Hematologic complications of alcohol use

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INTRODUCTION

Excess alcohol intake can affect multiple organ systems. This topic reviews the hematologic complications of excess alcohol intake including effects on red blood cells, white blood cells, and platelets.

The effects of alcoholic liver disease on the hemostatic system (increased risks of bleeding and thrombosis) are discussed separately. (See "Hemostatic abnormalities in patients with liver disease".)

The effects of alcohol on the liver and other organ systems are also discussed separately.

- **Acute toxicity** – (See "Ethanol intoxication in adults".)
- **Liver injury** – (See "Clinical manifestations and diagnosis of alcohol-associated fatty liver disease and cirrhosis".)
- **Neurologic complications** – (See "Overview of the chronic neurologic complications of alcohol".)
- **Psychological and social well-being** – (See "Risky drinking and alcohol use disorder: Epidemiology, clinical features, adverse consequences, screening, and assessment".)

MECHANISM OF ALCOHOL TOXICITY

Amount of alcohol consumed — Chronic heavy alcohol consumption (eg, for one to two years or more) has fairly reproducible effects on the hematologic system [1]. The amount of alcohol that constitutes heavy use in adults is as follows:

- **Males** – Heavy alcohol use is defined as chronic (daily) consumption of >80 grams of alcohol.

  This translates into a daily intake of approximately 250 mL of distilled spirits, more than 500 mL of fortified wine, one bottle (750 mL) of table wine, or 1.5 liters of beer (four 12-ounce cans or bottles).

- **Females** – Heavy alcohol use is defined as chronic (daily) consumption of >60 grams of alcohol.

  This translates into a daily intake of approximately 190 mL of distilled spirits, more than 375 mL of fortified wine, three-fourths of a bottle (560 mL) of table wine, or 1 liter of beer (three 12-ounce cans or bottles).

The reasons for the difference between males and females is unknown; it may represent differences in body weight, body fat versus total body water content, or liver size. (See 'Mitigating factors' below.)

The amount of alcohol in grams can be calculated based on the volume of the drink and the percentage of alcohol it contains. As an example, distilled spirits have an alcohol content of approximately 35 percent (35 g/dL); thus, 250 mL (2.5 dL) of distilled spirits would have 35 g/dL x 2.5 dL = 87.5 grams of alcohol.

Fortified wine (eg, port, sherry) refers to wine with an alcohol content of approximately 20 percent; table wine generally has an alcohol content of 10 to 13 percent [2]. Some "supersized alcopops" (flavored drinks containing alcohol) have an ethanol content equivalent to 5.5 standard drinks or roughly 80 grams of alcohol [3]. The alcohol content of other alcoholic beverages is illustrated in the figure (figure 1).

Intermittent binge drinking is common. The exposure and effect on hematologic parameters is challenging to define, but binge drinking does appear to have clinically significant affects in some individuals.

Additional information about alcohol use disorder and risky drinking, including amount of alcohol and other features, is presented separately. (See "Risky drinking and alcohol use disorder: Epidemiology, clinical features, adverse consequences, screening, and assessment" and "Screening for unhealthy use of alcohol and other drugs in primary care".)

Effects on the hematopoietic system — Alcohol use at concerning levels (>80 grams of alcohol daily for males or >60 grams daily for females) (see 'Amount of alcohol consumed' above) can cause a variety of hematologic complications, including anemia, leukopenia, and/or thrombocytopenia.

Alcohol can also cause macrocytosis without anemia and ring sideroblasts in the bone marrow (acquired sideroblastic anemia). In contrast, alcohol use does not appear to increase the risk for myelodysplastic syndrome (MDS) or lymphoma [4,5].

How alcohol exerts these effects is not completely understood. Direct toxic effects on hematopoietic cells, abnormalities in membrane phospholipids, and interference with folate utilization in metabolic pathways such as for DNA synthesis (figure 2) all may be involved [6,7].

The interaction between alcohol and folate is complex. Alcohol use does not induce folate deficiency per se, nor does it appear to impair folate absorption. However, serum folate levels will fall acutely after rapid alcohol intake. This is a consequence of alcohol effects on folate mobilization and utilization [8]. Chronic alcohol use can also be associated with poor nutrition, and folate deficiency is seen frequently in individuals with heavy alcohol intake and limited diets, along with other indicators of poor nutrition.

The individual's access to medical care can also profoundly impact the severity of these effects as more prolonged alcohol use without clinical intervention often allows the abnormalities to progress.

The adverse effects of alcohol on hematopoiesis may be mediated in part by metabolites of alcohol such as acetaldehyde [6,7]. Ingested alcohol (ethanol) is metabolized in the liver in part by alcohol dehydrogenase, which oxidizes alcohol to acetaldehyde while reducing nicotinamide adenine dinucleotide (NAD) to NADH. Acetaldehyde can produce red blood cell (RBC) protein-acetaldehyde adducts, which may generate immune responses against these modified proteins [9]. Immunoglobulin (Ig) A and IgM anti-acetaldehyde-protein adducts have been found in individuals with macrocytosis who consume excess alcohol [10]. (See "Pathogenesis of alcohol-associated liver disease", section on 'Alcohol metabolism'.)

Alcohol-induced liver disease, although a separate issue, may contribute to anemia through coagulopathy with or without concurrent gastrointestinal bleeding from portal hypertension that can be exacerbated by coagulation abnormalities. It may also contribute to anemia, leukopenia, and/or thrombocytopenia by causing splenomegaly and hypersplenism. (See "Hemostatic abnormalities in patients with liver disease" and "Splenomegaly and other splenic disorders in adults", section on 'Hypersplenism'.)

Other associated or complicating factors such as infection due to immunocompromise may also contribute. (See "Hepatitis C and alcohol" and "Risky drinking and alcohol use disorder: Epidemiology, clinical features, adverse consequences, screening, and assessment", section on 'Medical morbidity'.)

Mitigating factors — Studies of the impact of alcohol have been based on evaluations of individuals identified by the clinical history as heavy alcohol users or those stabilized medically following hospital admission [4,11,12]. These individuals may have other comorbidities, dietary deficiencies, and psychosocial behaviors that contribute to hematologic complications. It is possible that addressing these other conditions could mitigate the effects of alcohol.

Studies of healthy volunteers have demonstrated that the hematologic effects of approximately 160 grams of alcohol (500 mL of distilled spirits) per day could be mitigated by appropriate protein-calorie nutrition and folic acid supplementation [8].

Aside from diet, other modifying factors may include the overall size of the individual, proportion of lean body mass, and other highly individualized heritable variations such as levels of alcohol dehydrogenase activity [13]. Abnormally low body mass index (BMI) may be associated with more pronounced alcohol effects.

CYTOPENIAS

Anemia — Anemia (hemoglobin or hematocrit below the age- and sex-specific reference ranges) is a common complication of excess alcohol use, especially when coupled with comorbidities, nutritional deficits, and reduced access to medical care.

The cause of anemia is often multifactorial and may include more than one of the following [6,14-16]:

- Direct toxic effects of alcohol on red blood cell (RBC) production in the bone marrow
- Iron deficiency due to gastrointestinal bleeding from esophageal or gastric varices, alcoholic gastritis, ulcers, or other lesions
- Nutritional folate deficiency from the effects of a poor diet
- Chronic inflammation (also called anemia of chronic disease), which may be due to concurrent infection such as tuberculosis or chronic leg ulcers
- Hemolysis caused by RBC membrane abnormalities or other causes [17]

- Hypersplenism due to portal hypertension with sequestration of RBCs in the spleen

Even before anemia appears, approximately 90 percent of individuals with excessive alcohol intake have macrocytosis (mean corpuscular volume [MCV] above the reference range, typically in the range of 100 to 110 femtoliters [fL]) [6,14,18]. In some cases, this may be due to folate deficiency; this has become vanishingly rare in individuals who reside in countries with routine folate supplementation of foods, but it continues to occur in individuals with heavy alcohol use who are malnourished and have limited diets. Macrocytosis (and formation of target cells) can also occur as a consequence of liver disease and resulting changes to the lipid composition of RBC membranes. (See "Burr cells, acanthocytes, and target cells: Disorders of red blood cell membrane".)

Alcohol-induced macrocytosis can also occur in individuals who are folate and vitamin B12 (cobalamin) replete and do not have liver disease. The mechanism is unknown, but it may involve acetaldehyde adducts that accumulate in RBC membranes. It takes two to four months for the macrocytosis to disappear after the patient stops their alcohol intake. Macrocytosis may be blunted in individuals with concurrent iron deficiency, which causes microcytosis.

Hemolysis due to spur cell anemia (also a consequence of changes to RBC membranes) carries an extremely poor prognosis as it generally reflects severe liver disease. A case report described an individual with alcoholic cirrhosis and spur cell anemia who underwent orthotopic liver transplantation, which led to complete resolution of the spur cell anemia [17]. However, the anemia recurred when the patient resumed alcohol intake and developed graft failure. Other reports are presented separately. (See "Burr cells, acanthocytes, and target cells: Disorders of red blood cell membrane", section on 'RBC changes in liver disease'.)

Zieve syndrome, first reported in 1958, is a rare clinical syndrome comprising a triad of Coombs-negative hemolysis, cholestatic jaundice, and transient hyperlipidemia in heavy alcohol users, typically following an episode of acutely increased alcohol intake ("binge drinking"). The mechanism is unclear, but the hemolysis may be related to lipid accumulation in RBC membranes, and it will typically resolve with abstinence or, in the case of binge drinking, with return to baseline alcohol intake [19].

Iron handling in individuals with excess alcohol intake is complex. There may be iron deficiency due to bleeding, a functional block in iron incorporation (anemia of chronic disease/anemia of inflammation), and/or excess liver iron (or total body iron) due to an incompletely understood mechanism involving increased iron absorption from the gastrointestinal tract, perhaps related to increase gastric acid secretion or suppression of hepcidin. (See "Anemia of chronic disease/anemia of inflammation".)

Iron overload, in turn, can cause further hepatotoxicity, especially in individuals who are predisposed to increased iron absorption (eg, *HFE* mutation carriers). Details of iron absorption are discussed separately. (See 'Iron overload' below and "Regulation of iron balance", section on 'Intestinal iron absorption'.)

As discussed below, macrocytosis and/or anemia should not be attributed to alcohol unless or until other causes of macrocytosis and anemia have been excluded. (See 'Testing for RBC abnormalities' below.)

Leukopenia — Leukopenia (reduced white blood cell [WBC] count) is typically due to a fall in the neutrophil count as neutrophils are the most abundant WBCs. It is unusual for leukopenia or neutropenia to be severe (ie, the absolute neutrophil count [ANC] is rarely <1000/microL).

The cause of mild leukopenia or neutropenia may be multifactorial, similar to anemia, and many of the same conditions that contribute to anemia (folate deficiency, bone marrow suppression, and hypersplenism in patients with portal hypertension) may also cause some degree of leukopenia. (See 'Anemia' above.)

In addition to the decrease in WBC count, there also appears to be a difficult-to-characterize defect in neutrophil function induced by alcohol use. Neutrophil mobilization and bacterial killing may be impaired, and this may contribute to the immunocompromised state and increased susceptibility to infections in individuals with heavy alcohol use [6]. (See "Laboratory evaluation of neutrophil disorders", section on 'Overview of causes (neutrophil dysfunction)'.)

As long as hypersplenism is not the major cause, leukopenia from alcohol ingestion is typically transient and resolves in four to five days with cessation of alcohol intake.

Thrombocytopenia — Mild thrombocytopenia (eg, platelet count 70,000 to 149,000/microL) is extremely common in individuals with excess alcohol intake, with a prevalence as high as 80 percent of hospitalized adults in some series [6]. The platelet count rarely decreases below 30,000/microL, and serious bleeding due to isolated thrombocytopenia (without other coagulation abnormalities such as caused by severe liver disease) is rare in individuals with excess alcohol intake. However, other bleeding risk factors often co-occur. (See "Hemostatic abnormalities in patients with liver disease", section on 'Impaired hemostasis'.)

Contributing causes may include direct toxicity to platelet precursor cells (megakaryocytes), hypersplenism, and chronic liver disease-induced reductions in thrombopoietin. (See "Biology and physiology of thrombopoietin".)

In some patients, platelet function may also be abnormal leading to atraumatic bruising. (See "Inherited platelet function disorders (IPFDs)", section on 'Differential diagnosis'.)

Approaches to raising the platelet count in individuals with bleeding or those who require an invasive procedure are discussed below and in a separate topic review. (See 'Management' below and "Hemostatic abnormalities in patients with liver disease", section on 'Invasive procedures'.)

EVALUATION

Clinical assessment — The evaluation depends on which cytopenia(s) are present and whether an alcohol use disorder is known or suspected.

All individuals with a history of alcohol use who have one or more cytopenias should have a detailed assessment of alcohol use and a dietary history. Excess alcohol use should be considered as a cause of unexplained cytopenias, especially if there are abnormalities of liver function testing or other suggestive findings. (See "Screening for unhealthy use of alcohol and other drugs in primary care".)

Alcohol intake should be quantified, and responses such as "occasional drinking" or "social drinking" need to be defined. Screening tools for unhealthy alcohol use may provide clues when excess intake is unsuspected, but these focus primarily on behavioral aspects of dependence and cannot substitute for a quantitative history. Laboratory tests such as measurement of carbohydrate-deficient transferrin may have a role as biomarkers of alcohol use but are not widely available in the routine clinical setting [20]. (See "Screening for unhealthy use of alcohol and other drugs in primary care", section on 'Laboratory testing'.)

The history can also be used to identify features specific to a certain disorder (eg, limited diet suggestive of folate deficiency, melena suggestive of iron deficiency, medications that can cause hemolytic or megaloblastic anemia).

The physical examination should emphasize evaluating for signs of anemia, bleeding (eg, examination of the stool for occult blood), and evidence of portal hypertension (particularly splenomegaly).

Laboratory testing

Initial testing (all patients) — Laboratory evaluation of hematologic abnormalities in an individual with acute alcohol intoxication, a recent binge-drinking episode, or in the midst of alcohol withdrawal symptoms may be unproductive or misleading. An exception would be if red

blood cell (RBC) transfusion is planned. If that is the case, red cell folate and serum vitamin B12 should be obtained prior to transfusion.

Leukocytopenia, thrombocytopenia, and/or hemolysis will frequently resolve over several days to two weeks; bone marrow abnormalities also are likely to resolve with cessation of alcohol use. (See 'Hematologist/bone marrow testing' below.)

All individuals with a history of excess alcohol intake who have cytopenias when at their baseline health should have a review of the complete blood count (CBC) with differential, platelet count, and the RBC indices, especially the mean corpuscular volume (MCV). A reticulocyte count should be obtained. The peripheral blood smear should be evaluated for RBC morphology and abnormal findings such as multilobed neutrophils; if this cannot be done by the clinician themself, a manual differential with attention to RBC morphology should be requested and the report should be reviewed for flagged findings.

In addition, a chemistry panel with creatinine, blood urea nitrogen, total and direct bilirubin, albumin and total protein, aspartate and alanine transaminases, alkaline phosphatase, lactate dehydrogenase, and gamma glutamyl transferase should be obtained. Hepatitis C screening should be done if transaminases are elevated. (See "Screening and diagnosis of chronic hepatitis C virus infection".)

The subsequent laboratory testing can be done sequentially, with an initial focus on likely conditions followed by more extensive testing if the initial testing is unrevealing, or broader testing can be performed, especially if there is no obvious cause of the anemia and/or if there would be a significant burden of returning for additional testing. Likely conditions may be suggested by the patient history (eg, inadequate diet, history of melena) as well as the findings on the CBC, differential, platelet count, and reticulocyte count.

Regardless of which approach is chosen (broad initial testing or sequential testing), cytopenias should not be attributed exclusively to alcohol until other causes have been excluded or their resolution has been demonstrated.

Testing for RBC abnormalities

Microcytosis or microcytic anemia — Iron studies are appropriate to evaluate for iron deficiency. If serum ferritin and other iron studies are equivocal for a diagnosis of iron deficiency, a soluble transferrin receptor (sTfR) concentration may be obtained, and elevated sTfR may be used to identify iron deficiency. It appears that sTfR concentrations are not altered by alcohol intake, although this has not been extensively studied [21]. (See "Causes and

diagnosis of iron deficiency and iron deficiency anemia in adults", section on 'Diagnostic evaluation'.)

If iron deficiency is not found in an individual with microcytic anemia, hemoglobin testing for thalassemia may be performed. (See "Microcytosis/Microcytic anemia", section on 'Approach to the evaluation'.)

Sideroblastic anemia, which can be caused by chronic heavy alcohol use, can also cause microcytosis. (See "Sideroblastic anemias: Diagnosis and management", section on 'CBC and blood smear'.)

Macrocytosis or macrocytic anemia — A list of causes of macrocytosis and macrocytic anemia is presented in the table (table 1).

Reasonable initial testing includes the following:

- Reticulocyte count
- Folate and vitamin B12 levels
- Thyroid-stimulating hormone (TSH)
- Liver function tests
- HIV testing

An increased MCV can be caused by high levels of immunoglobulins, whether monoclonal or polyclonal; this is an artifact of cell counting caused when the RBCs form rouleaux or doublets, and it is rarely associated with macrocytosis of individual RBCs. Any process that causes rouleaux formation can cause macrocytosis. If this finding is seen on the blood film or if the tests above are negative, a serum protein electrophoresis (SPEP) should be ordered. If the SPEP is normal in these individuals, an erythrocyte sedimentation rate and/or C-reactive protein can be obtained.

Testing for folate deficiency differs depending on whether the individual has acute, heavy alcohol use or chronic use:

- **Acute alcohol use** – In the setting of acute, heavy alcohol use, RBC folate should be obtained rather than serum folate. Acutely, alcohol lowers the serum folate level even in patients who are not truly folate deficient. The result requires a normal vitamin B12 level for accurate interpretation; RBC folate levels may be suppressed by concurrent vitamin B12 deficiency. RBC folate levels may be increased by significant reticulocytosis and are unreliable in transfused patients. If RBC folate results are equivocal and vitamin B12 is

normal, serum or plasma homocysteine may be obtained. An elevated homocysteine level may identify folate or vitamin B12 deficiency.

- **Chronic alcohol use** – In individuals with chronic alcohol use (more than 1 to 2 years), the usual testing algorithm for folate should be followed. (See "Clinical manifestations and diagnosis of vitamin B12 and folate deficiency", section on 'Laboratory testing'.)

Measurement of the serum vitamin B12 level and the folate assessment (with testing appropriate to acute or chronic alcohol use) will usually establish the appropriate diagnosis. Elevated plasma homocysteine is highly sensitive to folate deficiency but also is caused by vitamin B12 deficiency and occasionally by excess alcohol use itself [22].

As stated above, some of these tests may be omitted or other tests may be added depending on the clinical presentation and burdens of returning for additional testing. (See "Diagnostic approach to anemia in adults".)

Anemia with a high reticulocyte count generally indicates hemolysis; the subsequent evaluation is discussed separately (see "Diagnosis of hemolytic anemia in adults"). Less commonly, reticulocytosis may occur during bone marrow recovery after an episode of bleeding or replacement of a missing nutrient (eg, folate present in a normal hospital diet). (See "Treatment of vitamin B12 and folate deficiencies", section on 'Typical response'.)

Blood smear findings suggestive of megaloblastic anemia include RBC macro-ovalocytosis, teardrop-shaped RBCs, and/or hypersegmented neutrophils (six or more lobes or a high proportion [more than 5 percent] with five lobes) (picture 1A-B) [18,23]. An MCV >110 femtoliters (fL) is more likely to be the result of megaloblastic anemia rather than alcohol alone or liver disease alone. However, alcohol is likely to be the most common cause of nutritional folate deficiency in the United States [6,14]. (See "Macrocytosis/Macrocytic anemia", section on 'Megaloblastic anemia'.)

Copper deficiency can cause normocytic or macrocytic anemia, with or without other cytopenias. Measuring the serum copper level may be indicated in certain individuals, especially those with risk factors for deficiency or suggestive morphologic findings in the bone marrow. (See "Sideroblastic anemias: Diagnosis and management", section on 'Copper deficiency'.)

If this testing is unrevealing, it may be reasonable to consult a hematologist for further advice and testing. The evaluation is discussed in more detail separately. (See 'Hematologist/bone marrow testing' below and "Macrocytosis/Macrocytic anemia".)

Normocytic anemia — Normocytic anemia may be seen with any of the causes listed above. Combined microcytosis from iron deficiency and macrocytosis from folate deficiency or one of the causes listed above may result in a normal MCV.

If the patient also has a chronic infection (eg, tuberculosis, chronic leg ulcers), anemia of chronic disease/inflammation may be present (see "Anemia of chronic disease/anemia of inflammation"). Treatment of the underlying infection(s) will reverse this component of the anemia.

Another cause of chronic liver disease other than alcohol, such as hepatitis C virus (HCV) infection, may be contributing to anemia, and HCV testing is appropriate in those with abnormal liver function tests. (See "Screening and diagnosis of chronic hepatitis C virus infection".)

Testing for additional cytopenias — Mild leukopenia and/or thrombocytopenia are common with certain nutrient deficiencies (folate, vitamin B12, copper) and with myelodysplasia. (See 'Macrocytosis or macrocytic anemia' above and 'Normocytic anemia' above.)

Hypersplenism due to increased portal pressures is another common cause of mild cytopenias. If an individual has mild cytopenias (absolute neutrophil count consistently higher than 1000/microL or platelet count greater than 50,000/microL) and splenomegaly caused by portal hypertension, and there are no other concerning findings on the examination or blood smear, it is reasonable to attribute the cytopenias to hypersplenism. (See "Hemostatic abnormalities in patients with liver disease", section on 'Thrombocytopenia and platelet dysfunction' and "Splenomegaly and other splenic disorders in adults", section on 'Hypersplenism'.)

Additional evaluations for cytopenias that are more severe and/or are not attributed to nutrient deficiencies, myelodysplasia, or hypersplenism are discussed in separate topic reviews:

- Leukopenia – (See "Approach to the adult with unexplained neutropenia" and "Approach to the adult with lymphocytosis or lymphocytopenia", section on 'Lymphocytopenia'.)
- Thrombocytopenia – (See "Diagnostic approach to thrombocytopenia in adults".)
- Combined cytopenias (bicytopenia or pancytopenia) – (See "Approach to the adult with pancytopenia".)

When to consult

Hematologist/bone marrow testing — Hematologist consultation and bone marrow examination generally are not needed in individuals with mild cytopenias attributed to alcohol

use, nutrient deficiencies (iron, folate, vitamin B12, copper), or mild hypersplenism.

Hematologist input is prudent for individuals with severe cytopenias (eg, hemoglobin <7 g/dL; absolute neutrophil count <1000/microL; platelet count <50,000/microL) or progressively worsening cytopenias, who may require the following:

- Growth factors for neutropenia and fever
- Additional evaluations and treatments for severe thrombocytopenia and bleeding
- Evaluation of concerning findings on the blood smear
- Bone marrow examination for possible myelodysplastic syndrome (MDS), other hematologic malignancy, or other causes of pancytopenia

  Although bone marrow aspiration and biopsy is not routinely done, it can exclude explanations for cytopenias not related to alcohol and may reveal changes characteristic of alcohol effect if performed shortly after acute alcohol ingestion.

  - Approximately one-fourth of patients will have ring sideroblasts (picture 2) [14].
  - Very heavy alcohol consumption may also be associated with vacuoles in proerythroblasts and granulocytic precursors, the cause of which is unknown [6]. In a series of 144 patients from Finland, 24 percent of severe alcohol users had vacuolated proerythroblasts [15].
  - Deposition of iron in lysosomal vesicles of plasma cells may precede other alcohol-associated bone marrow changes. These iron deposits can be seen with Prussian blue staining, and they appear to be a specific, although not necessarily sensitive, indicator of significant alcohol use [24].
  - The marrow may also become distinctly hypoplastic and very rarely even aplastic with pancytopenia [25,26].

  Abstinence results in reversal of the bone marrow hypoplasia, erythroid precursor vacuolization, and ring sideroblasts within two weeks. The time course of resolution of the iron deposition in plasma cells is less clear.

Since hypoplasia, ring sideroblasts, and/or vacuolated erythroid precursors can be features of MDS, bone marrow examination should be performed following at least two weeks of abstinence from alcohol if possible. Other features that may help distinguish alcohol effect from

MDS are discussed separately. (See "Clinical manifestations, diagnosis, and classification of myelodysplastic syndromes (MDS)", section on 'Evaluation'.)

Gastroenterologist/hepatologist — Gastroenterologist evaluation is appropriate to evaluate a suspected source of gastrointestinal bleeding. (See "Approach to acute upper gastrointestinal bleeding in adults" and "Approach to acute lower gastrointestinal bleeding in adults".)

Gastroenterologist or hepatology consult is also indicated in individuals with suspected cirrhosis to assist in the diagnosis, reduce the risk of complications such as variceal bleeding, and manage complications if/when they occur. (See "Cirrhosis in adults: Overview of complications, general management, and prognosis" and "Overview of medication adjustments for adult patients with cirrhosis".)

MANAGEMENT

Interventions for severe thrombocytopenia or bleeding — Leukopenia and thrombocytopenia are rarely severe enough to require interventions [6]. For leukopenia, discontinuing alcohol intake is usually appropriate; antibiotics may be indicated if infection is suspected.

For individuals with severe thrombocytopenia (platelet count <50,000/microL) attributed to chronic liver disease, a thrombopoietin receptor agonist can be used to raise the platelet count into a safe range for a surgical procedure [27]. (See "Hemostatic abnormalities in patients with liver disease", section on 'Invasive procedures'.)

Bleeding associated with severe liver disease and thrombocytopenia, which may be accompanied by clotting factor deficiencies, is discussed separately. (See "Hemostatic abnormalities in patients with liver disease", section on 'Bleeding'.)

Abstinence — The main treatment of alcohol-induced cytopenias is abstaining from alcohol intake and, for those with inadequate nutrition, resumption of an adequate balanced diet.

If a patient presents in an acute situation with alcohol intoxication, alcohol withdrawal, or in the immediate aftermath of a binge-drinking episode, management should focus on nutritional support including appropriate vitamin supplements, stabilization and management of acute situations such as gastrointestinal bleeding or infection, and management of withdrawal symptoms. (See "Alcohol withdrawal: Epidemiology, clinical manifestations, course, assessment, and diagnosis" and "Management of moderate and severe alcohol withdrawal syndromes".)

Alcohol cessation may require significant investment of time and effort, possibly including counseling and other psychosocial interventions and in some cases medication. This subject is discussed in detail separately. (See "Alcohol use disorder: Treatment overview".)

Nutrient replacement — For individuals who have additional conditions contributing to cytopenias, these should be treated concurrently:

- Folate or vitamin B12 deficiency – (See "Treatment of vitamin B12 and folate deficiencies", section on 'Treatment of folate deficiency'.)
- Iron deficiency – (See "Treatment of iron deficiency anemia in adults".)

Folate deficiency is generally due to dietary insufficiency. As noted above, diagnostic testing may be affected by recent alcohol intake, and presumptive treatment may be appropriate for some individuals. (See 'Macrocytosis or macrocytic anemia' above.)

In contrast, individuals with iron deficiency should be evaluated for sources of gastrointestinal blood loss, and those with vitamin B12 deficiency should be evaluated for causes of decreased absorption. (See "Causes and diagnosis of iron deficiency and iron deficiency anemia in adults", section on 'Search for source of blood and iron loss' and "Clinical manifestations and diagnosis of vitamin B12 and folate deficiency", section on 'Determining the underlying cause of vitamin B12 deficiency'.)

Expected resolution — The expected resolution of cytopenias depends on their cause. Anemia associated with nutrient deficiencies begins to resolve within two to four weeks of treatment. Alcohol-induced macrocytosis may require months of abstinence to normalize. Thrombocytopenia may be followed by rebound thrombocytosis before the platelet count normalizes. (See 'Rebound thrombocytosis' below.)

Cytopenias caused by hypersplenism generally persist despite cessation of alcohol. (See "Splenomegaly and other splenic disorders in adults", section on 'Hypersplenism'.)

Rebound thrombocytosis — Individuals with thrombocytopenia who stop drinking often experience a "rebound" thrombocytosis within a week or two of alcohol cessation, especially when combined with a varied diet as often occurs during or after hospitalization [28].

The typical time course of thrombocytosis is within one to two weeks after alcohol cessation. The platelet count may be as high as 600,000 to 900,000/microL. The platelet count returns to normal levels within another 7 to 10 days without further therapy [6].

This phenomenon represents a normal and transient response to a prior episode of thrombocytopenia. It does not require hematologic consultation or treatment unless the

platelet count remains persistently high for several weeks (eg, for more than four weeks) after the initial increase. The evaluation of thrombocytosis is discussed separately. (See "Approach to the patient with thrombocytosis".)

IRON OVERLOAD

Iron overload can occur in individuals with liver disease of any cause including alcoholic liver disease. Changes in iron studies suggestive of iron overload (high ferritin and transferrin saturation [TSAT]) occurred in approximately 9 percent of chronic alcohol users in one study [29]. (See "Clinical manifestations and diagnosis of alcohol-associated fatty liver disease and cirrhosis".)

Testing for iron overload may be done for any individual with mildly or moderately increased transaminases or for other suggestive symptoms or associated conditions. (See "Approach to the patient with abnormal liver biochemical and function tests" and 'Exacerbation of porphyria' below and "Approach to the patient with suspected iron overload", section on 'Typical clinical findings'.)

Liver disease also causes an increased serum ferritin level independent of total body iron stores due to the chronic inflammatory component (ferritin is an acute phase reactant) as well as release of ferritin into the circulation upon hepatocyte damage (the liver is a major storage site for iron). Thus, the proportion of individuals with excess alcohol use who have a high serum ferritin level is considerably higher than the proportion who have true iron overload.

Distinguishing between true iron overload and ferritin elevation without iron overload is important because iron accumulation can lead to oxidative damage, cell death, fibrogenesis, and complications including fatty liver, cirrhosis, and an increased risk for hepatocellular carcinoma [30,31].

Our approach to determining the presence of iron overload includes the following:

- Obtain iron studies including iron, ferritin, and transferrin saturation (TSAT).
- Perform T2-star magnetic resonance imaging (MRI) to evaluate hepatic iron overload for those patients with iron studies consistent with iron overload (ferritin ≥200 to 300 ng/mL [≥200 to 300 mcg/L] in men or ≥150 to 200 ng/mL [≥150 to 200 mcg/L] in women; TSAT ≥45 percent in men or ≥40 percent in women).
- Test for hereditary hemochromatosis using *HFE* genetic testing (and perhaps other genetic abnormalities as well, such as variants in the genes for transferrin receptor and hepcidin)

in those with evidence of iron overload. (See "*HFE* and other hemochromatosis genes".)

- Liver biopsy is generally not needed but may be helpful if there is a question about the diagnosis or the relative contribution of multiple diagnoses.

- Response to therapeutic phlebotomy may be helpful in confirming the diagnosis as long as the individual can tolerate the procedure.

This testing is discussed in more detail separately. (See "Approach to the patient with suspected iron overload".)

If hereditary hemochromatosis is present, the excess alcohol ingestion is an additive risk factor for hepatic iron overload, especially when liver disease is also present. (See "Management and prognosis of hereditary hemochromatosis" and "Management and prognosis of hereditary hemochromatosis", section on 'Limiting alcohol'.)

Criteria for initiating therapeutic phlebotomy in patients with alcohol-associated iron overload are not defined, and it is not clear that criteria identified for hereditary hemochromatosis are applicable. This subject is discussed in more detail separately. (See "Approach to the patient with suspected iron overload", section on 'Treatment'.)

EXACERBATION OF PORPHYRIA

Alcohol use can exacerbate symptoms in individuals with porphyria, either cutaneous or acute/neurovisceral.

As examples:

- **PCT** – Alcohol use has been reported to be an important and common susceptibility factor in many series of patients with porphyria cutanea tarda (PCT). (See "Porphyria cutanea tarda and hepatoerythropoietic porphyria: Pathogenesis, clinical manifestations, and diagnosis", section on 'Alcohol'.)

- **AIP** – Ethanol is a known inducer of hepatic delta-aminolevulinic acid synthase (ALAS1), the rate-limiting enzyme for heme synthesis in the liver. As a result, alcohol is a risk factor for provoking neurovisceral episodes in the acute porphyrias such as acute intermittent porphyria (AIP). (See "Acute intermittent porphyria: Pathogenesis, clinical features, and diagnosis", section on 'Ethanol and smoking'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Alcohol consumption".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Alcohol use — when is drinking a problem? (The Basics)")
- Beyond the Basics topics (see "Patient education: Risks and benefits of alcohol (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Pathophysiology** – Chronic heavy alcohol consumption in adults (>80 grams per day in males, >60 grams per day in females) has fairly reproducible effects on the hematologic system including anemia, leukopenia, thrombocytopenia, macrocytosis without anemia, and ring sideroblasts and other abnormalities in the bone marrow. The mechanisms are multifactorial. The amount of alcohol in different beverages is summarized in the figure (figure 1). (See 'Mechanism of alcohol toxicity' above and 'Cytopenias' above.)
- **Evaluation** – The evaluation depends on which cytopenia(s) are present. All individuals with alcohol use who have one or more cytopenias should have a detailed assessment of intake and a dietary history. The physical examination should emphasize signs of anemia,

bleeding (eg, examination of the stool for occult blood), and evidence of portal hypertension or liver decompensation (particularly splenomegaly). (See 'Clinical assessment' above.)

- **Laboratory testing** – Laboratory testing should be done when the person is at their baseline and at least two weeks after an acute episode of intoxication or binge drinking. Many abnormalities will resolve with abstinence. Those with persistent cytopenias should have a review of the complete blood count (CBC) with differential and platelet count; review of the red blood cell (RBC) indices, especially the mean corpuscular volume (MCV); reticulocyte count; blood smear review; chemistry panel; and liver function tests. (See 'Initial testing (all patients)' above.)

  - Individuals with microcytosis or microcytic anemia are evaluated for iron deficiency, keeping in mind that thalassemia (including thalassemia trait), anemia of chronic disease/anemia of inflammation (ACD/AI), and sideroblastic anemia can also cause microcytosis. Those with iron deficiency should have an evaluation for the cause. Individuals with macrocytosis or macrocytic anemia should have a reticulocyte count, serum folate and vitamin B12 levels, liver function tests, thyroid-stimulating hormone (TSH), HIV testing, and/or serum protein electrophoresis (table 1). Hepatitis C virus testing is appropriate if transaminases are elevated. Hematologist consultation is appropriate for severe cytopenias, signs of dysplasia on the blood smear, or unexplained pancytopenia. (See 'Testing for RBC abnormalities' above and 'When to consult' above.)

  - Common causes of leukopenia and thrombocytopenia include folate, vitamin B12, and copper deficiencies, and hypersplenism. Evaluation for other causes may be indicated. Thrombocytopenia is rarely severe, but some individuals may require interventions to raise the platelet count for an invasive procedure or to treat thrombocytopenia-associated bleeding. (See 'Testing for additional cytopenias' above and 'Interventions for severe thrombocytopenia or bleeding' above.)

- **Management** – The principal treatment is cessation of alcohol intake, which may require substantial investment of time and effort, possibly including counseling and other psychosocial interventions and in some cases medication. A varied diet is important, and iron, folate, vitamin B12, and copper should be replaced if deficient. Recovery occurs in two to four weeks. Macrocytosis may take months to resolve, and cytopenias due to hypersplenism may not improve. (See 'Abstinence' above and 'Nutrient replacement' above and 'Expected resolution' above.)

- **Rebound thrombocytosis** – Rebound thrombocytosis is common after recovery from alcohol-induced thrombocytopenia, with platelet counts as high as 600,000 to 900,000/microL. The platelet count generally returns to normal within 7 to 10 days, and further intervention or evaluation is not needed unless thrombocytosis persists for several weeks. (See 'Rebound thrombocytosis' above.)

- **Iron overload** – Iron overload can occur with liver disease of any cause. Liver disease can cause increased serum ferritin independent of total body iron stores; most patients with chronic alcohol consumption and an elevated ferritin do not have increased total body iron stores. (See 'Iron overload' above.)

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REFERENCES

1. https://health.gov/dietaryguidelines/2015/guidelines/appendix-9/ (Accessed on October 2 2, 2019).
2. de Beukelaar MF, Janse ML, Sierksma A, et al. How full is your glass? Portion sizes of wine, fortified wine and straight spirits at home in the Netherlands. Public Health Nutr 2019; 22:1727.
3. Rossheim ME, Thombs DL. Estimated blood alcohol concentrations achieved by consuming supersized alcopops. Am J Drug Alcohol Abuse 2018; 44:317.
4. Sweeney MR, Applebaum KM, Arem H, et al. Medical Conditions and Modifiable Risk Factors for Myelodysplastic Syndrome: A Systematic Review. Cancer Epidemiol Biomarkers Prev 2019; 28:1502.
5. Psaltopoulou T, Sergentanis TN, Ntanasis-Stathopoulos I, et al. Alcohol consumption and risk of hematological malignancies: A meta-analysis of prospective studies. Int J Cancer 2018; 143:486.

6. Girard DE, Kumar KL, McAfee JH. Hematologic effects of acute and chronic alcohol abuse. Hematol Oncol Clin North Am 1987; 1:321.
7. Lieber CS. Metabolism and metabolic effects of alcohol. Semin Hematol 1980; 17:85.
8. Eichner ER, Hillman RS. Effect of alcohol on serum folate level. J Clin Invest 1973; 52:584.
9. Niemelä O, Parkkila S. Alcoholic macrocytosis--is there a role for acetaldehyde and adducts? Addict Biol 2004; 9:3.
10. Koivisto H, Hietala J, Anttila P, et al. Long-term ethanol consumption and macrocytosis: diagnostic and pathogenic implications. J Lab Clin Med 2006; 147:191.
11. Seppä K, Laippala P, Saarni M. Macrocytosis as a consequence of alcohol abuse among patients in general practice. Alcohol Clin Exp Res 1991; 15:871.
12. SULLIVAN LW, HERBERT V. SUPPRESSION HEMATOPOIESIS BY ETHANOL. J Clin Invest 1964; 43:2048.
13. Ramchandani VA, Bosron WF, Li TK. Research advances in ethanol metabolism. Pathol Biol (Paris) 2001; 49:676.
14. Savage D, Lindenbaum J. Anemia in alcoholics. Medicine (Baltimore) 1986; 65:322.
15. Latvala J, Parkkila S, Niemelä O. Excess alcohol consumption is common in patients with cytopenia: studies in blood and bone marrow cells. Alcohol Clin Exp Res 2004; 28:619.
16. Ballard HS. The hematological complications of alcoholism. Alcohol Health Res World 1997; 21:42.
17. Malik P, Bogetti D, Sileri P, et al. Spur cell anemia in alcoholic cirrhosis: cure by orthotopic liver transplantation and recurrence after liver graft failure. Int Surg 2002; 87:201.
18. Seppä K, Sillanaukee P, Saarni M. Blood count and hematologic morphology in nonanemic macrocytosis: differences between alcohol abuse and pernicious anemia. Alcohol 1993; 10:343.
19. Liu MX, Wen XY, Leung YK, et al. Hemolytic anemia in alcoholic liver disease: Zieve syndrome: A case report and literature review. Medicine (Baltimore) 2017; 96:e8742.
20. Helander A, Wielders J, Anton R, et al. Standardisation and use of the alcohol biomarker carbohydrate-deficient transferrin (CDT). Clin Chim Acta 2016; 459:19.
21. Cylwik B, Chrostek L, Daniluk M, et al. The assessment of serum soluble transferrin receptor in alcoholics. Clin Exp Med 2010; 10:73.
22. Carmel R, James SJ. Alcohol abuse: an important cause of severe hyperhomocysteinemia. Nutr Rev 2002; 60:215.

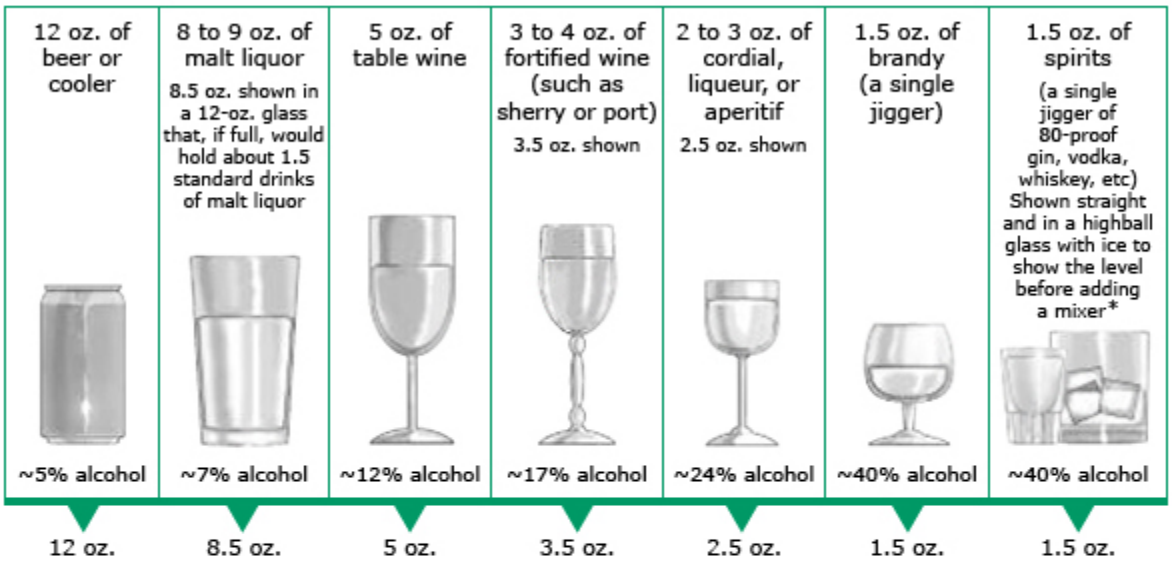
23. Savage DG, Ogundipe A, Allen RH, et al. Etiology and diagnostic evaluation of macrocytosis. Am J Med Sci 2000; 319:343.
24. McCurley TL, Cousar JB, Graber SE, et al. Plasma cell iron--clinical and morphologic features. Am J Clin Pathol 1984; 81:312.
25. Conrad ME, Barton JC. Anemia and iron kinetics in alcoholism. Semin Hematol 1980; 17:149.
26. Nakao S, Harada M, Kondo K, et al. Reversible bone marrow hypoplasia induced by alcohol. Am J Hematol 1991; 37:120.
27. Miller JB, Figueroa EJ, Haug RM, Shah NL. Thrombocytopenia in Chronic Liver Disease and the Role of Thrombopoietin Agonists. Gastroenterol Hepatol (N Y) 2019; 15:326.
28. Haselager EM, Vreeken J. Rebound thrombocytosis after alcohol abuse: a possible factor in the pathogenesis of thromboembolic disease. Lancet 1977; 1:774.
29. Lieb M, Palm U, Hock B, et al. Effects of alcohol consumption on iron metabolism. Am J Drug Alcohol Abuse 2011; 37:68.
30. Tavill AS, Qadri AM. Alcohol and iron. Semin Liver Dis 2004; 24:317.
31. Fletcher LM, Bridle KR, Crawford DH. Effect of alcohol on iron storage diseases of the liver. Best Pract Res Clin Gastroenterol 2003; 17:663.

Topic 7151 Version 33.0

GRAPHICS

What is a standard drink?

A standard drink in the United States is any drink that contains about 14 grams of pure alcohol (about 0.6 fluid ounces or 1.2 tablespoons). Below are US standard drink equivalents. These are approximate, since different brands and types of beverages vary in their actual alcohol content.



Many people don't know what counts as a standard drink and so they don't realize how many standard drinks are in the containers in which these drinks are often sold. Some examples:

- For **beer**, the approximate number of standard drinks in:
  - 12 oz. = 1
  - 16 oz. = 1.3
  - 22 oz. = 2
  - 40 oz. = 3.3
- For **malt liquor**, the approximate number of standard drinks in:
  - 12 oz. = 1.5
  - 16 oz. = 2
  - 22 oz. = 2.5
  - 40 oz. = 4.5
- For **table wine**, the approximate number of standard drinks in:
  - a standard 750-mL (25-oz.) bottle = 5
- For **80-proof spirits**, or "hard liquor," the approximate number of standard drinks in:
  - a mixed drink = 1 or more*
  - a pint (16 oz.) = 11
  - a fifth (25 oz.) = 17
  - 1.75 L (59 oz.) = 39

US: United States; oz.: ounces.

* It can be difficult to estimate the number of standard drinks in a single mixed drink made with hard liquor. Depending on factors such as the type of spirits and the recipe, a mixed drink can contain from 1 to 3 or more standard drinks.

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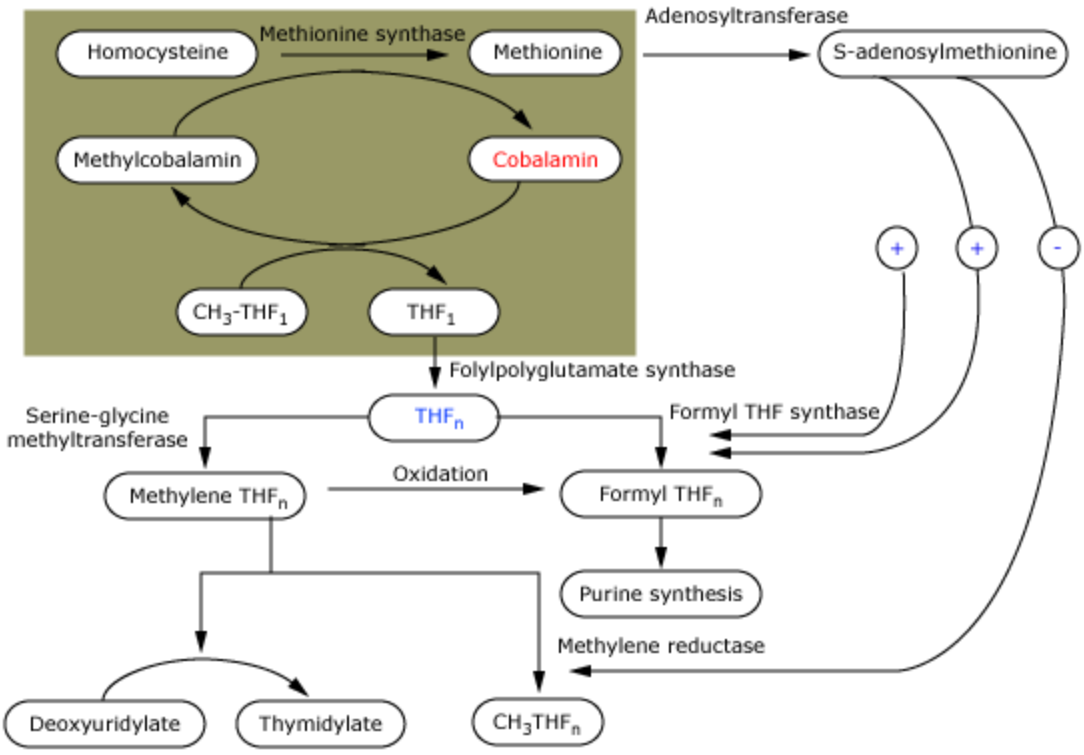
Graphic 56818 Version 5.0

Effects of cobalamin and folic acid on DNA synthesis



Interdependent cofactor activity of cobalamin and folate in intracellular DNA synthesis and metabolism. The + signs indicate enhancement, and the - signs indicate inhibition. Demethylation of methyl-tetrahydrofolate (CH3-THF) to THF is a critical step in DNA synthesis because THF is the substrate for the enzyme that converts (THF)-1 to the polyglutamated form (THF)n. Only polyglutamated (THF)n participates in purine synthesis.

CH3-THF: methyl-tetrahydrofolate.

Reproduced with permission from Tefferi, A, Pruthi, RK. The Biochemical Basis of Cobalamin Deficiency. Mayo Clin Proc 1994; 69:181

Graphic 79271 Version 3.0

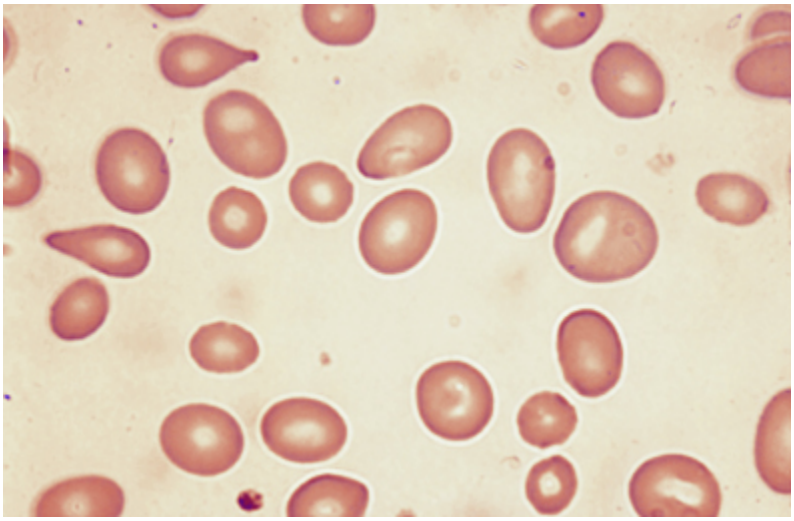
Causes and mechanisms of macrocytosis

Abnormalities of DNA metabolism
Vitamin B12 (cobalamin) deficiency
Folate deficiency
Drugs

Antiretroviral therapies for HIV infection (eg, zidovudine)
Azathioprine or 6-mercaptopurine
Capecitabine
Cladribine
Cytosine arabinoside
Hydroxyurea
Imatinib, sunitinib
Methotrexate
Shift to immature or stressed red cells
Reticulocytosis
Action of erythropoietin - skip macrocytes, stress erythrocytosis
Aplastic anemia/Fanconi anemia
Pure red cell aplasia
Primary bone marrow disorders
Myelodysplastic syndromes
Congenital dyserythropoietic anemias
Some sideroblastic anemias
Large granular lymphocyte (LGL) leukemia
Lipid abnormalities
Liver disease
Hypothyroidism
Mechanism unknown
Alcohol abuse
Multiple myeloma and other plasma cell disorders

Graphic 66772 Version 3.0

Macro-ovalocytes in vitamin B12 deficiency

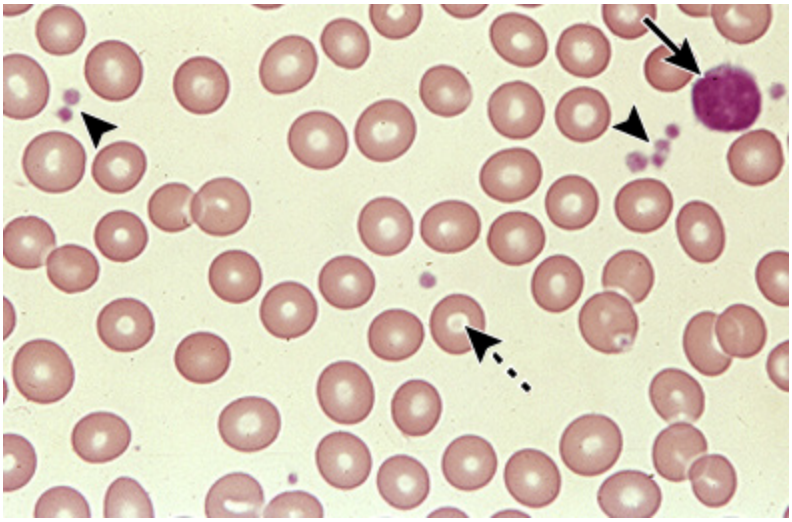


Peripheral smear shows marked macro-ovalocytosis in a patient with vitamin B12 deficiency. In this case, teardrop cells are an advanced form of macro-ovalocytes.

Courtesy of Stanley L Schrier, MD.

Graphic 74901 Version 6.0

Normal peripheral blood smear

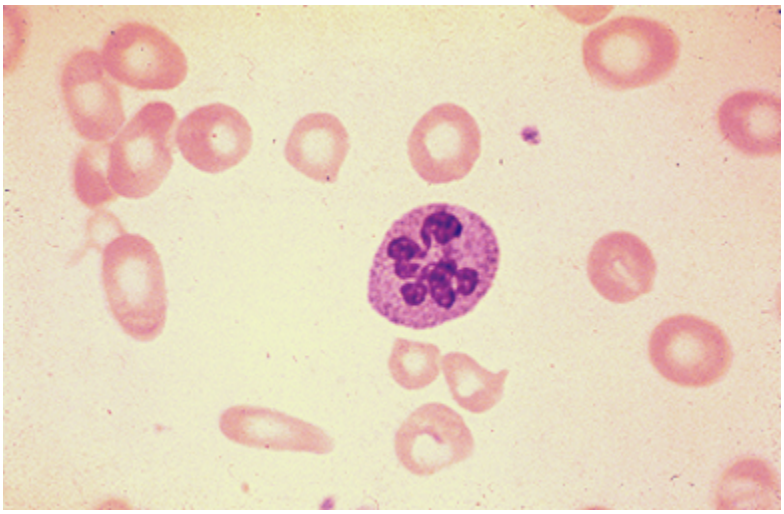


High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Peripheral blood smear showing megaloblastic changes

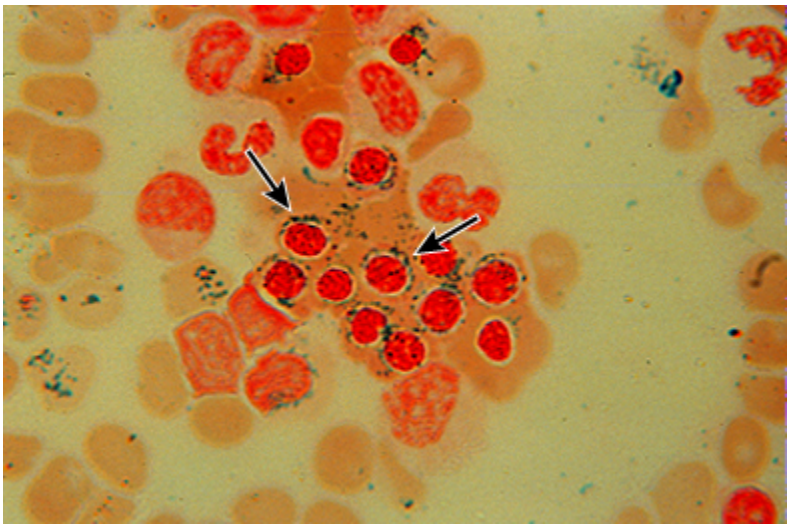


Peripheral blood smear showing a hypersegmented neutrophil (seven lobes) and macroovalocytes, a pattern that can be seen with vitamin B12 (cobalamin) or folate deficiency.

Courtesy of Stanley L Schrier, MD.

Graphic 58820 Version 5.0

Ring sideroblasts in refractory anemia with ring sideroblasts (RARS)



Prussian blue stain of the bone marrow in a patient with refractory anemia and ring sideroblasts (RARS). Blue-stained ferritin iron deposits in the mitochondria of erythroid precursors form an apparent ring around the nucleus (arrows).

Courtesy of Stanley L Schrier, MD.

Graphic 65887 Version 6.0

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