood pressure.
    (c) Monitoring of urine output and GFR.
    (d) Detection of urinary biomarkers when it is possible.
    (e) Renal biopsy with early nephrology consultation.
(5) Screening for sepsis by urine analysis, blood, urine, and ascitic fluid cultures.
(6) We must be stuck to well-known published guidelines to improve both management and outcome of children with HRS.

Table 5 Outcome of the studied cases in relation to rates of complete diagnosis of chronic hepatic disease, early detection of acute kidney injury, and management according to the adopted guidelines: Revised Consensus Recommendations of the International Club of Ascites (2015) and European Journal of Gastroenterology and Hepatology (2018)

Outcome	Frequency (*n*=11)	Rate among the studied cases (%)	Complete diagnosis of chronic hepatic disease (%)	Early detection of AKI (%)	Management according to guidelines (%)
Recovery with improvement of AKI	2	18.2	50	100	100
Death within 1 week from diagnosis of AKI	5	45.4	60	40	0
Died cases without well-known date of AKI	4	36.4	25	0	0

AKI, acute kidney injury.

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Conflicts of interest
None declared.

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