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Editorial Board Member of *World Journal of Clinical Cases*, M Anwar Iqbal, PhD, Professor, Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY 14642, United States. anwar_iqbal@urmc.rochester.edu

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MINIREVIEWS

Anemia in cirrhosis: An underestimated entity

Manish Manrai, Saurabh Dawra, Rajan Kapoor, Sharad Srivastava, Anupam Singh

ORCID number: Manish Manrai 0000-0002-5805-033X; Saurabh Dawra 0000-0002-7679-9491; Rajan Kapoor 0000-0001-8426-0421; Sharad Srivastava 0000-0003-3269-5989; Anupam Singh 0000-0002-7610-1807.

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Manish Manrai, Department of Internal Medicine, Armed Forces Medical College, Pune 411040, India

Saurabh Dawra, Sharad Srivastava, Department of Medicine and Gastroenterology, Command Hospital, Pune 411040, India

Rajan Kapoor, Department of Medicine, Command Hospital, Kolkata 70027, India

Anupam Singh, Department of Gastroenterology, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

Corresponding author: Manish Manrai, MBBS, MD, Professor, Department of Internal Medicine, Armed Forces Medical College, Solapur Road, Pune 411040, India. manishmanrai@yahoo.com

Abstract

Anemia in a patient with cirrhosis is a clinically pertinent but often overlooked clinical entity. Relevant guidelines highlight the algorithmic approach of managing a patient of cirrhosis presenting with acute variceal hemorrhage but day-to-day management in hospital and out-patient raises multiple dilemmas: Whether anemia is a disease complication or a part of the disease spectrum? Should iron, folic acid, and vitamin B complex supplementation and nutritional advice, suffice in those who can perform tasks of daily living but have persistently low hemoglobin. How does one investigate and manage anemia due to multifactorial etiologies in the same patient: Acute or chronic blood loss because of portal hypertension and bone marrow aplasia secondary to hepatitis B or C viremia? To add to the clinician's woes the prevalence of anemia increases with increasing disease severity. We thus aim to critically analyze the various pathophysiological mechanisms complicating anemia in a patient with cirrhosis with an emphasis on the diagnostic flowchart in such patients and proposed management protocols thereafter.

Key Words: Anemia; Cirrhosis; Iron deficiency anemia; Macrocytic anemia; Normocytic anemia

Core Tip: Anemia in a patient with cirrhosis is an important but often neglected disease

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association. The presence of anemia increases the risk of hepatic decompensation and liver-related mortality. Increased severity of anemia is directly proportional to worsening severity indices like model for end-stage liver disease score. Thus, understanding the underlying pathophysiological processes giving rise to anemia, its diagnosis, and management is an important management aspect. Moreover, no validated guidelines are dealing with this pertinent clinical aspect.

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INTRODUCTION

Anemia is a fairly common clinical condition. Its prevalence in the general population varies from 10%-24%[1]. However, in critically ill patients, and those with underlying malignancies or autoimmune disorders, the prevalence increases to 95%[2]. Anemia may be seen in 66%-75% of patients with liver cirrhosis[1,3]. Iron deficiency, which is the commonest type of anemia, has been observed in 22% of patients with compensated cirrhosis and 78% in those with decompensated disease. Apart from anemia, thrombocytopenia and leucopenia are other abnormal hematological indices seen in patients with cirrhosis. Thrombocytopenia is by far the commonest hematological abnormality seen in patients with cirrhosis followed by leucopenia and anemia [4]. The pathophysiological sequelae of cirrhosis adversely affect the synthetic and immunological functions of the liver. This manifests as hematological dysfunctions including anemia.

SIGNIFICANCE OF ANEMIA IN CIRRHOSIS

The presence of anemia in a cirrhotic patient can be considered a 'vicious cycle'. The following facts need consideration: The severity of iron deficiency anemia (IDA) increases with increasing Child's Pugh Turcotte (CTP) score: CTP A (26.5%), CTP B (59.2%), and CTP C (69%). Higher the degree of portal hypertension, the higher is the risk of developing severe anemia (< 10 gm/dL)[1]. Acute gastrointestinal (GI) bleed can be potentially catastrophic sequelae of portal hypertension[5]. Anemia by itself has been found to have an increased risk of hepatic decompensation and liver-related mortality in patients with compensated cirrhosis[6]. Anemic patients with cirrhosis have been reported to have higher model for end-stage liver disease (MELD) scores and lower albumin levels. The latest research has highlighted that hemoglobin (Hb) can be considered as a marker for severe disease. Conversely, the higher the MELD score, more likely is the possibility of having hematological complications[7]. Anemia has been postulated to have a pathophysiological role in the development of hepatorenal syndrome[8]. Besides increasing the risk of mortality, anemia is associated with a higher incidence of acute on chronic liver failure (ACLF) and increased risk of hospitalization[1]. The vicious cycle of portal hypertension, worsening disease severity, and anemia in cirrhosis are depicted in Figure 1. Moreover, blood transfusion in anemia can itself precipitate secondary iron (Fe) overload thereby increasing the risk of hepatocellular carcinoma (HCC) and mortality. Thus, it may be noteworthy to understand anemia as a part of the disease process rather than just a disease complication.

ETIOPATHOGENESIS OF ANEMIA IN CIRRHOSIS

The liver, owing to its unique portal circulation, synthetic and immunological functions can give rise to multiple hematological manifestations, and anemia in cirrhosis is often multifactorial (Table 1).

Table 1 Etiopathogenesis and prevalence of anemia in cirrhosis

Type of anemia	Etiology	Prevalence (%)	Ref.
Normocytic	Anemia of chronic disease	40-51.4	Singh *et al*[7], Özatli *et al*[56]
Microcytic	Acute blood loss (variceal hemorrhage)	5-15/yr; Increasing risk with severity of liver dysfunction and red wale marks on varices	Singh *et al*[7], European Association for the Study of the Liver[45]
	Portal hypertensive gastropathy	20-80	Gkamprela *et al*[37]
	Gastric antral vascular ectasia	4	Selinger and Ang[57]
	Peptic ulcer	35-53	Singh *et al*[7], Loperfido *et al*[58]
	Hemolytic anemia in patients on interferon and ribavirin	9-13	Gonzalez-Casas *et al*[3]
	Hemolytic anemia due to hypersplenism	24	Özatli *et al*[56]
Macrocytic anemia	Folic acid (Vit B9) deficiency	44	Herbert *et al*[59]
	Vit B12 (cyanocobalamin) deficiency	31.8 in PBC; 43 in NAFLD	Singh *et al*[7], Sharma and Jahnavi[60], Shizuma[61]

Vit: Vitamin; NAFLD: Nonalcoholic fatty liver disease.

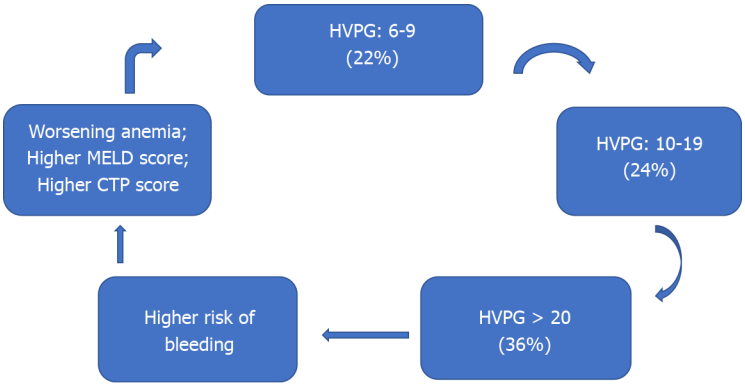

Figure 1 Vicious cycle of portal hypertension and anemia in chronic liver disease. HVPG: Hepatic venous pressure gradient; MELD: Model foe end stage liver disease; CTP: Child Turcotte Pugh score.

To understand the development of anemia, it is imperative to understand the critical role played by this oxygen-carrying micronutrient: Iron. 80% of the body's total iron stores (02-04 g) are stored as Hb in red blood cells (RBC). Ferric iron (Fe^{3+}) following its absorption in the duodenum is converted to ferrous iron (Fe^{2+}) by the action of ferric reductase duodenal cytochrome b. This iron is transported into the cytoplasm of the enterocyte and is either stored or exported by the iron exporter enzyme ferroportin. The next step involves oxidization of Fe^{2+} to Fe^{3+} form to ferroxidase hephaestin and ceruloplasmin (Cp). Fe^{3+} in combination with enzyme transferrin (Tf) undergoes circulation in the body. Erythrocyte precursors, known as erythroblasts, utilize a principal portion of Tf bound iron (Figure 2). A highly efficient recycling system in the spleen and hepatic macrophages ensures optimal utilization of iron stores. Thus, the human liver is an important component of this highly efficient iron homeostasis. The liver synthesizes proteins involved in iron homeostasis: Tf (80 kDa glycoprotein), Cp (copper linked serum ferroxidase), multi-subunit protein ferritin, and a 25 amino acid peptide, hepcidin.

IDA may occur secondary to acute or chronic blood loss. The various causes are variceal hemorrhage which usually presents with an overt GI bleed, and portal hypertensive gastropathy (may present with either overt or obscure GI bleed). The incidence of duodenal ulcer and ulcer-related bleed is more common in patients with cirrhosis. Besides, nutritional deficiencies including those of iron, Vitamin (Vit) B12, B6, and folate are common in patients suffering from cirrhosis. In addition, hypersplenism secondary to portal hypertension may contribute to iron deficiency. Amongst

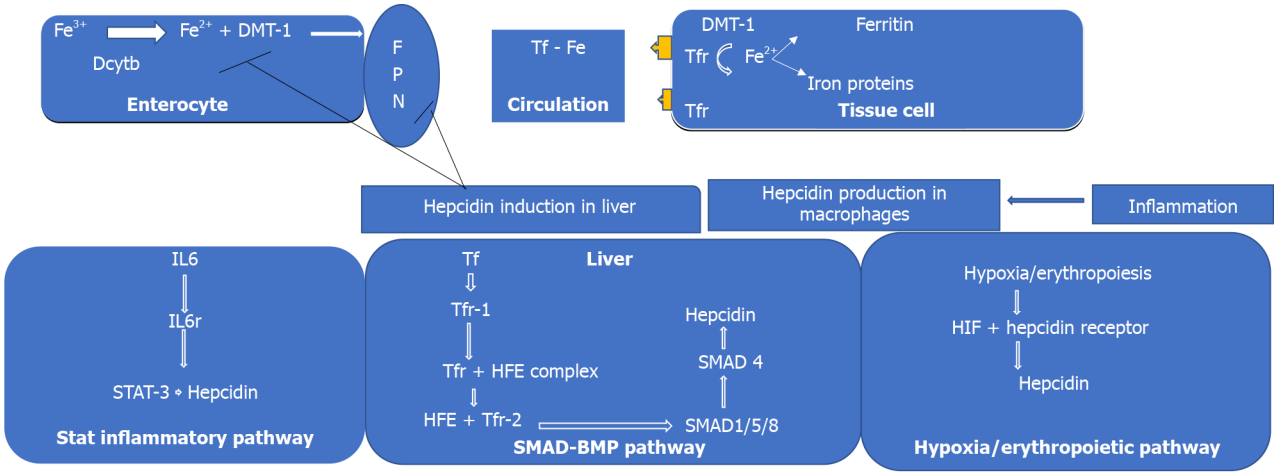

Figure 2 Pathophysiology of anemia and role of hepcidin. Fe^{2+}: Ferrous iron; Fe^{3+}: Ferric iron; Dyctb: Duodenal cytochrome B; DMT-1: Divalentmetaltransporter-1; FPN: Ferroportin; Tf: Transferrin; Tfr: Transferrin receptor; IL6: Interleukin 6; IL6r: Interleukin 6 receptor; STAT-3: Signaltransducer and activator of transcription proteins 3; HFE: Human homeostatic iron regulator; HIF: Hypoxia inducible factor.

the etiological agents leading to the development of cirrhosis, a few, in particular, have been found to have a predominant role in the pathogenesis of anemia: alcohol may cause blood loss because of alcohol-induced gastritis. It also has a direct toxic effect on erythroid precursors and may cause Vit B12, folic acid deficiency. Besides, alcohol-related malnutrition may lead to reduced iron absorption. Hepatitis B and C may cause bone marrow aplasia, Wilson's disease may be associated with hemolytic anemia in around 1%-12% of cases as copper released following hepatocyte necrosis causes oxidative dysfunction of phospholipids lining the RBC membrane leading to hemolysis and worsening of liver dysfunction[9]. Another form of acquired hemolytic anemia: Spur cell anemia may occur in alcohol-related cirrhosis wherein abnormal lipid metabolism leads to altered RBC membrane causing reduced deformability of RBC. A triad consisting of cholestatic jaundice, transient hyperlipidemia and hemolytic anemia — Zieve's syndrome has been rarely reported in alcohol-related cirrhosis[10].

Although now of historical interest, Ribavirin, a nucleoside anti-metabolite, used in the treatment of chronic hepatitis C (CHC), causes dose-related hemolytic anemia in around 10% of patients[11]. Autoimmune hemolytic anemia may also be seen in patients with autoimmune hepatitis. D-Penicillamine, a copper chelating agent, used in the treatment of Wilson's disease, in turn, may cause iron chelation manifesting as IDA. Another drug used in Wilson's disease, Trientine, may cause sideroblastic anemia[9]. However, the most common cause of anemia in cirrhosis is anemia of chronic disease, which develops secondary to an underlying chronic inflammatory state. Before we proceed further to understand the pathophysiology of anemia of chronic disease in cirrhosis, it is worthwhile to mention the proposed hypothesis of 'Eryptosis': Programmed cell death of erythrocytes which may contribute to anemia. This is akin to apoptosis of nucleated cells despite the absence of organelles involved in apoptosis. In a murine model, a high bilirubin level has been shown to increases Ca^{2+} influx, sphingomyelinase activation within erythrocytes, thereby triggering eryptosis[12].

Anemia of chronic disease and the critical role of hepcidin

It is worthwhile to emphasize the role of 'Hepcidin' (hepatic bactericidal protein), an iron regulatory hormone, produced in excess by the liver, in maintaining iron homeostasis. Increased iron levels in plasma and increased iron storage stimulates hepcidin production which further blocks dietary iron absorption and storage. In iron deficiency states hepcidin production is suppressed, which ensures increased dietary iron absorption. Erythropoietic processes cause high iron consumption to suppress hepcidin production. This ensures that stored iron is released by hepatocytes and macrophages and intestinal absorption of dietary iron increases. In chronic inflammatory states like cirrhosis hepcidin production is mediated by two distinct mechanisms: Interleukin-6 (IL-6) (a pro-inflammatory cytokine), mediated as well as IL-6 independent pathways. It is especially pertinent to understand that in inflammatory states like cirrhosis, increased body iron stores no longer suppress hepcidin

production *i.e.*, even if plasma iron level is low, hepcidin production is increased by IL-6 mediated pathway (while under normal circumstances, hepcidin production should have been downregulated in iron deficiency).Moreover, in cirrhosis, hepcidin is produced by myeloid cells by activating toll-like receptor-4, a receptor present on surface membranes of neutrophils and macrophages. This excess of iron gets trapped within the cells causing reduced availability of iron for forming Hb and thereby manifesting as anemia of chronic disease[2,13]. Three major pathways control stimuli related and basal hepcidin expression. The best-studied is the SMAD/bone morphogenetic signaling pathway which explains the evolution of anemia in inflammatory disorders. IL-6 is an inflammatory mediator that activates the Janus kinases-Signal transducer and activator of transcription proteins (JAK-STAT-3) pathway by binding to IL-6 receptor (IL6-R). STAT-3, in turn, causes increased hepcidin expression. The other important pathway involves binding of Tf to transferrin receptor-1 (Tfr-1) which in turn causes dissociation of transferrin receptor-1-human homeostatic iron regulator (Tfr-1 HFE complex). The available HFE interacts with Tfr-2 to increase BMP6 mediated phosphorylation of SMAD1/5/8. SMAD 1/5/8 further recruits SMAD4 to increase hepcidin expression. The least understood pathway is the one wherein hypoxia and erythropoiesis inhibit hepcidin expression by direct binding of hypoxia-inducible factor (HIF) to the promoter region of the hepcidin receptor. Figure 2 explains the pathophysiological role of Hepcidin in the development of anemia[13-15].

HEPCIDIN AS A BIOMARKER IN LIVER DISEASE

Hepcidin has been postulated as a potential biomarker in liver fibrosis and cirrhosis. Alcohol, a well-established cause of liver cirrhosis has been associated with low hepcidin levels. Low hepcidin levels have been documented in individuals with chronic alcohol consumption and preserved liver functions. Low hepcidin levels have been shown to worsen liver fibrosis in patients with CHC and CHB infection as well as autoimmune liver disease. Diagnostic use however is limited by lack of standardization especially in patients with liver disease[16].

While the pathophysiological mechanisms involved in iron deficiency and chronic inflammation leading to the development of anemia in cirrhosis have been described in the literature, the pathophysiological changes leading to macrocytic anemia have been poorly understood. It has been postulated that splenomegaly secondary to portal hypertension causes secondary hemolysis which in turn causes increased plasma volume and macrocytosis. Alcohol per se can cause secondary malnutrition and folic acid deficiency besides adversely affecting erythropoiesis in the bone marrow.

TYPES OF ANEMIA IN CIRRHOSIS

To co-relate with the underlying pathogenesis and to evaluate a patient with anemia with underlying cirrhosis, anemia may be classified as per the RBC indices, as follows: Normocytic: Anemia of chronic disease; Microcytic: Acute variceal hemorrhage, chronic blood loss due to portal gastropathy, alcohol-related gastritis or intestinal malabsorption, treatment-related (D-Penicillamine); Macrocytic: Vit B12, B6, Folate deficiency; Hemolytic: Wilson's disease, Spur cell anemia, Autoimmune hemolytic anemia, treatment-related (Ribavirin); Aplastic: Hepatitis B, hepatitis C related; and Sideroblastic: Drug-induced (Trientene in Wilson's disease).

DIAGNOSTIC EVALUATION IN A CASE OF ANEMIA IN CIRRHOSIS

Anemia in cirrhosis is independently associated with increased mortality and morbidity. Moreover, there could be an interplay involving multiple etiologies. Therefore, it becomes imperative to have a simple, easily available, yet informative diagnostic algorithm to aid in the diagnosis and thereafter management of the predominant etiology of anemia in cirrhosis.

The following parameters may be considered as baseline laboratory investigations for the evaluation of anemia in cirrhosis. Since there are multiple pathogenic mechanisms into play, none of these parameters are specific to diagnose the cause of anemia in cirrhosis. However, each of these investigations is an important tool for initial screening as well as prognosis for the severity of the underlying liver disease.

These parameters include: Hb level; White blood count (WBC) and differential cell count (DLC); Platelet count; RBC indices; Mean corpuscular volume (MCV); Absolute reticulocyte count; Serum iron studies; Serum ferritin; Transferrin saturation (TSAT); and Hepcidin.

Hb level

Estimation of Hb is the initial screening method for the diagnosis of anemia. World Health Organization (WHO) classifies anemia as < 13 g/dL for men, < 12 g/dL for non-pregnant females and < 11 g/dL for pregnant females[17]. Hb, being an easily reproducible test across different laboratories and with a lower coefficient of variance vs. hematocrit, is the preferred investigation. Moreover, variables like patients' serum glucose and storage time of samples do not affect the measurement of Hb[18]. Complete cell count including WBC, DLC, and platelet count, estimate the bone marrow function. Hypersplenism, Vit B12 deficiency, aplasia secondary to hepatitis B or C may cause pancytopenia in patients with cirrhosis.

Absolute reticulocyte count and reticulocyte index

Absolute reticulocyte count and reticulocyte index (reticulocyte count which has been adjusted to the degree of anemia) is a useful screening test to ascertain the appropriate bone marrow response to anemia. An abnormal reticulocyte count along with low Hb concentration is associated with increased mortality in liver transplantation (LT) patients[19].

RBC indices

Red cell distribution width: Red cell distribution width (RDW) has been suggested as a potential marker of inflammatory diseases. Studies on this aspect have shown conflicting results. Some researchers have postulated that RDW increases with worsening liver disease. They have shown that increased RDW is associated with increased 3-mo mortality in decompensated cirrhosis[20,21]. Other researchers, however, have provided evidence to the contrary and failed to prove any statistical significance with worsening liver disease or any significance in differentiating the type of anemia in cirrhosis[22].

MCV

Changes in erythrocyte membrane morphology and erythrocyte volume have been documented in patients with cirrhosis irrespective of the presence of anemia. Macrocytosis and normocytosis are the most frequently observed changes in cirrhosis [23]. MCV is an important investigation in the diagnosis of anemia with a high predictive value in diagnosing alcohol-related liver diseases as well as alcohol abuse. Studies have demonstrated that macrocytosis (MCV > 100 fL) was seen in 64%-84.5% of patients with alcohol consumption > 80 g/d even in the absence of anemia[24,25]. Vit B 12 and folate deficiency, increased deposition of cholesterol in RBC membrane, presence of immature RBCs' (20% larger than mature erythrocytes), may all contribute to macrocytosis in cirrhosis. In patients with hepatitis B-related decompensated cirrhosis, macrocytosis is associated with severe disease (determined by higher MELD scores) and a higher risk of death secondary to HCC[26,27].

Serum iron studies

Serum ferritin: The hepatocyte is the principal site of production of ferritin, a marker of iron homeostasis and an acute phase reactant. Serum ferritin level < 30 μg/dL has a sensitivity of 92% to diagnose IDA in the general population[28,29]. However, in patients with underlying inflammatory disorders and cirrhosis a value < 100 μg/dL has a better predictive value to diagnose IDA[30]. Systemic analysis on the utility of measuring ferritin in patients with cirrhosis revealed that values, 15 g/dL were highly specific to establish a diagnosis of IDA in cirrhosis while values > 100 g/dL virtually ruled out IDA[31].

Another important fact worth considering is that 10%-30% of patients with cirrhosis have iron overload. This is particularly significant in individuals with nonalcoholic fatty liver disease, alcoholic liver diseases, CHC, and primary biliary cholangitis. Excess iron has been demonstrated in 8% of patients with an advanced liver disease akin to hemochromatosis even in the absence of specific genetic mutations. Iron excess may initiate the second process of liver injury and increases the risk of HCC[32]. Besides diagnosing IDA and predicting increased risk of HCC, elevated levels of serum ferritin have also been shown to independently predict mortality similar to MELD score in patients of end-stage liver disease[33].

TSAT

High serum ferritin and low transferrin are oft-reported findings in cirrhosis. Available literature suggests that transferrin and TSAT are independent predictors of mortality in ACLF and decompensated Cirrhosis[34]. TSAT value < 20% may be considered the level to initiate treatment for IDA[35]. EASL recommends TSAT > 45% in females and > 50% in males as a screening biochemical test for hereditary hemochromatosis[36]. However, the TSAT value needs to be read in the clinical context as TSAT has acute phase reactivity is affected by diurnal and dietary fluctuations of serum iron[37].

Serum transferrin receptor

The level of transferrin receptors in the serum can be used to ascertain the iron stores. It can be used to differentiate IDA (levels raised in IDA) from anemia of chronic disease[38]. In patients with cirrhosis, serum transferrin receptor is 91.6% sensitive and 84.6% specific to diagnose IDA in the absence of hemolysis and acute blood loss[39]. Lack of standardized tests, availability, and cost remain the limitations to its widespread use in clinical setting[37].

Folic acid, Vit B12, Vit B6

Deficiency of Vit B12, B6, and folic acid may be a contributing factor to the development of anemia in cirrhosis. European Society for Clinical Nutrition and Metabolism guidelines recommend baseline screening for Vit and micronutrients in all patients with cirrhosis[40]. However, the laboratory assays for detecting micronutrient deficiencies are not standardized for patients with cirrhosis. The various assays are Erythrocyte folate level < 140 ng/mL, plasma pyridoxal 5' phosphate level < 20 nmol/mL, and methylmalonic acid level > 0.4 μmol/L qualify as folic acid, Vit B6 and Vit B12 deficiency respectively[41].

MANAGEMENT

The management of anemia in a patient with cirrhosis may be considered under the following subheads: Patients with ongoing/acute bleeding; Patient without active/acute bleeding.

MANAGEMENT OF A PATIENT OF ANEMIA IN CIRRHOSIS WITH ONGOING/ACUTE BLEEDING

GI bleed is the second most common cause of decompensation in a patient with cirrhosis[38]. Bleeding esophageal varices, which constitute the predominant source of the variceal bleed, is associated with 10%-20% mortality over 6 wk. Initial management focuses on maintenance of intravascular volume and 'restrictive transfusion strategy' *i.e.*, initiating transfusion at Hb level < 7 g/dL to maintain Hb between 7-9 g/dL. This has been found to have a survival benefit in patients with Child's A and B cirrhosis and it also decreases the risk of rebleeding in all patients with cirrhosis[42,43,44]. Intravenous splanchnic vasoconstrictors (terlipressin, somatostatin, octreotide), antibiotic prophylaxis, and intravenous proton pump inhibitors are recommended in the initial management of all cases of acute variceal bleed[45]. Combination treatment of endoscopic variceal ligation (EVL) and intravenous vasoconstrictors is the 'standard of care'. Early rebleeding or failure of endoscopic therapy has been reported in 10%-15% of all patients with acute variceal bleed[5]. Rescue transjugular intrahepatic portosystemic shunt (TIPS) may be considered in such patients in addition to EVL and intravenous vasoconstrictors. Those patients with increased risk of re-bleeding (Child C status, score < 14 and no contraindications for TIPS), may be considered for pre-emptive TIPS and as a bridge to eventual LT[45]. Nonselective beta-blockers in addition to EVL form the cornerstone of management strategy to prevent a rebleed.

MANAGEMENT OF A PATIENT OF ANEMIA IN CIRRHOSIS WITH NO EVIDENCE OF ACUTE/ONGOING GI BLEED

Once the predominant cause has been identified, treatment should be initiated to provide symptomatic relief besides addressing the underlying disease, reduction of portal pressure, prevention of progressive fibrosis besides management of complications, and screening for HCC. The definite treatment, however, remains as LT.

MANAGEMENT OF IDA IN CIRRHOSIS

Treatment aims to provide symptomatic relief, replace iron stores and normalize RBC indices. Management of IDA secondary to acute blood loss has already been discussed in the section on 'Management of anemia in cirrhosis with acute/ongoing GI bleed'. The efficacy of the available tests to diagnose IDA and to assess the adequacy of treatment has inherent drawbacks in patients with cirrhosis. These have been highlighted in the discussion on 'specific investigations' mentioned above. There are no available guidelines to manage a case of anemia in cirrhosis. Experience gained from the management of anemia in patients with chronic kidney disease (CKD), another progressive inflammatory disorder, may be utilized in patients with cirrhosis. Iron can be given as oral iron preparations (indicated for mild anemia > 11 g/dL or < 10.9 g/dL but > 8 g/dL): Divalent iron salts, ferrous sulphate, ferrous gluconate and ferrous fumarate. Ferrous sulfate is the universally available form[46]. Traditionally the recommended dose in IDA is 100 -200 mg of elemental iron, preferably empty stomach, of which 10%-20% of elemental iron is absorbed. Although evidence is scarce, ascorbic acid 250-500 mg/d may be prescribed along with oral iron preparations. Treatment may be prescribed for a minimum of 3 mo to achieve adequate replacement for iron stores[47]. Oral iron preparations are associated with considerable side effects: altered metallic taste, nausea, occasional vomiting, epigastric burning sensation, constipation, or diarrhea[48]. Patients with cirrhosis may have a suboptimal response (< 1g/dL increase in Hb after 3 wk of therapy) owing to malabsorption or disease complications like hepatic encephalopathy (HE) because of constipation. Recent evidence suggests that altering the dosing schedule *i.e.*, the alternate-day schedule may be as effective as the traditional daily dose regimen[49]. Newer oral preparations like sucrosomial iron (SI) have been tried with efficacy similar to injectable iron in non-dialysis dependent CKD patients but not in patients with cirrhosis[50].

Failure of oral iron therapy, malabsorption, severe IDA are some of the universally accepted indications of intravenous (IV) iron therapy. Some or all of these may be present in patients of cirrhosis with IDA. IV iron preparations have different pharmacokinetics vs. oral iron preparations. Once into the bloodstream, elemental iron is taken up by macrophages and released *via* ferroportin thus circumventing, intestinal absorption[51]. Adverse effects can vary from minor infusion reactions (rash, palpitation, myalgia, chest discomfort) to serious anaphylactoid reactions causing respiratory or hemodynamic changes. Among the available IV iron preparations, maximum single dose that can be administered and minimum administration time are as follows: Fe gluconate: 125 mg (30-60 min), Fe-sucrose: 200 mg (30 min), Fe-carboxymaltose: 1000 mg (15 min), Fe-isomaltoside: 20 mg Fe/kg (15 min), Ferumoxytol: 510 mg (15 min) respectively[48].

Blood transfusion (packed RBC transfusion) is generally reserved for patients who remain symptomatic despite IV iron therapy or are hemodynamically unstable. The key concept is not to target a normal Hb level but one at which iron supplementation can be safely initiated[52].

MANAGEMENT OF ANEMIA OF CHRONIC DISEASE IN PATIENTS WITH CIRRHOSIS

Two distinct yet complementary treatment strategies may be adopted while managing a patient with cirrhosis with anemia of chronic disease. The first caters to 'silencing' the underlying disease and managing its complications. Although, LT is the only definite cure, prevention of fibrosis, cessation of alcohol, treatment for HBV and HCV, all have a role to play. The second strategy involves managing nutritional deficiencies. Thus, it is imperative to treat co-existing IDA, Vit B12, B6, or folate deficiencies[53]. This also brings to light the often ignored or neglected dietary prescription in patients

Table 2 Ongoing trials on evaluation and management of anemia in cirrhosis

S No	Trial name	Clinical Trials.gov identifier	Aim	Ref.
1	Etiopathogenesis of anemia in chronic liver disease	NCT04622449	(1) To determine the prevalence of various etiologies of anemia in patients with liver disease; and (2) Association of liver disease severity as measured by MELD, MELD Na and CTP scores with severity of anemia	Premkumar [62]
2	Iron deficiency anemia in children with liver cirrhosis	NCT03482076	To determine prevalence of IDA in liver cirrhosis	Mohamed [63]
3	Lactoferrin in treatment of Fe deficiency anemia in cirrhosis	NCT04335058	(1) Correction of anemia (time frame: 1 mo): Number of participants achieving hemoglobin level > 12 g/dL iron deficiency anemia in patients with chronic liver disease of any etiology; and (2) Correction of anemia (time frame: 3 mo): Number of participants achieving hemoglobin level > 12 g/dL	Premkumar [64]

MELD: Model for end-stage liver disease; CTP: Child Turcotte Pugh score; IDA: Iron deficiency anemia.

with cirrhosis. Sound dietary advice especially rich in elemental iron, and other micronutrients need to be ingrained into every hospital visit by the patient. Certain treatment strategies that might be considered in future clinical trials arethiamine derivative fursultiamine: Ferroportin antagonist[54] for which the only presently approved indication is Vit B1 deficiency. Prolyl hydroxylase enzyme (PHD) inhibitors are tried in clinical trials for the management of the anemia of chronic disease especially CKD. PHD inhibitor stabilizes HIF which in turn leads to a positive effect on erythropoiesis and iron metabolism[55].

VIT B12, B6, AND FOLIC ACID SUPPLEMENTATION

Micronutrient deficiencies are common in patients with cirrhosis. For patients with suspected or proven folic acid deficiency IV supplementation with 0.4-4 mg of folic acid daily for 3 d followed by recommended daily allowance (RDA) of 400 µg/d is advisable. In case of suspected intestinal malabsorption IV dosage may be prolonged. Folic acid supplementation > 1 mg/d may mask Vit B12 deficiency. The RDA for Vit B6 is 1.3 mg/d for men and women 19-50 years of age, 1.5 mg and 1.7 mg for women and men > 51 years of age respectively. The recommended dosage for Vit B12 in patients with concomitant neuropsychiatric signs is 1000 µg intramuscular every alternate day for 3 wk followed by monthly 1000 µg intramuscular injections or 1000-2000 µg oral supplementation[41].

MANAGEMENT OF ANEMIA IN CIRRHOSIS: WORK IN PROGRESS

Anemia is present in 60%-75% of all patients with cirrhosis[3]. The presence of anemia and various RBC indices, serum ferritin, TSAT, have all been independently associated with worsening disease severity and poor prognosis. However, to date, there are no universally available guidelines that dwell on this common but rather difficult to treat disease manifestation. There are lacunae in our understanding of disease and its management. Furthermore, the available parameters for the diagnosis and evaluation of anemia, and the laboratory assays have not been standardized or validated in patients with cirrhosis.

IDA is a potentially treatable condition and unlike other chronic inflammatory conditions like CKD and inflammatory bowel disease, cut-off values of serum ferritin and TSAT have not been validated in cirrhosis. How do we diagnose IDA in cirrhosis? What is the best method of replacement of elemental iron in cirrhosis? Definite randomized controlled trials (RCTs) are lacking on this management aspect. The ongoing RCTs have been highlighted in Table 2. What is the protocol for diagnosing and supplementing other micronutrient deficiencies *e.g.*, Folic acid, Vit B12, B6 which contribute to the development of anemia in cirrhosis? When and how often to supplement and reevaluate for assessment of body stores for these micronutrients? How does one prevent or screen for iron overload, which by itself is associated with increased mortality in cirrhosis? Last but not the least, should the presence of anemia or indices like serum ferritin be incorporated into existing severity scores like MELD

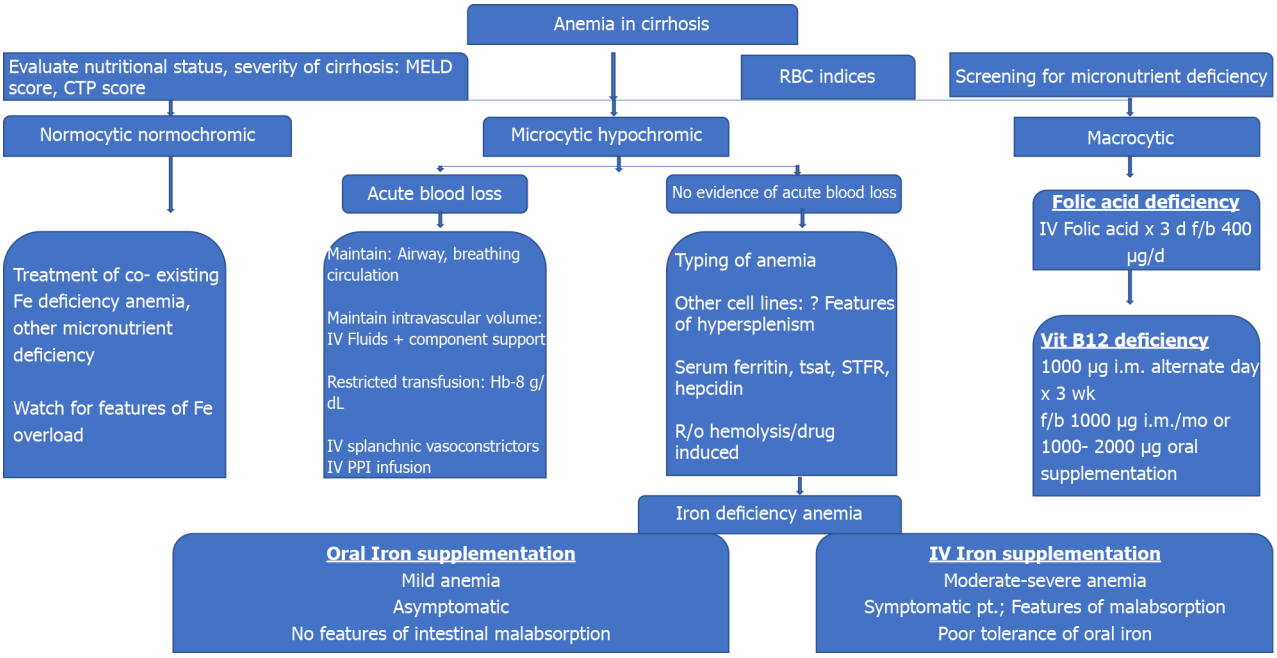

Figure 3 Management of anemia in cirrhosis.

score to improve their prognostic accuracy? All these are areas of potential research and may help us decipher this enigma and its potential contribution to the outcome of cirrhosis!

We have proposed an algorithm for evaluation and management of anemia in cirrhosis as per available evidence (Figure 3); it will require validation and subsequent modification prospectively. More so when more research is carried out to fill the lacunae in the existing understanding of the subject.

CONCLUSION

The evaluation and management of anemia in cirrhosis is an important aspect of disease management. IDA is a potentially treatable cause of anemia wherein RBC indices and serum iron studies have prognostic significance. Patients should be screened for deficiency of micronutrients like Folic acid, Vit B12, Vit B6 at baseline and supplementation should be initiated. Future research into various aspects dealing with diagnosis, management of anemia, and newer therapeutic modalities is the need of the hour. In addition, the role of anemia in the prognostication of cirrhosis is an area that needs further research in prospective trials.

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