BMJ Best Practice

Folate deficiency

Straight to the point of care

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Summary

Folate deficiency classically presents as megaloblastic anaemia, with absence of neurological signs.

Common causes include malabsorption, drugs and toxins, states of increased demand, and dietary deficiency. Hereditary folate malabsorption and other inborn errors of folate metabolism are rare causes.

In early disease, haemoglobin and mean corpuscular volume are normal. In severe disease, patients present with symptomatic anaemia and pancytopenia.

Maternal folate deficiency is associated with fetal neural tube defects (NTDs).

Diagnosis is confirmed by the presence of low serum folate and/or low red blood cell folate. Elevated plasma homocysteine levels are helpful in situations of diagnostic difficulty.

Vitamin B12 (cobalamin) deficiency must be ruled out before initiating folic acid therapy, as the therapy may mask neurological manifestations of underlying vitamin B12 deficiency.

Oral folic acid is usually considered sufficient therapy. Underlying cause should be identified and treated.

Food fortification programmes instituted in some countries have decreased the incidence of folate deficiency and associated anaemia and fetal NTDs.

Definition

Megaloblastic anaemia without neuropathy is the classic manifestation of folate deficiency.[1]

Folate, also known as vitamin B9, is present in green vegetables, legumes, and some fruits.

Deficiency arises due to malabsorption, drugs and toxins, increased demand, or dietary deficiency.

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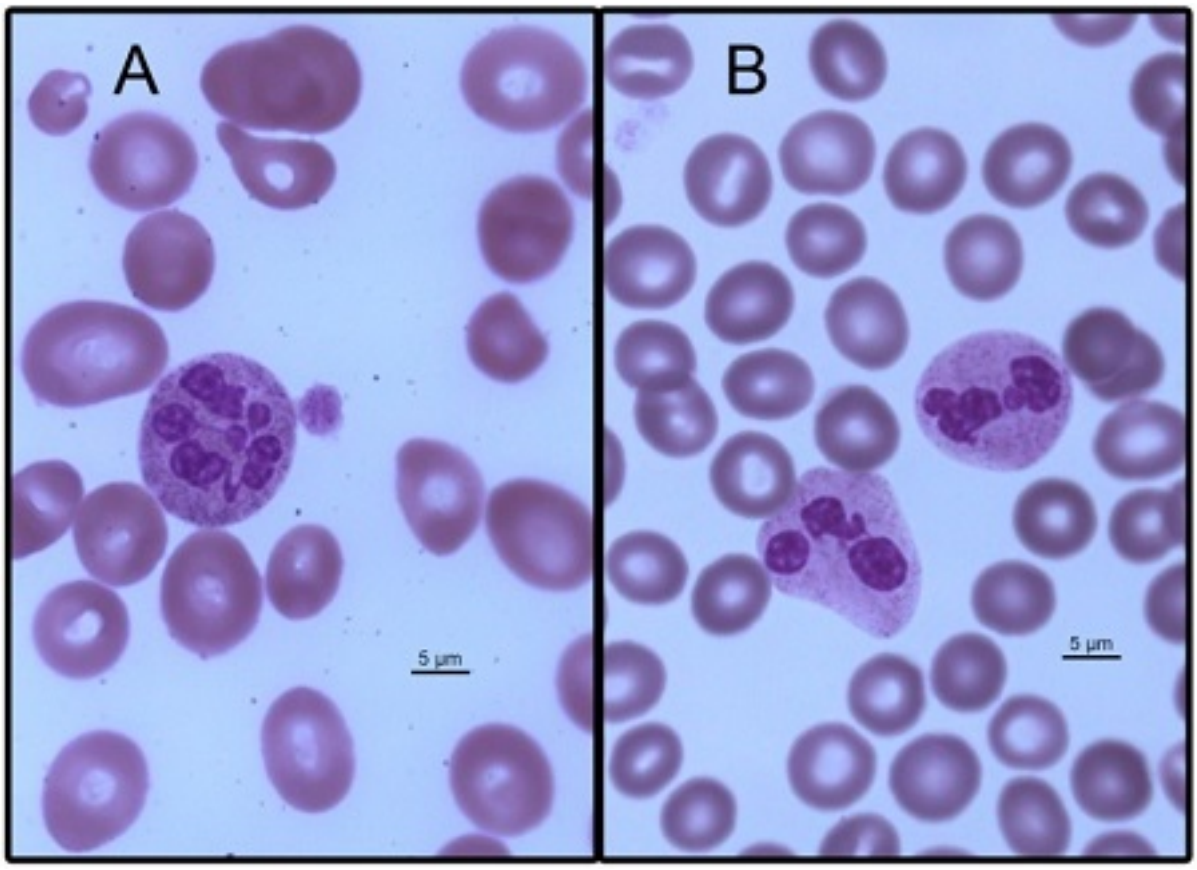

Megaloblastic macrocytic anemia: A. Peripheral blood smear of a patient with megaloblastic anemia. B. Peripheral blood smear of healthy individual

Photomicrograph from Mark J. Koury, MD; used with permission

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Epidemiology

The prevalence and the magnitude of folate deficiency across the world are variable. The condition occurs commonly in countries without folic acid fortification of cereal-grain products, and rarely in countries with folic acid fortification.[3] [4] [5]

Several national surveys have shown that folate deficiency can be a public health problem in the absence of fortification. The primary age groups affected include pre-school children (33.8% of the folate-deficient population in Venezuela), pregnant women (48.8% in Costa Rica and 25.5% in Venezuela), and older people (15% in the UK).[3] One large review of global folate deficiency in women of reproductive age, who are at increased risk of neural tube defect-affected pregnancies when maternal folate levels are low, reported folate deficiency <5% in higher-income countries and >20% in many low-income countries.[5]

Mandatory folic acid fortification of enriched cereal-grain products was initiated in the US in 1996 and Canada in 1998. Subsequently, surveys of regional and nationally representative populations have shown that serum and red blood cell folate concentrations have increased in the general population in these countries.[6] [7]

Aetiology

Folate is present in dietary sources such as green leafy vegetables, legumes, and fruits. In addition, it is present in synthetic form, as folic acid, in fortified cereal-grain products. Folate is also known as vitamin B9.

Folate intake can be inadequate for various reasons:[8] [9]

- Consumption of unfortified cereals (e.g., rice or wheat) as a staple diet by certain populations
- Excessive cooking, destroying folate, in green vegetables and legumes
- Poor dietary intake by older people
- Intake of special diets that are low in folate by patients with certain medical conditions, such as phenylketonuria
- Goats' milk, which is almost completely deficient in folate, being given exclusively to infants.

Intestinal malabsorption of folate occurs in disorders of the small intestine, such as tropical sprue and coeliac disease (non-tropical sprue), and after extensive intestinal resection.

Increased demand in pregnancy, lactation, and prematurity can lead to folate deficiency.

Increased loss of folate occurs in patients undergoing chronic dialysis, and decreased folate is seen in disorders of increased cell turnover, such as chronic haemolytic disease and exfoliative dermatitis.

Medications including sulfasalazine, trimethoprim, methotrexate, pyrimethamine, and anticonvulsants (e.g., phenytoin, phenobarbital) can cause folate deficiency. Folate deficiency in alcohol-use disorder is caused by multiple mechanisms.

Hereditary folate malabsorption and other inborn errors of folate metabolism are rare causes of folate deficiency.[10] Polymorphisms of the enzyme methylenetetrahydrofolate reductase can cause mildly reduced folate levels and mild hyperhomocysteinaemia.

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THEORY

Pathophysiology

Natural dietary folates are present as polyglutamates. The main dietary sources of folate are green leafy vegetables, legumes, some fruits, and fortified cereals.

Folate deficiency affects all rapidly dividing cells. Owing to significant folate catabolism and small losses through excretion from the urine, skin, and bile, body folate must be replenished from the diet. Humans cannot synthesise folate de novo.

Most dietary folate is metabolised to 5-methyl-tetrahydrofolate (5-methyl-THF) when it crosses the intestinal mucosa. When 5-methyl-THF enters the cells in the body, it is catalysed to tetrahydrofolate by the vitamin B12-dependent enzyme methionine synthase. THF is then polyglutamated (by the enzyme folylpolyglutamate synthetase) and retained in the cell.

Folate, in its reduced form tetrahydrofolate, is a 1-carbon transporter that serves as an essential co-enzyme for three key intracellular processes involved in cell viability and growth: DNA synthesis and repair, methylation reactions, and dihydronicotinamide adenine dinucleotide phosphate (NADPH) generation.[11] [12]

Folate is essential for the de novo synthesis of purines and thymidylate.[13] Folate deficiency impairs DNA synthesis and repair, which retards cell division and leads to apoptosis of haematopoietic cells in the marrow.[14] The loss of erythropoietic cells causes anaemia. More severe folate deficiency can cause thrombocytopenia and neutropenia subsequent to precursor cell death. Marrow cells that have impaired DNA synthesis, but do not undergo apoptosis, have prolonged cell cycle durations, and relatively increased protein accumulation during the protracted cell cycle, which results in macrocytosis.[14]

Both folate and vitamin B12 (cobalamin) are cofactors in methylation of homocysteine to form methionine; therefore, deficiency of either vitamin increases homocysteine (a biomarker of folate deficiency). Methyl-THF supplies the methyl group for the formation of methyl-cobalamin, which methylates homocysteine, regenerating methionine - an essential amino acid. NADPH reduces glutathione, which mitigates oxidative stress in rapidly dividing cells.

Neural tube defects

Folate is required for normal development of the central nervous system (CNS). The finding of low folate status in women who had children with neural tube defects (NTDs), and the prevention of recurrent NTDs with folic acid supplementation, led to clinical trials demonstrating that folic acid supplements before and during pregnancy prevented some NTDs.[15] NTDs commonly associated with maternal folate deficiency include anencephaly and spina bifida.

NTDs are thought to result from a combination of genetic predisposition and environmental factors that cause failure of neural tube closure during embryogenesis, which occurs at days 21 to 28 post-conception.[16] [17] The role of folate in neural tube development has not been fully elucidated, but decreased methylation of DNA, causing variation in gene expression, may play a role.[18]

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Case history

Case history #1

A 70-year-old man presents for a routine physical examination. He complains of fatigue, shortness of breath, and painful swallowing. He admits to daily alcohol consumption and decreased consumption of fresh vegetables and fruits. Physical examination reveals pallor, glossitis, flow murmur, and normal neurological examination.

Other presentations

Sub-clinical folate deficiency can manifest as macrocytosis without severe anaemia. Unexplained elevation of mean corpuscular volume should trigger testing for folate deficiency, in addition to work-up for other causes of macrocytosis.[2]

Certain physiological or disease states that cause dietary insufficiency, malabsorption, and increased demand are associated with a high risk for folate deficiency. Awareness of the various causes, and vigilance for the haematological findings, can lead to early recognition and treatment of folate deficiency.

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Approach

Folate deficiency in the classic form presents as anaemia with decreased reticulocyte numbers and oval macrocytosis (mean corpuscular volume [MCV] >100 femtolitres). Severe folate deficiency can present as pancytopenia (anaemia, neutropenia, and thrombocytopenia).

Neurological signs and symptoms are not typically seen in patients with folate deficiency.

Alternative explanations, such as co-existing vitamin B12 (cobalamin) deficiency, thiamine deficiency, or alcohol-use disorder, should be considered in cases of macrocytic anaemia with neurological signs and symptoms.

Risk groups

Certain patient groups are at increased risk for developing folate deficiency. The following groups should be considered when taking a medical history:

- Low socio-economic groups with poor nutrition
- Older people with poor dietary intake
- People who misuse alcohol (producing a sharp decline in serum folate within a few days)
- Pregnant and lactating women and preterm infants (increased demand)
- People with chronic haemolytic anaemia or chronic exfoliative dermatitis (increased cell turnover increases folate requirement)
- People taking drugs that interfere with folate absorption and metabolism, including sulfasalazine, trimethoprim, pyrimethamine, methotrexate, and anticonvulsants (e.g., phenytoin, phenobarbital)
- People with hereditary folate malabsorption and inborn errors of folate metabolism, often manifesting in early life
- People with chronic diarrhoeal states and other intestinal disorders (can cause poor absorption of folate)
- Chronic dialysis patients (folate is water soluble and lost in the dialysis fluid)
- Infants who are fed goats' milk exclusively, and children with inborn errors of metabolism given a synthetic diet.

Symptoms and signs

Megaloblastic anaemia is the hallmark of folate deficiency.

Severe folate deficiency presents as symptomatic macrocytic anaemia and pancytopenia; non-severe folate deficiency includes signs of macrocytosis without anaemia.

Symptomatic inquiry should cover symptoms associated with anaemia, including fatigue, palpitations, shortness of breath, dizziness, headaches, jaundice, loss of appetite, and weight loss. Patients may complain of painful swallowing, inflammation of the tongue (glossitis), and discomfort at the corners of the mouth (angular stomatitis) in severe folate deficiency.

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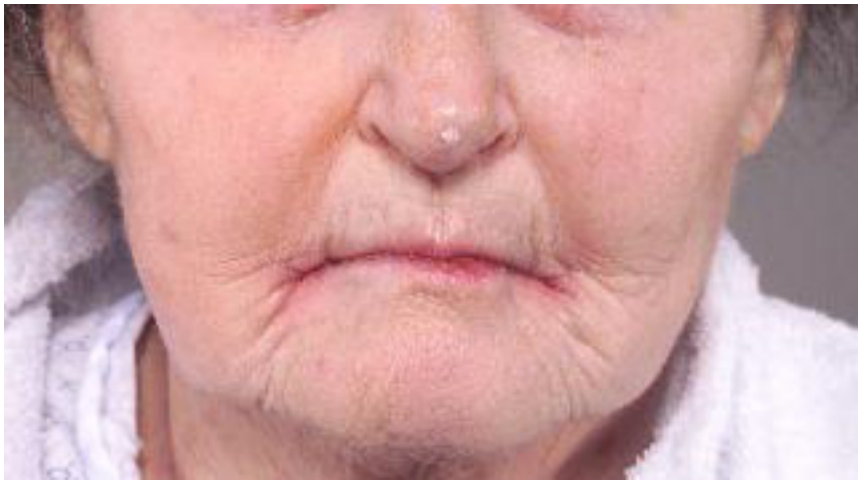

Angular cheilitis

From the collection of Dr Wanda C. Gonsalves; patient consent obtained

Symptoms of underlying disease should also be elucidated, such as chronic diarrhoea and weight loss, or failure to thrive in intestinal disorders.

A complete physical examination should be performed, to look for signs of anaemia (pallor, tachycardia, tachypnoea, heart murmurs, signs of heart failure, jaundice) and underlying disease (e.g., signs of chronic alcohol misuse, haemolytic anaemia, exfoliative dermatitis). Petechiae may be present in those with thrombocytopenia.

Neurological dysfunction, although rarely reported, is not typically present. The exceptions are children with inborn errors of folate absorption and metabolism, who often have severe myelopathy and neurological dysfunction.

Initial tests

All patients with suspected folate deficiency should have a full blood count with peripheral blood smear and reticulocyte count.

Haematological findings

- In the classic case of severe folate deficiency, the patient presents with severe anaemia, oval macrocytosis (MCV >100 femtolitres), and elevated mean corpuscular haemoglobin. Corrected reticulocyte counts are decreased. As anaemia advances, poikilocytes and teardrop cells appear. In extremely severe anaemia, receding macrocytosis has been reported, a probable effect of poikilocytosis and red blood cell (RBC) fragmentation.[40]
- Classic findings may not always be present, or may be altered:
    - In early folate deficiency states, the haemoglobin and MCV are normal. As the deficiency progresses, there is an increase in MCV, followed by reduced haemoglobin.
    - Macrocytosis can be masked by co-existing iron deficiency or thalassaemia. Iron studies may not reveal deficiency initially; the true iron status becomes evident several days after initiating folic acid therapy.
    - Transfusion of infants with pancytopenia can lead to neutropenia and thrombocytopenia as the only haematological features.

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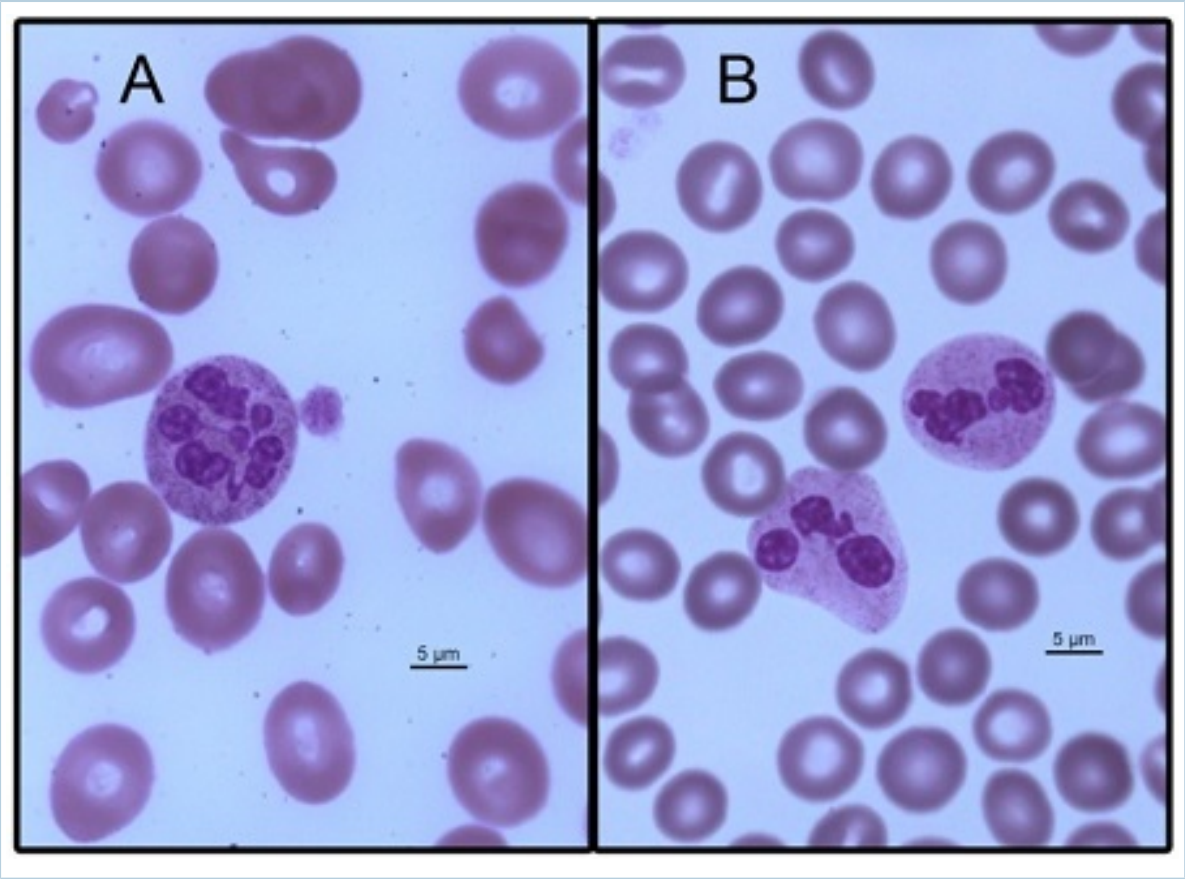
- The presence of hypersegmented neutrophils is a characteristic feature of folate deficiency. It is defined as the presence of 5 lobes in >5% of neutrophils, or the presence of one or more neutrophils with 6 or more lobes. Hypersegmentation often precedes anaemia, but is not found in sub-clinical vitamin deficiencies. It can also be present in patients receiving medications that inhibit DNA synthesis (e.g., 5-fluorouracil, hydroxyurea) and, rarely, in patients with myelofibrosis, chronic myelogenous leukemia, or a benign hereditary condition.



Megaloblastic macrocytic anaemia: A. Peripheral blood smear of a patient with megaloblastic anaemia. B. Peripheral blood smear of healthy individual
Photomicrograph from Mark J. Koury, MD; used with permission

- Neutropenia and thrombocytopenia are present in advanced folate deficiency.

Confirmatory tests

As the initial screen, measuring serum folate level is recommended in suspected folate deficiency.

Serum folate depends on intake, and falls rapidly into the deficient range during deprivation.[1] [54] Approximately 5% of patients who have folate deficiency will have normal serum folate levels.[55] [56] The RBC folate level decreases more slowly during the 3- to 4-month turnover period of RBCs. Although RBC folate may be a better indicator of tissue folate levels, the assay is complex and more expensive than serum folate assessment. RBC folate level can be low in vitamin B12 deficiency.

Serum folate <7 nanomol/L (<3 nanograms/mL) indicates folate deficiency and often leads to morphological features (megaloblastic changes in bone marrow and macrocytic anaemia).[55] A folate level between 7 nanomol/L and 11 nanomol/L (3 nanograms/mL and 5 nanograms/mL) can cause metabolic changes (elevated plasma homocysteine), and therefore is suspicious for folate deficiency.

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When serum folate levels are normal or borderline, in the presence of a strong clinical suspicion, RBC folate (lower limit of normal: <317 nanomol/L [<140 nanograms/mL]) and plasma homocysteine levels (>15 micromol/L; may be indicative of folate deficiency) can be obtained to aid diagnosis.[55] [57]

False-negative serum folate test results can be found after recent folate intake. False-positive low serum folate test results may be found in patients with anorexia, alcohol consumption, normal pregnancy, and in patients on anticonvulsant medications.[57]

Contributory tests

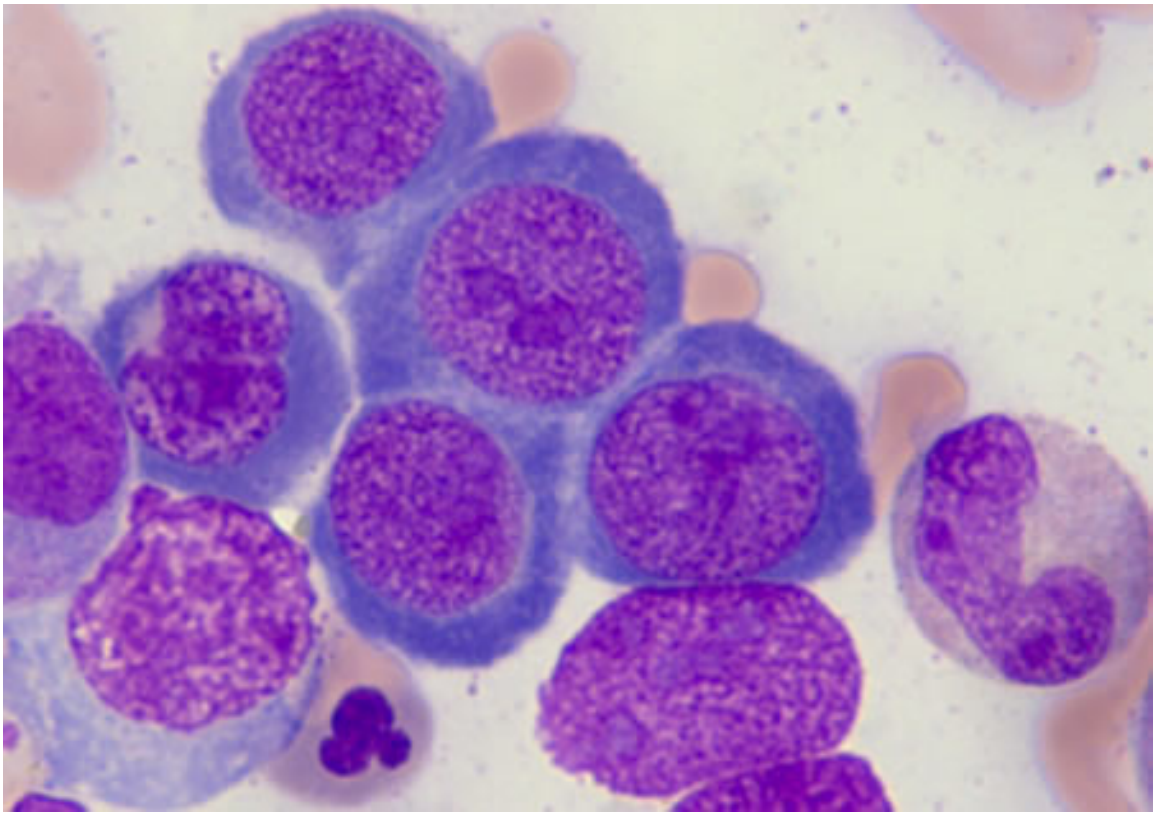
Further testing should include bilirubin, liver function tests, lactate dehydrogenase (LDH), haptoglobin, and serum iron studies.

Biochemical tests

- The laboratory signs of ineffective erythropoiesis and haemolysis co-exist with macrocytosis and anaemia; these include elevated LDH, increased unconjugated bilirubin, and low haptoglobin. Serum iron, ferritin, and transferrin receptor levels are elevated.[40]

Bone marrow aspirate and biopsy

- Examination of bone marrow shows megaloblastic erythropoiesis. The morphological hallmark of megaloblastic anaemia are erythroblasts that are larger than expected based on cytoplasmic appearance, with large, uncondensed nuclei. Late-stage erythroblasts may have lobulated nuclei. Giant band cells and metamyelocytes are seen.



Megaloblastic marrow cells

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- Bone marrow examination is not necessary to confirm the diagnosis of folate deficiency, although it can be used to exclude important causes of macrocytic anaemia and pancytopenia, such as myelodysplasia or aplastic anaemia.

Differential diagnosis

Underlying vitamin B12 deficiency should be ruled out before implementing therapy with folic acid, because such therapy may mask neurological complications of untreated vitamin B12 deficiency. However, it is important to note that vitamin B12 deficiency and folate deficiency can co-exist in certain patients.

Vitamin B12 deficiency can cause megaloblastic anaemia with similar symptoms and signs as those of folate deficiency.[8] Neurological signs are, however, absent in folate deficiency (with the exception of children with inborn errors of folate absorption and metabolism, or those who have experienced severe antenatal folate deficiency).

Plasma or serum methylmalonic acid levels rise in vitamin B12 deficiency but are normal in folate deficiency. Homocysteine levels rise in both vitamin B12 deficiency and folate deficiency.[58] [59] Levels of methylmalonic acid and homocysteine can be affected by renal function.

Evaluating underlying aetiology

Once folate deficiency is diagnosed, recognition of the underlying precipitating cause is important to prevent ongoing folate deficiency states.

History and exam

Key diagnostic factors

presence of risk factors (common)

- Key risk factors are low dietary folate intake; age >65 years; alcohol-use disorder; pregnancy or lactation; prematurity; intestinal malabsorption disorders; use of trimethoprim, methotrexate, anticonvulsants, sulfasalazine, or pyrimethamine; infantile intake of goats' milk; and congenital defects in folate absorption and metabolism.

Other diagnostic factors

prolonged diarrhoea (common)

- Chronic diarrhoeal states (such as tropical sprue and coeliac disease [non-tropical sprue]) and inflammatory bowel disease lead to poor absorption of folate.

loss of appetite and weight loss (common)

- Symptom of megaloblastic anaemia, the hallmark of folate deficiency. Weight loss is an objective vital sign in megaloblastic anaemia that results from both loss of appetite and increased energy demands of ineffective erythropoiesis.

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fatigue (common)

- Symptom of megaloblastic anaemia, the hallmark of folate deficiency.

shortness of breath (common)

- Symptom of megaloblastic anaemia, the hallmark of folate deficiency.

dizziness (common)

- Symptom of megaloblastic anaemia, the hallmark of folate deficiency.

pallor (common)

- Megaloblastic anaemia, the hallmark of folate deficiency, can present as pallor.

headache (common)

- Symptom of megaloblastic anaemia, the hallmark of folate deficiency.

tachycardia (common)

- Can be a finding of anaemia.

tachypnoea (common)

- Can be a finding of anaemia.

heart murmur (common)

- Can be a finding of anaemia.

signs of heart failure (common)

- Can be a finding of anaemia. Signs include displaced apical impulse, gallop rhythm, and elevated jugular venous pressure.

signs of chronic alcohol misuse (common)

- Examination may reveal signs of underlying disease associated with folate deficiency.

signs of haemolytic anaemia (common)

- Examination may reveal signs of underlying disease (including pallor, jaundice, systolic flow murmur, hepatosplenomegaly) associated with folate deficiency, but related to increased cell turnover.

signs of exfoliative dermatitis (common)

- Examination may reveal signs of underlying disease, mainly exfoliation of skin, associated with folate deficiency.

painful swallowing (uncommon)

- Severe deficiency can cause inflammation of the oral mucosa, which results in painful swallowing.

petechiae (uncommon)

- Advanced deficiency can cause thrombocytopenia, which can result in development of petechiae.

glossitis (uncommon)

- Severe deficiency can cause glossitis; vitamin B12 (cobalamin) deficiency can also cause this problem.

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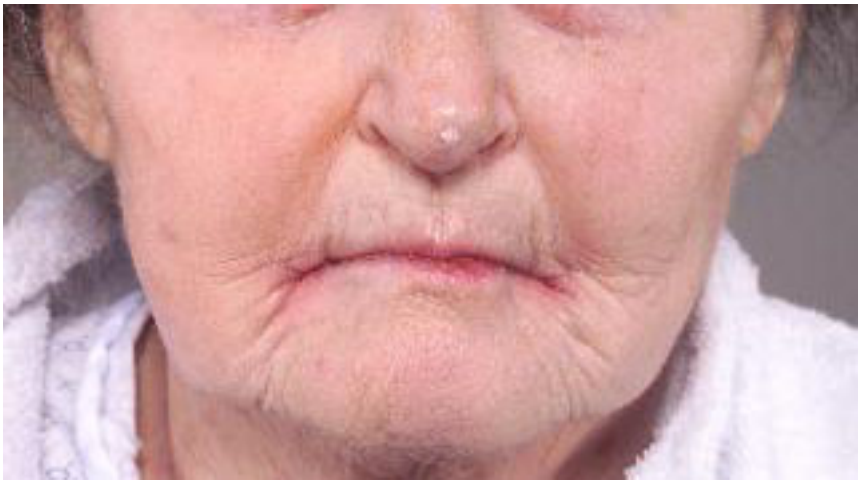
angular stomatitis (uncommon)

- Severe deficiency can cause angular stomatitis; other vitamin deficiency states can also produce the same picture.



Angular cheilitis

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neurological deficits in children (uncommon)

- Neurological signs and symptoms are not typically seen in patients with folate deficiency. Exceptions are children with inborn errors of folate absorption and metabolism, or those who have experienced severe antenatal folate deficiency, who often have severe myelopathy and neurological dysfunction.
- Manifestations in the central nervous system are likely to be explained by the involvement of folate in the synthesis of methionine and S-adenosylmethionine, which are essential for normal development of the central nervous system. Vitamin B12 (cobalamin) deficiency may present as megaloblastic anaemia with neurological findings.

DIAGNOSIS

Risk factors

Strong

low dietary folate intake

- Low dietary folate intake was the most common cause of folate deficiency until fortification of cereal-grain products with folic acid began in the late 1990s in the US (Food and Drug Administration, 1996), Canada, and parts of South America.
- Countries with folic acid fortification have increased the folate levels in the general population, and reduced the incidence of neural tube defects (NTDs) and related neural malformations in neonates.[7] [19] [20] The increase in folate levels in the US general population has resulted in low dietary intake becoming an extremely rare cause of folate deficiency anaemia.[21]
- In low- and middle-income countries, folate fortification has increased serum/plasma folate levels and, among women of reproductive age, reduced the prevalence of folate deficiency and pregnancies with NTDs.[22]
- In countries without folic acid fortification, the potential persists for a significant percentage of the population to be folate deficient. In these countries, folate intake can be poor in the lower socio-economic groups, in vulnerable populations such as pregnant women, and in populations who rely on

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unfortified cereals (e.g., wheat and rice) with low consumption of green vegetables and legumes.[4] [23]

- The recommended intake of folate by adults is based on the amount required to normalise red blood cell folate, which in turn maintains normal levels of serum folate and plasma homocysteine. The recommended dietary allowance for folate increases from 150 micrograms/day at age 1 year, to 200-400 micrograms/day in adults.[24] [25] [US Department of Agriculture and US Department of Health and Human Services: dietary guidelines for Americans, 2020-2025] (https://www.dietaryguidelines.gov) [NIH: dietary supplement fact sheet - folate] (https://ods.od.nih.gov/factsheets/Folate-HealthProfessional)

age >65 years

- Poor intake of foods rich in folate can lead to folate deficiency in older people. In the pre-fortification era in the US, older people formed 10.8% of the folate-deficient population.[3]

alcohol-use disorder

- Most people consuming >80 g ethanol per day (about 1.5 litres of beer, 750 mL of wine, or 6 servings of distilled ethanol at 14 g/serving) have been found to be folate-deficient in the pre-fortification era.[26]
- Folate deficiency in people with alcohol-use disorder is rare in the US post-fortification.[27]
- Folate deficiency in chronic alcohol-use disorder is caused by multiple mechanisms, including low intake, poor absorption, reduced enterohepatic circulation and storage in the liver, and increased urinary excretion.[9]

pregnant or lactating

- Pregnant and lactating women have an increased folate demand, which can result in folate deficiency. In lactating women, breast milk concentrations of folate are maintained but at the expense of maternal folate status.[28]
- Folate deficiency during pregnancy is strongly associated with fetal neural tube defects, 70% of which can be prevented by increased folic acid supplementation.[29] [30] [31]
- Women who are planning to conceive or who are capable of becoming pregnant should receive pre-conception folic acid supplementation at a dose of 400-800 micrograms/day, with higher doses (up to 5 mg/day) recommended for certain risk groups.[32] [33] [34] The UK National Institute for Health and Care Excellence recommends 5 mg/day in certain risk groups.[35] [36]
- In the US, the recommended dietary allowance for folate during pregnancy and lactation varies from 400-800 micrograms/day depending upon factors such as diet, inclusion of food fortified with folic acid, socio-economic status, and individual medical history. [US Department of Agriculture and US Department of Health and Human Services: dietary guidelines for Americans, 2020-2025] (https://www.dietaryguidelines.gov) [NIH: dietary supplement fact sheet - folate] (https://ods.od.nih.gov/factsheets/Folate-HealthProfessional)

prematurity

- Red blood cell folate concentrations fall significantly in the first 2 to 3 months in preterm infants, whether breastfed or formula-fed.[37] Routine supplementation of folic acid for preterm infants is required.[38]
- Folate levels are adequate in preterm infants fed modern formulas enriched with folic acid and in breastfed infants given folic acid supplements.[39]

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intestinal malabsorptive disorders

- Chronic diarrhoeal states (e.g., coeliac disease [non-tropical sprue], tropical sprue, and inflammatory bowel disease), other intestinal disorders (e.g., malignant infiltration, amyloidosis, Whipple's disease, and scleroderma), and extensive resection of the small intestine can lead to poor absorption of folate.[40]
- In the post-fortification era in the US, folate deficiency was found in 3.6% of newly diagnosed cases of coeliac disease compared with 0.3% of age-matched controls.[41]

use of trimethoprim, methotrexate, sulfasalazine, pyrimethamine, or anticonvulsants (e.g., phenytoin, phenobarbital)

- These drugs interfere with folate function or absorption by inhibiting enzymes in folate metabolism, and by other unknown mechanisms.[42]

infantile intake of goats' milk

- Goats' milk is almost completely deficient in folate. Exclusive intake in infants can cause folate deficiency.

congenital defects in folate absorption and metabolism

- Rare but potentially life-threatening. Defects include hereditary folate malabsorption, methylenetetrahydrofolate reductase deficiency, glutamate formiminotransferase deficiency, and functional methionine synthase deficiency.
- Presentation is often during infancy, with varying combinations of megaloblastic anaemia, failure to thrive, chronic diarrhoea, neurological deficits, and developmental delay.[10]

Weak

states of increased cell turnover

- Increased desquamation of cells in exfoliative dermatitis, and increased cell turnover in chronic haemolytic anaemias, can cause folate deficiency.

intake of special diet

- Patients with inborn errors of metabolism, such as phenylketonuria, who are on special diets that lack folate, may develop folate deficiency.

chronic dialysis

- Folate is lost during dialysis, and folic acid supplements are generally used in chronic dialysis.

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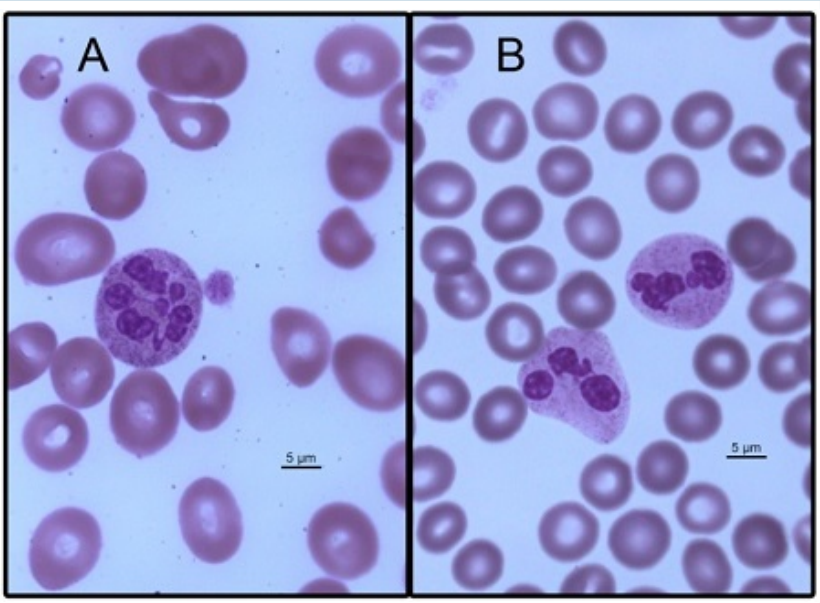
Investigations

1st test to order

Test	Result
peripheral blood smear • Macrocytic anaemia and hypersegmented neutrophils are classically seen in folate and vitamin B12 (cobalamin) deficiencies. Macrocytes are seen in early folate deficiency, but they can also be present in other conditions.  *Megaloblastic macrocytic anaemia: A. Peripheral blood smear of a patient with megaloblastic anaemia. B. Peripheral blood smear of healthy individual* *Photomicrograph from Mark J. Koury, MD; used with permission*	**macrocytosis, anisocytosis, poikilocytosis, hypersegmented neutrophils**
FBC • Elevated mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) can precede anaemia by a few weeks; thrombocytopenia and neutropenia are seen in advanced cases.[40] Can be seen in other conditions. Not useful to rule out folate deficiency.	**low haemoglobin, elevated MCV and MCH; increased MCV and MCH may be absent or less than expected in combined folate and iron deficiency; thrombocytopenia, neutropenia**
reticulocyte count • Low count indicates decreased production. Can be present in other deficiency states or marrow failure disorders.	**low corrected reticulocyte count**

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Other tests to consider

Test	Result
serum folate • Earliest indicator of folate deficiency. Performed as initial screening test. May not detect the 5% of patients who have folate deficiency but normal serum folate levels.[55] [56]	**low**
red blood cell folate • Better indicator of tissue folate status than serum folate.[56] Can help detect the 5% of folate deficient patients with normal serum folate. • May be normal in acute folate deficiency. • Red blood cell folate is low in >50% of patients with vitamin B12 (cobalamin) deficiency. • A more complex and expensive test than serum folate.	**low**
serum vitamin B12 • Extremely important test. • Underlying vitamin B12 (cobalamin) deficiency should be ruled out before implementing therapy with folic acid, because such therapy may mask neurological complications of untreated vitamin B12 deficiency. • Vitamin B12 deficiency and folate deficiency can co-exist in certain patients.	**normal**
serum LDH • Sign of ineffective erythropoiesis, present in advanced anaemia. • Not useful to rule in or rule out folate deficiency.	**elevated**
serum unconjugated bilirubin • Sign of ineffective erythropoiesis, present in advanced anaemia. • Not useful to rule in or rule out folate deficiency.	**elevated**
serum iron panel • Sign of ineffective erythropoiesis. • • Not useful to rule in or rule out folate deficiency.	**elevated serum iron, ferritin, transferrin**
plasma or serum methylmalonic acid • Levels rise in vitamin B12 (cobalamin) deficiency but are normal in folate deficiency.[58] [59] • Level affected by renal function.	**normal**
plasma homocysteine • Useful in borderline folate levels, suspected combined deficiency states, and folate-deficient patients with normal serum folate.[55] • Elevated in >95% of patients with vitamin B12 (cobalamin) deficiency. • Sensitivity is only 86% in detecting clinical folate deficiency states.[58] • Expensive. • Level affected by renal function.	**elevated**
bone marrow aspirate/biopsy • Classic findings in both folate and vitamin B12 (cobalamin) deficiencies. • Not required to confirm diagnosis.	**megaloblastic changes, erythroid hyperplasia, abnormal nuclear appearance**

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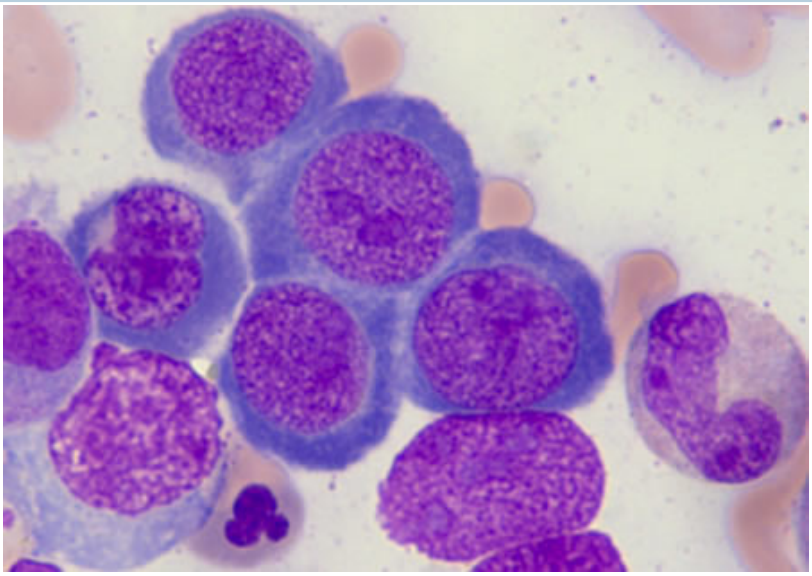
Test	Result
 *Megaloblastic marrow cells* *Photomicrograph from Mark J. Koury, MD; used with permission*	

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Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Vitamin B12 (cobalamin) deficiency	• May be associated with neurological and neuropsychiatric manifestations, specifically: decreased vibration sense, peripheral neuropathy, gait abnormalities, dementia, depression, and visual impairment. • Clinical and haematological response to treatment confirms diagnosis.	• Serum vitamin B12 levels are low. • Both homocysteine and methylmalonic acid are elevated.
Thiamine-responsive megaloblastic anaemia	• Diabetes mellitus and sensorineural deafness are present, in addition to megaloblastic anaemia. • Megaloblastic anaemia and diabetes mellitus respond partially to thiamine therapy.	• Ringed sideroblasts are seen in the bone marrow. • Serum folate level is normal.
Hereditary orotic aciduria	• Growth retardation, neurological abnormalities, and obstructive uropathy are associated with hypochromic megaloblastic anaemia, with or without congenital malformations and immune deficiency. • Replacement of uridine corrects anaemia, reduces orotic crystalluria, and improves other sequelae.	• Orotic acid crystalluria is present. • Serum folate level is normal.
Alcoholic liver disease	• Nutritional deficiencies and macrocytic anaemia may be the presenting features. History reveals alcohol misuse.	• Elevated liver enzymes. • Liver biopsy shows fatty liver, inflammation, and/or cirrhosis.
Hypothyroidism	• Constipation, weight gain, cold intolerance, hoarse voice, bradycardia, dry/rough skin, delayed tendon reflexes.	• Elevated thyroid-stimulating hormone, low T4, and low T3. • Serum folate level is normal. Homocysteine levels are often elevated.[60]
Myelodysplastic syndrome	• Gradual-onset fatigue often present, and 20% of patients have splenomegaly.	• Macrocytic anaemia may be associated with neutropenia and thrombocytopenia. • Peripheral smear findings include dimorphic anaemia;

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Condition	Differentiating signs / symptoms	Differentiating tests
	• May be associated with prior chemotherapy or radiation exposure.	large, hypogranular platelets; hypogranulated, hyposegmented neutrophils with Dohle bodies; and circulating myeloblasts. • Bone marrow shows dyserythropoiesis; hypogranulated, hyposegmented granulocytic precursors; increased myeloblasts; and megakaryocytes showing fewer or disorganised nuclei. Ringed sideroblasts are seen in the bone marrow in certain sub-types of myelodysplastic syndrome. • Cytogenetic analysis and fluorescence in-situ hybridisation can identify specific chromosomal abnormalities. • Mutations in specific genes are associated with myelodysplasia.
Aplastic anaemia	• History of prior viral illness, chemical exposure, or drug use may be present. • Bleeding, lassitude, and symptoms of infection are usually present. Ecchymosis and signs of infection may be present, in addition to pallor.	• Macrocytic anaemia, neutropenia, thrombocytopenia, and reticulocytopenia are present. Absence of glycosylphosphatidylinositol-anchored proteins, when associated with paroxysmal nocturnal haemoglobinuria. • Bone marrow aspirate and biopsy show decreased cellularity and paucity of all three lineage precursors.
Pure red blood cell aplasia	• If in infancy, family history may be present. • May be associated with abnormal phenotype, and with signs and symptoms related to cardiovascular and renal anomalies.	• Macrocytic anaemia and reticulocytopenia are the hallmarks. • Elevated erythrocyte adenosine deaminase is present in 70% to 80% of patients. Ribosomal protein genes and GATA1 mutations in Diamond-Blackfan anaemia. • Bone marrow examination shows isolated red blood cell hypoplasia or aplasia. Other cell lines are generally uninvolved.

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Condition	Differentiating signs / symptoms	Differentiating tests
Drug-induced macrocytosis	• Associated with intake of certain drugs, such as DNA synthesis-inhibiting drugs, immunosuppressive drugs, anticonvulsants, and antiviral medications.	• Usually a clinical diagnosis. • Serum folate level is normal.
Diphyllobothriasis	• Presents with abdominal discomfort, diarrhoea, vomiting, weakness, weight loss, and occasionally acute abdominal pain due to intestinal obstruction, cholangitis, or cholecystitis. Additional features are megaloblastic anaemia and neurological abnormalities secondary to vitamin B12 (cobalamin) deficiency.	• Stool examination reveals characteristic eggs of the fish tapeworm *Diphyllobothrium latum* . • Serum vitamin B12 levels are low. • Serum folate is normal.

Screening

Screening for folate deficiency is not routinely recommended. However, in patients with diseases that are associated with folate deficiency, early detection can lead to folic acid supplementation, which is a simple correction of the underlying cause. Supplementation can prevent the development of megaloblastic anaemia and fetal neural tube defects.

At-risk populations

Certain populations are at increased risk of developing deficiency:

- Low socio-economic groups with poor nutrition
- Older people with poor dietary intake
- People who misuse alcohol
- Pregnant or lactating women and preterm infants
- People with chronic haemolytic anaemia or chronic exfoliative dermatitis
- People taking drugs that interfere with folate absorption and metabolism
- People with hereditary folate malabsorption and inborn errors of folate metabolism
- People with chronic diarrhoeal states and other intestinal disorders
- Chronic dialysis patients
- Infants who are fed goats' milk exclusively, and children with inborn errors of metabolism given a synthetic diet.

Screening tests

Full blood count (FBC) may show increased mean corpuscular volume with or without low haemoglobin. This result triggers further testing for causes of macrocytosis, which includes serum folate level. At-risk populations are tested in general for folate deficiency if the FBC is abnormal.

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Approach

Oral folic acid replacement is the preferred therapy (because several effective pathways of specific and non-specific folate absorption operate throughout the small intestine).[55] Folic acid is a synthetic, oxidised form of folate.[52] Oral preparations of folic acid are inexpensive and stable.[40]

Parenteral folic acid may be considered in severe malabsorption states. Patients with hereditary folate malabsorption require large doses of folic acid that are often given parenterally in specialised regimens.

Ruling out vitamin B12 (cobalamin) deficiency is important because initiation of folic acid therapy may mask neurological manifestations of underlying vitamin B12 deficiency.

In states of severe megaloblastic anaemia, where it is essential to initiate therapy immediately, concomitant folic acid and vitamin B12 should be given. Tests for vitamin B12 deficiency should be ordered, in addition to those for folate deficiency. Test results determine subsequent therapy.

Folinic acid, a reduced form of folic acid, can be converted to biologically active tetrahydrofolate without the action of dihydrofolate reductase. Consequently, it can be used to prevent folate deficiency in patients taking drugs that affect the enzyme dihydrofolate reductase, such as methotrexate, pyrimethamine, and trimethoprim.[52]

Acquired folate deficiency

Severe anaemia symptoms

- Folate deficiency-induced anaemia is generally well compensated. When the anaemia is severe and is associated with symptoms of heart failure, packed red blood cell (RBC) transfusion should be considered. Blood should be transfused slowly, with the use of diuretic drugs to avoid volume overload. Folic acid replacement therapy should be instituted simultaneously. Patients should be monitored for hypokalaemia following the commencement of folic acid therapy for severe megaloblastic anaemia.[61]

Non-severe anaemia symptoms

- Patients with megaloblastic anaemia due to acquired causes of folate deficiency respond well to folic acid replacement therapy. Oral folic acid should be instituted once a diagnosis of deficiency is confirmed. Folic acid is better absorbed than natural folate (in food) in malabsorption states; hence, oral therapy is usually adequate to treat deficiency. Haematological findings are corrected after about 8 weeks.
- Additional management strategies are essential in certain conditions.
    - Pregnant and lactating women need daily doses of folic acid.[24] The recommended dietary allowance (RDA) for folate during pregnancy and lactation varies from 400-800 micrograms/day depending upon factors such as diet, inclusion of food fortified with folic acid, socio-economic status, and individual medical history. [US Department of Agriculture and US Department of Health and Human Services: dietary guidelines for Americans, 2020-2025] (https://www.dietaryguidelines.gov) [NIH: dietary supplement fact sheet - folate] (https://ods.od.nih.gov/factsheets/Folate-HealthProfessional)
    - Chronic malabsorption states need continued folic acid supplementation if the underlying disorder is not fully corrected.

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- Haematological disorders with increased RBC turnover may need continued replacement of folic acid to meet the chronic demand; patients taking continued folic acid supplementation should have vitamin B12 levels monitored periodically to prevent a missed diagnosis of vitamin B12 deficiency. Randomised clinical trials of folic acid supplementation in the common haemolytic state sickle cell disease are lacking.[62]
- Dietary modifications are important in certain populations: older people and lower socio-economic groups need dietary modifications to include legumes, leafy vegetables, and fruits.[63] In addition, folic acid may be supplemented by taking multivitamin preparations, or by national food fortification programmes that enrich certain foods, such as cereals, with folic acid.

Asymptomatic patients

- Oral folic acid therapy should be given to asymptomatic patients with documented folate deficiency, with or without macrocytosis.

Inborn errors of folate metabolism

Treatment of children with inborn errors of folate metabolism requires extremely large doses of folic acid that are started early in infancy and often given parenterally.[10] [40] The goal of therapy is to maintain both blood and cerebrospinal fluid folate levels.

Inborn errors of folate metabolism require different treatment approaches:

- Hereditary folate malabsorption, caused by mutations in the proton-coupled folate transporter, is treated with daily folinic acid (calcium folinate) injections.
- Severe methylenetetrahydrofolate reductase deficiency, the most common disorder of folate metabolism, is treated with betaine (a substrate for betaine homocysteine methyltransferase that catalyses conversion of homocysteine to methionine without requiring folate or vitamin B12). In addition, folic acid, cyanocobalamin, riboflavin, methionine, pyridoxine, and levocarnitine have been tried.[10]
- Glutamate formiminotransferase deficiency is treated with folic acid plus methionine.[64] [65]
- Anecdotal evidence suggests that dihydrofolate reductase deficiency may respond to folinic acid (calcium folinate).[66]
- Cerebral folate transport deficiency is characterised by decreased folate transport across the blood-brain barrier. It is frequently caused by antibodies to folate receptor proteins that transport folate into the central nervous system (CNS). Multiple neuropsychiatric disorders result from decreased folate transport to the brain, but may respond to treatment with folinic acid (which delivers folate to the CNS via the reduced folate carrier protein).[67] [68]

Management of underlying disorders

Evaluation and treatment of underlying disorders is essential to prevent and treat ongoing deficiency states. Ongoing losses of folate may need continued replacement (e.g., chronic haemolytic anaemia and exfoliative dermatitis need continued daily folic acid supplementation). Malabsorption states need correction of underlying disease and vitamin supplementation. Folate deficiency due to certain drugs may need modification of drug therapy.

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Monitoring response to therapy

Reticulocyte response at 1 week, and the blood count normalisation at 8 weeks from the start of therapy, are useful parameters to monitor treatment response. Monitoring serum folate level has little value. Homocysteine levels fall within a few days of therapy and may be used to assess treatment response.

Reticulocyte count can be assessed at the end of the first week of therapy.[40] Increased haemoglobin level and reticulocytosis within 7 to 10 days of starting treatment suggests a positive response.[40]

Mean corpuscular volume (MCV) may increase during the first few days of treatment, presumably because of reticulocytosis.[69] As normocytic RBCs replace macrocytes, MCV decreases to normal range, usually within about 8 weeks of beginning treatment.[70] [71]

Neutrophil hypersegmentation may persist during the first 2 weeks of therapy, but platelet and white blood cell count rise in the first week of therapy.

In patients with ongoing losses, periodic monitoring of serum folate may be considered.

At risk of folate deficiency

Folic acid supplementation can prevent folate deficiency in states of increased demand (e.g., pregnancy and lactation), and in conditions with folate malabsorption (e.g., coeliac disease) or loss (e.g., chronic haemolytic disorder).

There is conclusive evidence that use of folic acid supplementation pre-conceptually and during pregnancy reduces the incidence of fetal neural tube defects (NTDs).[15] [31] [43] Population-based studies suggest that female fetuses/infants may derive greater benefit (rate of decrease in NTDs) from maternal folic acid supplementation than males.[72] [73]

Continued folic acid supplementation beyond the first trimester until the end of pregnancy may confer neurodevelopmental benefits.[74] Further randomised trials are needed.

Pregnancy and lactation

- Guidelines recommend pre-conception folic acid supplementation at a dose of 400-800 micrograms/day for the prevention of fetal NTDs in women who are planning to conceive or who are capable of becoming pregnant.[32] [33] [34] Higher doses (up to 4 mg/day) are recommended for certain risk groups. The UK National Institute for Health and Care Excellence recommends 5 mg/day in certain risk groups.[35] [36] Canadian guidelines use the following risk stratification for women at risk for a fetal NTD, or other folic acid-sensitive congenital anomaly:[32]
    - Low risk: no personal or family history of fetal NTD or folate-related congenital abnormalities
    - Medium risk: family history of fetal NTD; personal history in the patient or male partner of folate-related congenital abnormality; or diabetes, teratogenic medication, or malabsorption in the patient
    - High risk: personal history of fetal NTD in the patient or her male partner; or previous fetal NTD birth by the patient.
- In the US, the RDA for folate during pregnancy and lactation varies from 400-800 micrograms/day depending upon factors such as diet, inclusion of food fortified with folic acid, socio-economic status, and individual medical history. [US Department of Agriculture and US Department of Health and Human Services: dietary guidelines for Americans, 2020-2025] (https://

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www.dietaryguidelines.gov) [NIH: dietary supplement fact sheet - folate] (https://ods.od.nih.gov/factsheets/Folate-HealthProfessional)

- The World Health Organization recommends an RBC folate level >906 nanomol/L (400 nanograms/mL) in women of reproductive age.[44]
    - Randomised clinical trial data suggest that a plasma folate level of 25.5 nanomol/L (11 nanograms/mL) corresponds to the recommended RBC folate level (≥906 nanomol/L [≥400 nanograms/mL]) in most situations.[45] Higher plasma folate levels (34.6 nanomol/L [15 nanograms/mL) are required in women with vitamin B12 (cobalamin) deficiency.
    - For maximal protection against fetal NTDs, the optimal calculated RBC folate level is 1000-1300 nanomol/L (442-574 nanograms/mL) at the end of the first 4 weeks of pregnancy, when neural tube closure is achieved.[46]
- The US Preventive Services Task Force advises that the critical period for beginning supplementation is at least 1 month before conception.[33]
    - Reproductive-age women (without folate fortification) randomised to 800 micrograms/day folate supplementation were more likely to achieve desirable RBC-folate concentrations (≥906 nanomol/L [≥400 nanograms/mL]) at 4 weeks than women receiving 400 micrograms/day.[47] Similar results were reported at an 8-week timepoint.
- Evidence suggests that folic acid supplementation during pregnancy reduces megaloblastic anaemia in mothers. While there is no conclusive evidence that supplementation prevents premature birth, stillbirth, neonatal mortality, or miscarriage, data from the Screening for Pregnancy Endpoints (SCOPE) study indicate that folic acid supplementation during pregnancy is associated with a lower risk of small for gestational age infants without increasing the risk for large for gestational age infants.[48] [49] [50]
- In low- and middle-income countries, maternal multiple micronutrient supplementation with iron and folic acid reduces the number of infants born at low birth weight.[51]

Folate malabsorption and loss

- Correction of the underlying cause and/or folic acid supplementation can prevent folate deficiency in patients with malabsorptive disorders, such as tropical sprue and coeliac disease (non-tropical sprue).
- Increased folate loss occurs in patients with chronic haemolytic disorder (due to increased cell turnover), and in those undergoing chronic dialysis (due to loss of folate in dialysis fluid). Daily folic acid supplementation may be required in these patients to prevent folate deficiency.
- Patients taking drugs that interfere with folate absorption and metabolism may require supplementation with oral or parenteral folinic acid to prevent folate deficiency. Folinic acid, a reduced form of folic acid, can be converted to biologically active tetrahydrofolate without the action of dihydrofolate reductase, which is inhibited by drugs such as methotrexate, pyrimethamine, and trimethoprim.[52] Folinic acid supplementation can reduce the risk of hepatotoxicity and gastrointestinal side effects in patients with rheumatoid arthritis.[53] In some cases, where a drug has reduced efficacy when administered with folinic acid, a change to another drug may be required.

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Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial		(summary)
at risk of folate deficiency due to pregnancy or lactation		
	1st	**oral folic acid + multivitamin supplementation**
at risk of folate deficiency due to malabsorption disorders, chronic haemolytic disorder, or chronic dialysis		
	1st	**oral folic acid supplementation + treatment of underlying disorder**
at risk of folate deficiency due to medication		
	1st	**folinic acid**

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Acute (summary)		
acquired: macrocytosis without anaemia		
	1st	oral folic acid replacement
	plus	treatment of underlying disorder
acquired: macrocytic anaemia and pancytopenia		
	1st	oral folic acid replacement
	plus	treatment of underlying disorder
▪ with heart failure	plus	packed red blood cell transfusion
congenital folate metabolism defects		
	1st	parenteral folic acid replacement
▪ glutamate formiminotransferase deficiency	plus	methionine
congenital folate malabsorption		
	1st	folinic acid or folic acid
▪ with methylenetetrahydrofolate reductase deficiency	plus	amino acid and vitamin replacement
congenital cerebral folate transport deficiency		
	1st	folinic acid

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Treatment algorithm

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Initial

at risk of folate deficiency due to pregnancy or lactation

1st **oral folic acid + multivitamin supplementation**

Primary options

» folic acid: low risk: 0.4 to 0.8 mg orally once daily starting 1-3 months before pregnancy and continuing until 6 weeks postnatally or the end of lactation; medium risk: 1 mg orally once daily starting 1-3 months before pregnancy and continuing through the first 12 weeks of pregnancy, followed by 0.4 to 1 mg once daily from week 13 of pregnancy and continuing until 6 weeks postnatally or the end of lactation; high risk: 4-5 mg orally once daily starting 1-3 months before pregnancy and continuing through the first 12 weeks of pregnancy, followed by 0.4 to 1 mg once daily from week 13 of pregnancy and continuing until 6 weeks postnatally or the end of lactation

» There is conclusive evidence that use of folic acid supplementation pre-conceptually and during pregnancy reduces the incidence of fetal neural tube defects (NTDs).[15] [31] [43]

» Population-based studies suggest that female fetuses/infants may derive greater benefit (rate of decrease in NTDs) from maternal folic acid supplementation than males.[72] [73] Continued folic acid supplementation beyond the first trimester until the end of pregnancy may confer neurodevelopmental benefits.[74] Further randomised trials are needed.

» Guidelines recommend pre-conception folic acid supplementation at a dose of 400-800 micrograms/day for the prevention of fetal NTDs in women who are planning to conceive or who are capable of becoming pregnant.[32] [33] [34] Higher doses (up to 4 mg/day) are recommended for certain risk groups. The UK National Institute for Health and Care Excellence recommends 5 mg/day in certain risk groups.[35] [36] Canadian guidelines use the following stratification for women at risk for fetal NTD, or other folic acid-sensitive congenital anomaly:[32]

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Initial

» Low risk: no personal or family history of fetal NTD or folate-related congenital abnormalities.

» Medium risk: family history of fetal NTD; personal history in the patient or male partner of folate-related congenital abnormality; or diabetes, teratogenic medication, or malabsorption in the patient.

» High risk: personal history of fetal NTD in the patient or her male partner; or previous fetal NTD birth by the patient.

» In the US, the recommended dietary allowance for folate during pregnancy and lactation varies from 400-800 micrograms/day depending upon factors such as diet, inclusion of food fortified with folic acid, socio-economic status, and individual medical history. [US Department of Agriculture and US Department of Health and Human Services: dietary guidelines for Americans, 2020-2025] (https://www.dietaryguidelines.gov) [NIH: dietary supplement fact sheet - folate] (https://ods.od.nih.gov/factsheets/Folate-HealthProfessional)

» The World Health Organization recommends a red blood cell (RBC) folate level >906 nanomol/L (400 nanograms/mL) in women of reproductive age.[44]

» Randomised clinical trial data suggest that a plasma folate level of 25.5 nanomol/L (11 nanograms/mL) corresponds to the recommended RBC folate level (≥906 nanomol/L [≥400 nanograms/mL]) in most situations.[45]

» For maximal protection against fetal NTDs, the optimal calculated RBC folate level is 1000-1300 nanomol/L (442-574 nanograms/mL) at the end of the first 4 weeks of pregnancy, when neural tube closure is achieved.[46]

» The US Preventive Services Task Force advises that the critical period for beginning supplementation is at least 1 month before conception.[33] Reproductive-age women (without folate fortification) randomised to 800 micrograms/day folate supplementation were more likely to achieve desirable RBC-folate concentrations (≥906 nanomol/L [≥400 nanograms/mL]) at 4 weeks than women receiving 400 micrograms/day.[47] Similar results were reported at an 8-week timepoint.

» Evidence suggests that folic acid supplementation during pregnancy reduces

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Initial

megaloblastic anaemia in mothers. While there is no conclusive evidence that supplementation prevents preterm birth, stillbirth, neonatal mortality, or miscarriage, data from the Screening for Pregnancy Endpoints (SCOPE) study indicate that folic acid supplementation during pregnancy is associated with a lower risk of small for gestational age infants without increasing the risk for large for gestational age infants.[48] [49] [50]

» In low- and middle-income countries, maternal multiple micronutrient supplementation with iron and folic acid reduces the number of infants born at low birth weight.[51]

at risk of folate deficiency due to malabsorption disorders, chronic haemolytic disorder, or chronic dialysis

1st **oral folic acid supplementation + treatment of underlying disorder**

Primary options

» folic acid: 1 mg orally once daily

» Correction of underlying cause and/or folic acid supplementation can prevent folate deficiency in patients with malabsorption disorder, such as tropical sprue and coeliac disease (non-tropical sprue).

» Increased folate loss occurs in patients with chronic haemolytic disorder (due to increased cell turnover), and in those undergoing chronic dialysis (due to loss of folate in dialysis fluid). Daily folic acid supplementation may be required in these patients to prevent folate deficiency.

at risk of folate deficiency due to medication

1st **folinic acid**

Primary options

» folinic acid: consult specialist for guidance on dose

» Folinic acid is a reduced form of folic acid that can be converted to biologically active tetrahydrofolate without the enzyme dihydrofolate reductase. Folinic acid can be used to prevent folate deficiency in patients taking drugs that affect dihydrofolate reductase activity, such as methotrexate, pyrimethamine, and trimethoprim.[52] Folinic acid supplementation can reduce the risk of hepatotoxicity and

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Initial

gastrointestinal side effects in patients with rheumatoid arthritis.[53] In some cases, where a drug has reduced efficacy when administered with folinic acid, a change to another drug may be required.

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Acute

acquired: macrocytosis without anaemia

1st **oral folic acid replacement**

Primary options

» folic acid: children: 1 mg orally once daily; adults: 1-5 mg orally once daily for 4 months (or until term in pregnancy), maximum 15 mg/day

» Ruling out vitamin B12 (cobalamin) deficiency is important because initiation of folic acid therapy may mask neurological manifestations of underlying vitamin B12 deficiency.

» Oral folic acid therapy should be given to asymptomatic patients with documented folate deficiency, with or without macrocytosis.

» Oral folic acid should be instituted once deficiency is diagnosed. Folic acid is better absorbed than natural folate (in food) in malabsorption states; hence, oral therapy is usually adequate.

» Haematological findings are corrected after about 8 weeks.

plus **treatment of underlying disorder**

Treatment recommended for ALL patients in selected patient group

» Evaluation and treatment of underlying disorders is essential to prevent and treat ongoing deficiency states.

» Ongoing losses of folate may need continued replacement (e.g., chronic haemolytic anaemia and exfoliative dermatitis need daily folic acid supplementation). Randomised clinical trials of folic acid supplementation in the common haemolytic state sickle cell disease are lacking.[62] Patients taking continued folic acid supplementation should have vitamin B12 levels monitored periodically to prevent a missed diagnosis of vitamin B12 deficiency.

» Malabsorptive states need correction of underlying disease and vitamin supplementation.

» Folate deficiency due to medication may need modification of drug therapy.

» Certain populations (older people and lower socio-economic groups) need dietary modifications to include legumes, leafy vegetables, and fruits.[63] In addition, folate may

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Acute

be supplemented by taking multivitamins or by national food fortification programmes that enrich certain foods, such as cereals, with folic acid.

acquired: macrocytic anaemia and pancytopenia

1st **oral folic acid replacement**

Primary options

» folic acid: children: 1 mg orally once daily; adults: 1-5 mg orally once daily

OR

» folic acid: children: 1 mg orally once daily; adults: 1-5 mg orally once daily
-and-
» cyanocobalamin: consult specialist for guidance on dose

» Ruling out vitamin B12 (cobalamin) deficiency is important because initiation of folic acid therapy may mask neurological manifestations of underlying vitamin B12 deficiency.

» In states of severe megaloblastic anaemia where it is essential to initiate therapy immediately, concomitant folic acid and vitamin B12 should be given. Tests for vitamin B12 deficiency should be ordered, in addition to those for folate deficiency. Test results determine subsequent therapy.

plus **treatment of underlying disorder**

Treatment recommended for ALL patients in selected patient group

» Assessment and treatment of underlying disorders is essential to prevent and treat ongoing deficiency states.

» Ongoing losses of folate may need continued replacement (e.g., chronic haemolytic anaemia and exfoliative dermatitis need continued daily folic acid supplementation). Randomised clinical trials of folic acid supplementation in the common haemolytic state sickle cell disease are lacking.[62] Patients taking continued folic acid supplementation should have vitamin B12 levels monitored periodically to prevent a missed diagnosis of vitamin B12 deficiency.

» Malabsorptive states need correction of underlying disease and vitamin supplementation.

» Folate deficiency due to certain drugs may need modification of drug therapy.

MANAGEMENT

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Acute

with heart failure — **plus** — **packed red blood cell transfusion**

Treatment recommended for ALL patients in selected patient group

Primary options

» furosemide: children: 1-2 mg/kg intravenously/intramuscularly every 6-12 hours initially, increase according to response, maximum 6 mg/kg/dose, or 0.5 to 2 mg/kg orally every 6-12 hours initially, increase according to response, maximum 6 mg/kg/dose; adults: 20-80 mg orally every 6-8 hours initially, increase according to response, maximum 600 mg/day, or 20-40 mg intravenously/intramuscularly every 6-12 hours initially, increase according to response, maximum 80 mg/dose

» Folic acid replacement therapy and packed red blood cell transfusion should be started simultaneously in patients with severe anaemia and symptoms of heart failure.

» Hypokalaemia can occur after the initiation of folic acid therapy for severe megaloblastic anaemia. Serum potassium should be monitored and replaced as needed.[61]

» Blood should be transfused slowly, with the use of diuretic drugs to avoid volume overload.

congenital folate metabolism defects

congenital folate metabolism defects — **1st** — **parenteral folic acid replacement**

Primary options

» folic acid: consult specialist for guidance on dose

» Treatment of children with inborn errors of folate metabolism requires extremely large doses of folic acid, often given parenterally in specialised regimens.[10] [40]

glutamate formiminotransferase deficiency — **plus** — **methionine**

Treatment recommended for ALL patients in selected patient group

Primary options

» methionine: consult specialist for guidance on dose

» Glutamate formiminotransferase deficiency is treated with folic acid plus methionine.[64] [65]

congenital folate malabsorption

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Acute

congenital folate malabsorption

1st **folinic acid or folic acid**

Primary options

» folinic acid: 3-6 mg intramuscularly once daily

OR

» folic acid: consult specialist for guidance on higher doses

» Hereditary folate malabsorption is treated with daily folinic acid injections or very high doses of oral folic acid.[75]

» Patients with dihydrofolate deficiency may respond to folinic acid.[66]

with methylenetetrahydrofolate reductase deficiency

plus **amino acid and vitamin replacement**

Treatment recommended for ALL patients in selected patient group

Primary options

» betaine

--AND--

» folic acid
-and/or-
» cyanocobalamin
-and/or-
» riboflavin
-and/or-
» pyridoxine
-and/or-
» methionine
-and/or-
» levocarnitine

» Betaine is given to patients with severe deficiency.

» In addition, folic acid, cyanocobalamin, riboflavin, methionine, pyridoxine, and levocarnitine are used in varying combinations, and are often ineffective without betaine.

» Consult specialist for guidance on doses.

congenital cerebral folate transport deficiency

1st **folinic acid**

Primary options

» folinic acid: consult specialist for guidance on dose

MANAGEMENT

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Acute

» Cerebral folate transport deficiency is characterised by decreased folate transport across the blood-brain barrier and thus low levels of 5-methyltetrahydrofolate in the cerebrospinal fluid.

» It is treated successfully with folinic acid.

Primary prevention

Folic acid supplementation can prevent folate deficiency in states of increased demand (e.g., pregnancy and lactation) and in conditions with folate malabsorption (e.g., coeliac disease) or loss (e.g., chronic haemolytic disorder).

There is conclusive evidence that folic acid supplementation pre-conceptually and during pregnancy reduces the incidence of fetal neural tube defects (NTDs).[15] [31] [43]

Pregnancy and lactation

- Guidelines recommend pre-conception folic acid supplementation at a dose of 400-800 micrograms/day for the prevention of NTDs in women who are planning to conceive or who are capable of becoming pregnant.[32] [33] [34] Higher doses (up to 4 mg/day) are recommended for certain risk groups. The UK National Institute for Health and Care Excellence recommends 5 mg/day in certain risk groups.[35] [36] Canadian guidelines use the following stratification for women at risk of fetal NTD or other folic acid-sensitive congenital anomaly:[32]
    - Low risk: no personal or family history of fetal NTD or folate-related congenital abnormalities.
    - Medium risk: family history of fetal NTD; personal history in the patient or male partner of folate-related congenital abnormality; or diabetes, teratogenic medication, or malabsorption in the patient.
    - High risk: personal history of fetal NTD in the patient or her male partner; or previous fetal NTD birth by the patient.
- In the US, the recommended dietary allowance for folate during pregnancy and lactation varies from 400-800 micrograms/day depending upon factors such as diet, inclusion of food fortified with folic acid, socio-economic status, and individual medical history. [US Department of Agriculture and US Department of Health and Human Services: dietary guidelines for Americans, 2020-2025] (https://www.dietaryguidelines.gov) [NIH: dietary supplement fact sheet - folate] (https://ods.od.nih.gov/factsheets/Folate-HealthProfessional)
- The World Health Organization recommends a red blood cell (RBC) folate level >906 nanomol/L (400 nanograms/mL) in women of reproductive age.[44]
    - Randomised clinical trial data suggest that a plasma folate level of 25.5 nanomol/L (11 nanograms/mL) corresponds to the recommended RBC folate level (≥906 nanomol/L [≥400 nanograms/mL]) in most situations.[45] Higher plasma folate levels (34.6 nanomol/L [15 nanograms/mL) are required in women with vitamin B12 (cobalamin) deficiency.
    - For maximal protection against fetal NTDs, the optimal calculated RBC folate level is 1000-1300 nanomol/L (442-574 nanograms/mL) at the end of the first 4 weeks of pregnancy, when neural tube closure is achieved.[46]
- The US Preventive Services Task Force advises that the critical period for beginning supplementation is at least 1 month before conception.[33]

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- Reproductive-age women (without folate fortification) randomised to 800 micrograms/day folate supplementation were more likely to achieve desirable RBC-folate concentrations (≥906 nanomol/L [≥400 nanograms/mL]) at 4 weeks than women receiving 400 micrograms/day.[47] Similar results were reported at an 8-week timepoint.

Evidence suggests that folic acid supplementation during pregnancy reduces megaloblastic anaemia in mothers. While there is no conclusive evidence that supplementation prevents premature birth, stillbirth, neonatal mortality, or miscarriage, data from the Screening for Pregnancy Endpoints (SCOPE) study indicate that folic acid supplementation during pregnancy is associated with a lower risk of small for gestational age infants, without increasing the risk for large for gestational age infants.[48] [49] [50]

In low- and middle-income countries, maternal multiple micronutrient supplementation with iron and folic acid reduces the number of infants born with low birth weight.[51]

Folate malabsorption and loss

- Correction of the underlying cause and/or folic acid supplementation can prevent folate deficiency in patients with malabsorptive disorders, such as tropical sprue and coeliac disease (non-tropical sprue).
- Increased folate loss occurs in patients with chronic haemolytic disorder (due to increased cell turnover), and in those undergoing chronic dialysis (due to loss of folate in dialysis fluid). Daily folic acid supplementation may be required in these patients to prevent folate deficiency.
- Patients taking drugs that interfere with folate absorption and metabolism may require supplementation with oral or parenteral folinic acid to prevent folate deficiency. Folinic acid, a reduced form of folic acid, can be converted into biologically active tetrahydrofolate without the action of dihydrofolate reductase, which is inhibited by drugs such as methotrexate, pyrimethamine, and trimethoprim.[52] Folinic acid supplementation can reduce the risk of hepatotoxicity and gastrointestinal side effects in patients with rheumatoid arthritis.[53] In some cases, where a drug has reduced efficacy when administered with folinic acid, a change to another drug may be required.

Secondary prevention

Continued folic acid supplementation is necessary in certain conditions with poor folate absorption or ongoing losses (e.g., coeliac disease, chronic haemolytic disease) and states of increased demand (e.g., pregnancy, lactation, prematurity).

National food fortification can prevent folate deficiency on a large scale.[99] This can positively affect the folate status of the population at large, and specifically that of certain vulnerable populations, such as pregnant and lactating women and older people.

Patient discussions

Dietary modifications are important in populations consuming folate-poor diets.[63] The main dietary sources of folate are green leafy vegetables, legumes, some fruits, and fortified cereals.

Reducing alcohol intake is essential in folate deficiency caused by alcohol-use disorder. Drugs causing folate deficiency should be avoided if possible to prevent ongoing deficiency.

Any underlying cause (e.g., tropical sprue and coeliac disease [non-tropical sprue]) should be diagnosed and treated. Compliance with daily folate intake and follow-up are essential to achieve complete cure.

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Monitoring

Monitoring

Reticulocytosis can be assessed at the end of the first week of therapy.[40] It is important to determine completeness of response after 8 weeks of therapy, when blood counts should have normalised.[70] [71]

Homocysteine levels fall within a few days of therapy and may be used to assess treatment response.

Inadequate response indicates a co-existing cause of anaemia, such as iron deficiency or vitamin B12 (cobalamin) deficiency.

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FOLLOW UP

Complications

Complications	Timeframe	Likelihood
exacerbation of seizures by intravenous folic acid	**short term**	**low**
Large doses of intravenous folic acid have been reported to exacerbate seizures in patients with underlying seizure disorders.[89] Intravenous folic acid use is often limited to treatment of severe malabsorption disorders and certain inborn errors of folate metabolism.		
reduced therapeutic efficacy of anti-malarial therapy sulfadoxine-pyrimethamine	**short term**	**low**
Several randomised controlled clinical trials have demonstrated that folic acid supplementation reduces the therapeutic efficacy of sulfadoxine-pyrimethamine in patients with *Plasmodium falciparum* malaria.[93] [94] [95]		
haematological deficits	**long term**	**high**
Inadequately treated or untreated patients will have megaloblastic anaemia, leukopenia, and thrombocytopenia.		
fetal neural tube defects	**long term**	**high**
Folate deficiency in pregnant women increases the incidence of fetal neural tube defects.[29] [30] [31] This can be effectively prevented by increasing folic acid intake pre-conceptually and during pregnancy.[15] [31] [43] For women who are planning to conceive or who are capable of becoming pregnant, pre-conception folic acid supplementation is recommended at a dose of 400-800 micrograms/day, with higher doses (up to 5 mg/day) recommended for certain risk groups.[32] [33] [34] The UK National Institute for Health and Care Excellence recommends 5 mg/day in certain risk groups.[35] [36] In the US, the recommended dietary allowance for folate during pregnancy and lactation varies from 400-800 micrograms/day depending upon factors such as diet, inclusion of food fortified with folic acid, socio-economic status, and individual medical history. [US Department of Agriculture and US Department of Health and Human Services: dietary guidelines for Americans, 2020-2025] (https://www.dietaryguidelines.gov) [NIH: dietary supplement fact sheet - folate] (https://ods.od.nih.gov/factsheets/Folate-HealthProfessional)		
progression of neuropathy due to folic acid therapy in vitamin B12 (cobalamin) deficiency	**long term**	**high**
Initiation of folic acid therapy may mask neuropathy and cognitive impairment in underlying vitamin B12 deficiency.[86] [87] [88] This can be prevented by prompt diagnosis and treatment of vitamin B12 deficiency before instituting folic acid therapy.		
cardiovascular disease and venous thrombosis	**long term**	**low**
Moderate elevation of plasma homocysteine is associated with cardiovascular disease, stroke, and venous thrombosis.[77] [78] Although folic acid supplementation may reduce plasma homocysteine levels, there is insufficient evidence to show that homocysteine-lowering interventions can reduce the risk of cardiovascular and cerebrovascular diseases.[79] [80]		

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Complications	Timeframe	Likelihood
colorectal cancer	**long term**	**low**
High folate levels inhibit malignant transformation, but high folate levels may also enhance the growth of established malignancies.[81] Some studies have suggested a possible link between low folate status and colorectal cancer.[81] Other studies suggest a temporal association between folic acid fortification and an increase in colorectal cancer and prostate cancer.[82] [83] Evidence is not sufficiently clear to recommend increased folate intake for populations at risk for developing colorectal cancer.[84] [85]		
toxicity associated with excessive folate intake	**long term**	**low**
Evidence is emerging of possible toxicities associated with excess folate intake as a result of folic acid food fortification and use of dietary supplements containing folic acid.[90] Toxicities include progressive neurological damage, cognitive impairment (particularly in individuals with concomitant vitamin B12 [cobalamin] deficiency), and enhanced growth of malignant tumours (specifically colonic tumours).[87] [88] [90] [91] A prospective observational study noted a 'U-shaped' relationship between maternal multivitamin intake and risk of autism spectrum disorder (ASD). High maternal plasma folate levels (>60.3 nanomol/L [>26.5 nanograms/mL]) and vitamin B12 levels (≥536.8 picomol/L [≥0.23 nanograms/mL]) at birth were also associated with increased risk of ASD (hazard ratio 2.5, 95% CI 1.3 to 4.6).[92]		
risk of psychosis	**variable**	**low**
Low serum folate level is associated with a higher risk of developing schizophrenia spectrum disorders.[96] One meta-analysis identified significantly lower serum folate levels in patients with a first episode of psychosis compared with healthy controls.[97] One randomised controlled trial found that vitamin B12 and folic acid supplements reduced the negative symptoms of schizophrenia in patients with low-functioning folate hydrolase 1 polymorphisms, compared with placebo.[98]		

Prognosis

Prognosis and outcome of folic acid therapy

In acquired folate-deficient megaloblastic anaemia, daily folic acid supplementation brings about haematological remission and replenishes body stores within approximately 4 months.[76]

Continued folic acid supplementation

Patients with ongoing folate loss (e.g., malabsorption disorders, chronic haemolytic anaemia, exfoliative dermatitis) and those with a continued state of increased demand (e.g., pregnancy, lactation, prematurity) require continued supplementation of folic acid.

Because these patient groups are at risk for recurrence of folate deficiency, and for masking of underlying vitamin B12 (cobalamin) deficiency with folic acid therapy, it is advisable to monitor such patients periodically for folate and vitamin B12 deficiencies.

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FOLLOW UP

Risk factor avoidance

Alcohol, other drugs, and toxins that lead to folate deficiency should be avoided.

Dietary modification

Patients should include foods rich in folate.[63] Alternatives include consuming foods fortified with folic acid or supplementing folate through multivitamin intake.

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Diagnostic guidelines

United Kingdom

Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition (https://www.nice.org.uk/guidance/CG32)

Published by: National Institute for Health and Care Excellence **Last published:** 2017

Treatment guidelines

United Kingdom

Antenatal care (https://www.nice.org.uk/guidance/ng201)

Published by: National Institute for Health and Care Excellence **Last published:** 2021

North America

Folic acid supplementation for the prevention of neural tube defects (https://www.uspreventiveservicestaskforce.org/uspstf/topic_search_results?topic_status=P)

Published by: US Preventive Services Task Force **Last published:** 2023

Pre-conception folic acid and multivitamin supplementation for the primary and secondary prevention of neural tube defects and other folic acid-sensitive congenital anomalies (https://www.jogc.com/issue/S1701-2163(15)X7600-6)

Published by: Society of Obstetricians and Gynaecologists of Canada **Last published:** 2015

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Online resources

1. US Department of Agriculture and US Department of Health and Human Services: dietary guidelines for Americans, 2020-2025 (https://www.dietaryguidelines.gov) *(external link)*

2. NIH: dietary supplement fact sheet - folate (https://ods.od.nih.gov/factsheets/Folate-HealthProfessional) *(external link)*

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Key articles

- Pfeiffer CM, Sternberg MR, Zhang M, et al. Folate status in the US population 20 y after the introduction of folic acid fortification. Am J Clin Nutr. 2019 Nov 1;110(5):1088-97. Full text (https://academic.oup.com/ajcn/article/110/5/1088/5555582) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31504109?tool=bestpractice.bmj.com)
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Images

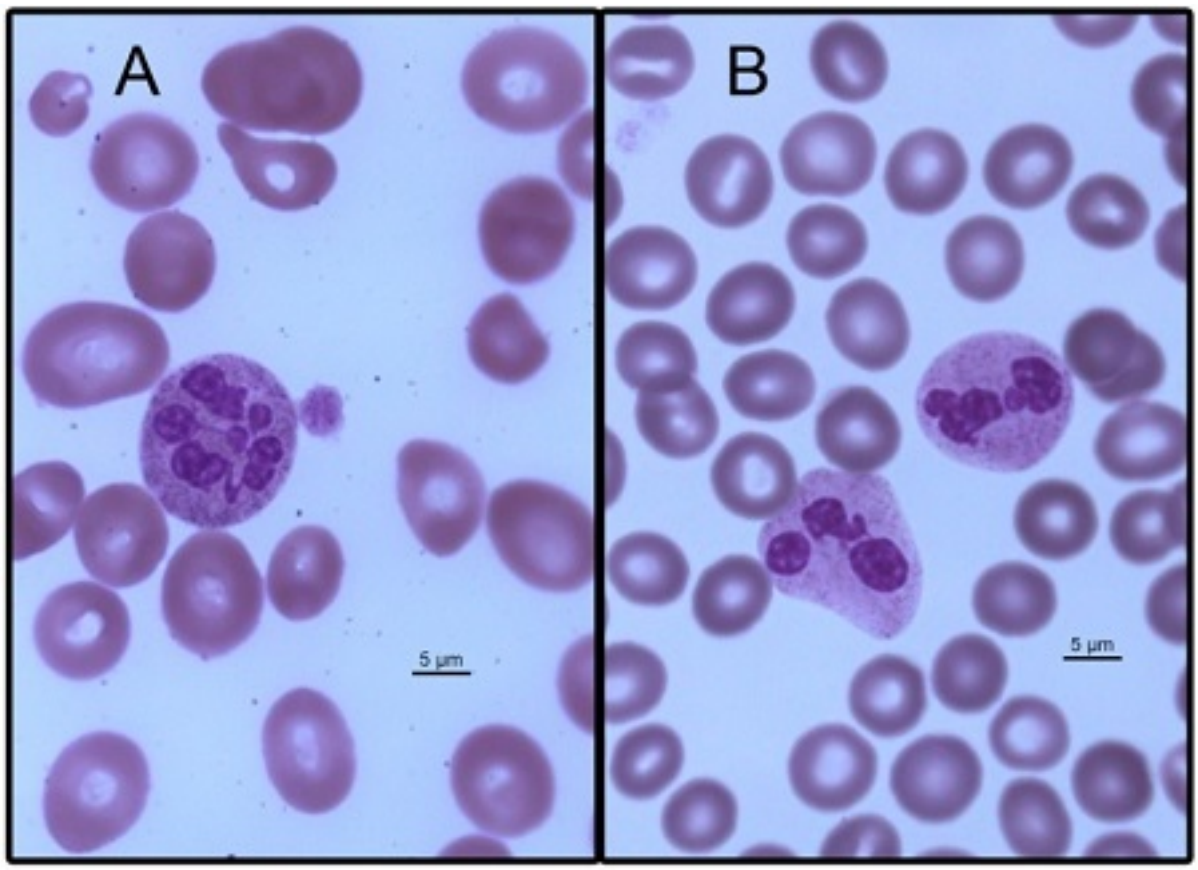

Figure 1: Megaloblastic macrocytic anemia: A. Peripheral blood smear of a patient with megaloblastic anemia. B. Peripheral blood smear of healthy individual

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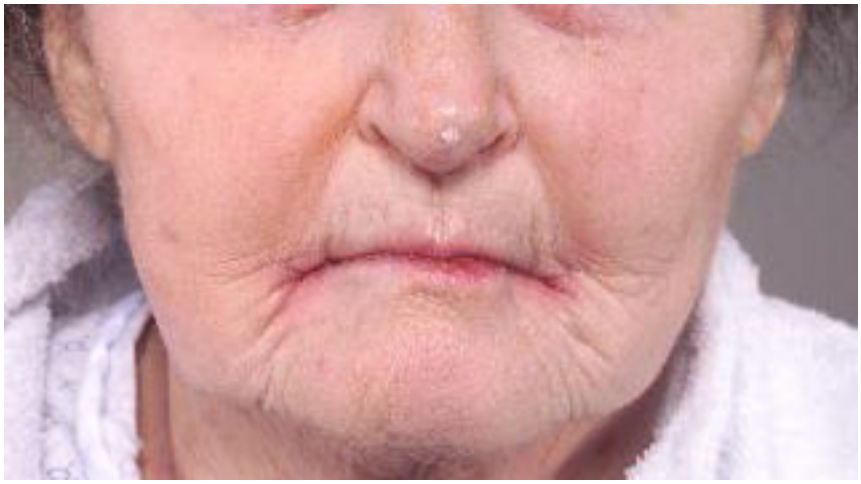

Figure 2: Angular cheilitis

From the collection of Dr Wanda C. Gonsalves; patient consent obtained

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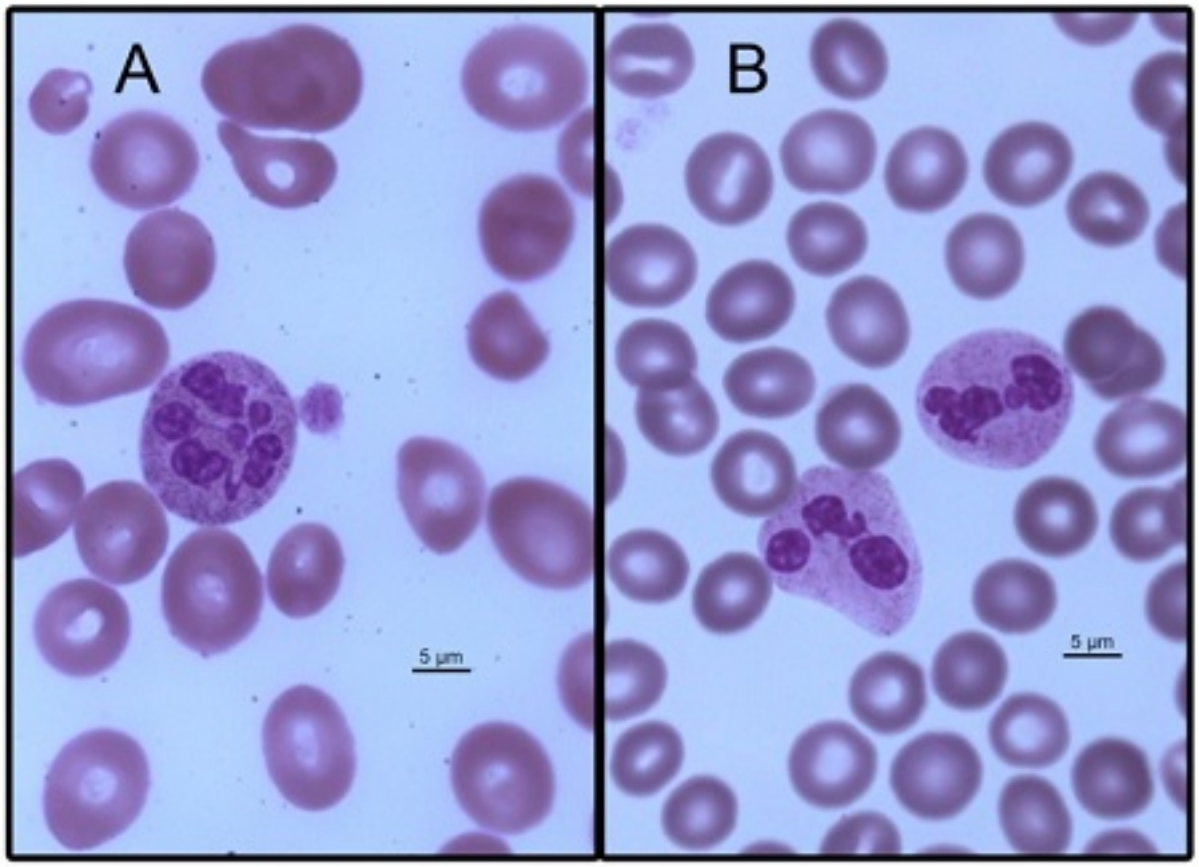

Figure 3: Megaloblastic macrocytic anaemia: A. Peripheral blood smear of a patient with megaloblastic anaemia. B. Peripheral blood smear of healthy individual

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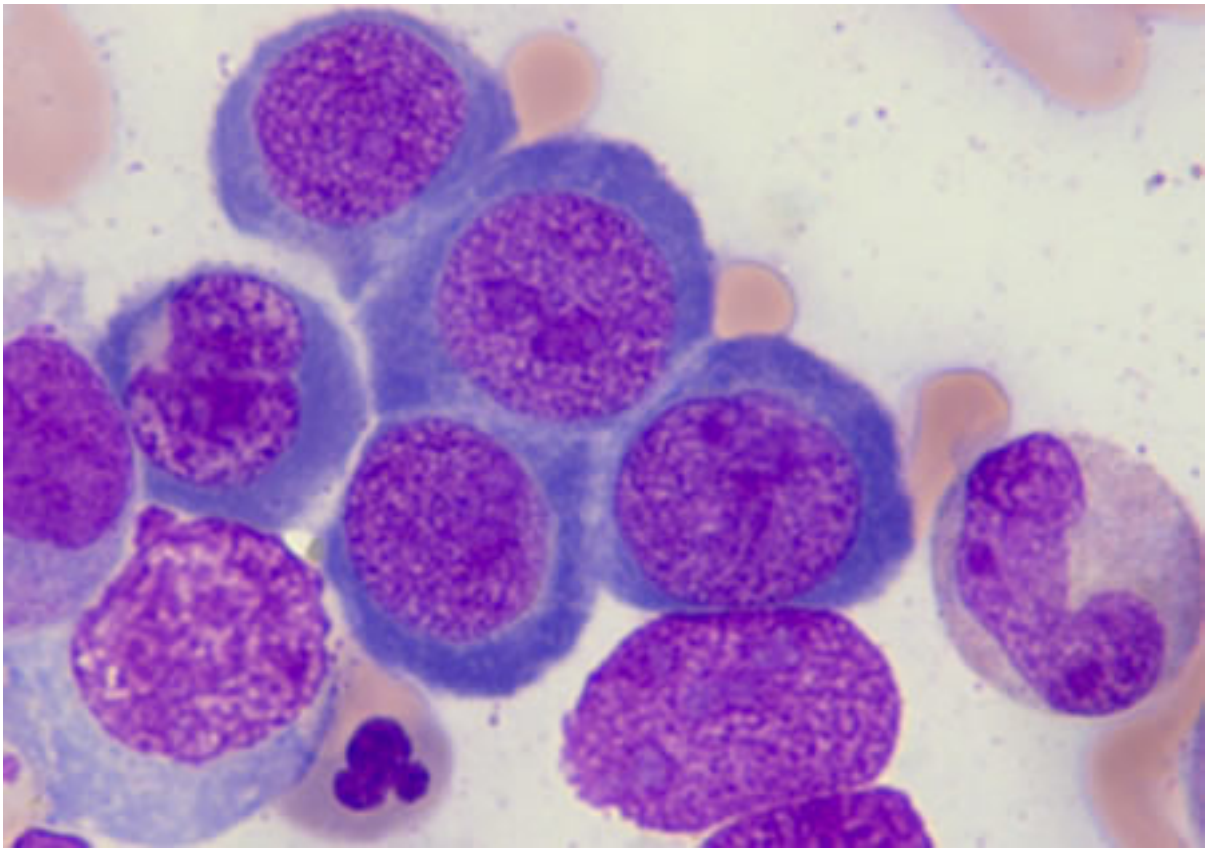

Figure 4: Megaloblastic marrow cells

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

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5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
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WC1H 9JR
UK

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Contributors:

// Authors:

Mark Koury, MD

Professor of Medicine, Emeritus (Hematology/Oncology)
Vanderbilt University Medical Center, Nashville, TN
DISCLOSURES: MK declares that he has no competing interests.

Allison P. Wheeler, MD

Assistant Professor of Pathology, Microbiology, and Immunology
Assistant Professor of Pediatrics (Pediatric Hematology-Oncology), Vanderbilt University Medical Center, Nashville, TN
DISCLOSURES: APW declares that she has no competing interests.

Mohammed Sika, PhD

Research Professor of Medicine (Nephrology)
Vanderbilt University Medical Center, Nashville, TN
DISCLOSURES: MS declares that he has no competing interests.

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// Peer Reviewers:

Ralph Green, MD, PhD, FRCPath

Professor and Chair
Department of Pathology and Laboratory Medicine, University of California Davis School of Medicine, Sacramento, CA
DISCLOSURES: RG is the author of reference(s) cited in this topic.

Jack Metz, MB, BCh, MD, DSc(Med), FRCPath, FCAP, FRCPA, FRS(SA), DSc Med(Hon Caus)

Emeritus Professor and Consultant Haematologist
Dorevitch Pathology, Heidelberg, Victoria, Australia
DISCLOSURES: JM declares that he has no competing interests.